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Research

Keywords: Epidemiology, sarcoidosis, incidence, prevalence, Puerto Rico

Posted Date: August 5th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-53470/v1>

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Research Article

Epidemiology of Sarcoidosis in Puerto Rico: A population-based study from 2016 to 2018

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Abstract

Background: Sarcoidosis is a systemic granulomatous and inflammatory disorder with significant variability in ethnicity and geographical distribution. There is no descriptive data about the epidemiology of the disease among the geographically isolated Puerto Rican population.

Objective: To estimate the incidence, prevalence, distribution, and healthcare burden of sarcoidosis in a large nationwide population-based cohort in Puerto Rico.

Methods: We conducted a descriptive and retrospective analysis using the health administrative claim database from the Puerto Rico Health Insurance Administration (ASES) from 2016 to 2018. The International Classification of Diseases-Tenth Revision coding (D86) was used for case detection. Data on sex and age were used to estimate incidence and prevalence.

Results: A total of 539 sarcoidosis cases were identified over the 3-year study. The median age at diagnosis was 59 years old. The average annual incidence rate was 9.4/100,000. The baseline prevalence was 15.4 per 100,000. Females represented the 67.5% of the cases. The frequency of sarcoidosis in women was higher than in males starting at the age range 18-34 years (GLM $p < 0.03$). Patients with lung and unspecified sarcoidosis predominates with 37% and 32% of cases, respectively.

Conclusions: Annual incidence rate of sarcoidosis in Island Puerto Ricans is among the highest in a single geographically isolated ethnic group reported globally. The overall mean age of individuals with sarcoidosis in Puerto Rico represent the oldest among previous epidemiological surveys conducted worldwide.

Introduction

Sarcoidosis is a chronic multisystemic disorder of unknown etiology characterized by the presence of granulomatous inflammatory lesions most commonly involving the lungs and adjacent lymph nodes (1). The liver, skin, eyes, spleen, salivary glands, heart, nervous system, muscles, bones, and other organs may also be involved (2). The disease can range from an acute self-limiting process to progressive chronic scarring which may permanently impair organ function.

Once considered a rare disease, sarcoidosis is now known to occur globally, affecting both sexes and all ethnicities and ages (3). Worldwide geographical and demographic variations have been observed in sarcoidosis occurrence. The highest incidence and prevalence rates are found in Northern Europeans and African Americans, with an average onset between 47 and 51 years old (3). Literature review consistently describes Puerto Rican Hispanics living on the U.S mainland as one of the ethnic groups to be at a higher risk of developing the disease (4, 5, 6, 23). Such reports have indicated that sarcoidosis in Puerto Rican Hispanics involves only lungs and skin (5,6). However, there are no epidemiological studies to clarify better the heterogeneity of the disease on the island of Puerto Rico.

The availability of nationwide healthcare databases allows for specific information regarding the incidence and prevalence of a disease across an entire population for individuals with healthcare insurance for a specific period (7,8). In addition, it allows researchers to compare disparities across racial / ethnic groups. The databases' access to identify sarcoidosis may provide the healthcare systems with tools to assess the human and economic costs of the disease, improve efficiency, and optimize management. Also, it has an advantage that members may be more likely to follow through with the tests and procedures needed to confirm the diagnosis.

Approximately half of Puerto Rico's 3.2 million residents have low incomes and depend upon the public health system for their medical care (9). The Puerto Rico Department of Health made a cooperative agreement with the Puerto Rico Health Insurance Administration (PRHIA) also known as Administración de Seguros de Salud de Puerto Rico (ASES), to administer the island-wide universal health insurance system (10). Since 1993, ASES has the responsibility of implementing, managing, and negotiating through contracts with insurers and health service organizations to offer services to approximately 1.5 million indigent medical Puerto Ricans. There are two main healthcare systems administered by ASES: Mi Salud (VITAL or PSG-Plan de Salud del Gobierno), which provides healthcare services to over a million people across the island and the Medicare “Platino” with approximately 250,000 patients (10).

The purpose of this study was to estimate the incidence, prevalence, distribution and healthcare burden of sarcoidosis in a large nationwide population-based cohort in Puerto Rico, using the available access to claims data from ASES.

2.0 Methodology

2.1 Data Source and Collection

An analytical file of patients with sarcoidosis was done using the ASES encrypted database, which represents approximately 1.6 million patients annually. The database contains information regarding patient age, sex, enrollment history, medical diagnoses, procedures performed and payment amounts for the time period spanning January 2016 to December 2018. We selected patients living in Puerto Rico who filed medical claims from two government healthcare plans (“PSG” and “Platino”) under the D86 code “sarcoidosis” of the International

Classification of Disease, Tenth Revision, Clinical Modification (ICD-10-CM; 11). All data from both PSG and Platino files were merged. Patient information collected included age, sex and all medical claims with the following diagnostic codes: D860 - Sarcoidosis of lung, D861 - Sarcoidosis of lymph nodes, D862 - Sarcoidosis of lung with sarcoidosis of lymph nodes, D863 - Sarcoidosis of skin, D8681 - Sarcoid meningitis, D8682 - Multiple cranial nerve palsies in sarcoidosis, D8683 - Sarcoid iridocyclitis, D8684 - Sarcoid pyelonephritis, D8685 - Sarcoid myocarditis, D8686 - Sarcoid arthropathy, D8687 - Sarcoid myositis, D8689 - Sarcoidosis of other sites, D869 - Sarcoidosis, unspecified, 135 - Sarcoidosis, 3214 - Meningit D/T Sarcoidosis All lines with ICD-10 codes which had “NULL” were excluded from the analysis.

2.2 Data analysis

Incidence and Prevalence:

Data for patients with sarcoidosis retrieved for the years 2016-2018 were characterized for 1-year periods. Unique cases were identified during the 1-year period as “new” if the patient had an assignment of ICD-10 code D86 at a first visit. Calculation of the incidence of sarcoidosis was based on the number of new cases seen in the year. Patients classified as “continuing” had filed one or more claims for sarcoidosis during the 2016-2018 period. Calculation of the prevalence of sarcoidosis was based on the total number of individuals visiting medical institutions who were assigned ICD-10 code D86. Comorbidities that accompany sarcoidosis in Puerto Rico under the period of study were identified using the ICD-10-CM diagnosis codes.

Economic Burden:

The economic burden of sarcoidosis was determined using patients with both medical and pharmacy benefits under the ICD-10 code 86 and their subcategories. Utilization of selected health

care services known for sarcoidosis patients (physician office, emergency, laboratory & exams, inpatient, home & preventive care, surgery, medical equipment & supplies, office administered drugs) was assessed. Prescription drug claims was used to determine the cost of care and medications for all beneficiaries with sarcoidosis.

Statistical analyses:

Categorical variables were compared using simulated Chi-square test. To analyze the tendency of the prevalence of sex by age, the generalized lineal model analysis was performed. The risk estimates of developing sarcoidosis in women with an increase of age was calculated from a Poisson regression model using the generalized linear model (12). All analysis and graphics were produced using *ggplot* R version 3.6.0 (13). The frequency of new cases was calculated with *comparedDF* package program (14). We performed an ordered Generalized Linear Model (12) to evaluate if the change in frequency by sex and age were similar.

2.3 Ethics

This is a descriptive, non-interventional study involving the use of unidentified data. Nevertheless, it was revised and approved by the Institutional Review Board of the San Juan Bautista School of Medicine (IRB # EMSJBIRB-16-2019).

3.0 Results

3.1 Baseline characteristics of patients with sarcoidosis in Puerto Rico 2016-2018

Over the 3-year study period, we identified 539 unique individuals which have been diagnosed with sarcoidosis, with an average of 180 new cases per year. The group consisted of 175 men (32.5%) and 364 women (67.5%), with a median age at diagnosis of 59 years old. The annual average incidence rate was 9.4 per 100,000 insured patients. The overall incidence of sarcoidosis in Puerto Rico showed a slight decrease during the surveyed period (10.0 and 8.8 for 2017 and 2018, respectively; Table 1). The average of continuing cases from 2016 to 2018 was 224, with an annual average prevalence rate of 15.4 per 100.000. The overall prevalence of sarcoidosis in Puerto Rico per 100,000 insured patients showed a slight decrease during years 2016 and 2018 (16.9, 15.5 and 13.9, respectively; Table 1).

The age and sex distribution of patients with sarcoidosis in Puerto Rico from 2016 to 2018 is shown in Figure 1a. Individuals from 0-17 years of age showed the lowest frequency of patients with sarcoidosis. Women 65+ years represent the highest frequency of patients with sarcoidosis. The frequency of sarcoidosis in women was higher than in males starting at the age range 18-34 years (Figure 1a). While the male frequency rate reached a plateau in the 55-64-yr-old group, females showed a peak at 65+ year-old (Figure 1a). To test if the differences in the frequency of sarcoidosis by age range and sex are significant, we used an Ordered Generalized Linear Model. We used a model including the age group category ("0-17", "18-34", "35-44", "45-54", "55-64", "65+"), sex and the interaction between both the variables. The result show that both age range and sex influence the frequency of sarcoidosis, being the rate of change in frequency in sarcoidosis much higher in females than in males (Ordered GLM $p < 0.03$) (Figure 1b).

3.2 Organ involvement in sarcoidosis

We evaluated the frequency of specific organ involvement of sarcoidosis in Puerto Rico from 2016 to 2018 (Figure 2a). The most frequent type of sarcoidosis is identified in the lungs with 352 unique and continuing cases (37%). Unspecified sarcoidosis was the second most common (305 new and continuing cases; 32%). Sarcoidosis of lymph nodes & lungs, other sites and skin were 7.7, 7.5 and 6.6%, respectively. The frequency of lung and unspecified sarcoidosis decreased slightly among years of this study (Figure 2a).

We next compared the characteristics of the patients by sex and organ involvement (Figure 2b). Lung, unspecified, other sites, and skin sarcoidosis were more frequent in females than in males but not statistically significant (Pearson's Chi squared test= 5.96; df =3; p = 0.11).

3.3 Comorbidities

We evaluated the frequency and types of the comorbidities that accompany sarcoidosis in Puerto Rico under the period of study. Regression analysis results showed a clear correlation between an increase in the number of comorbidities with age (Figure 3a). Statistically significant differences in the number of comorbidities between women and men is observed for ages before 50 (Figure 3a).

Figure 3b presents the diseases most frequently reported as comorbidity in sarcoidosis patients. Of the 493 patients with associated comorbidities, the five most common diagnosis was hypertension in 69% of patients, followed by Genito urinary disorders (67.7%), Diabetes type 2

(53.5%), Hyperlipidemia (48.5%) and Anemia (45%). In addition to each patient being assigned an ICD-10 code associated with Sarcoidosis, patients had multiple other comorbidities (mean of 6.2).

3.4 Healthcare resources and cost of sarcoidosis care in Puerto Rico

We assessed the healthcare resources and cost of sarcoidosis care to government insurance payers in Puerto Rico during the 2016 to 2018 period of study (Table 2). The analysis included cost of health care and prescription drug used to new and continuing patients. Health care resource utilization was categorized as office administered drugs, laboratory & exams, emergency, outpatient / inpatient office visits, surgery, home care, preventive care, durable medical equipment/ supplies, and Other. The total cost during the 3-year period was approximately \$162,349.98. The mean annual health care cost for a patient with sarcoidosis per year is approximately \$328.64.

The overall cost of sarcoidosis-related medications prescribed for new and continuing cases of patients with sarcoidosis from 2016 to 2018 is shown in Table 2. Sarcoidosis-related medications included first-line therapy for sarcoidosis, drugs for treatment of side effects associated with sarcoidosis-related drugs use and medications for co-morbid conditions not associated with sarcoidosis. Treatments were categorized under corticosteroids, Non-Steroidal Anti-Inflammatory (NSAIDs), immunosuppressors and antimalarials (hydroxychloroquine). The mean annual cost of treatment for a patient with sarcoidosis is approximately \$17,003.35 per patient. The categories of corticosteroids, hydroxychloroquine and immunosuppressors accounted for a 55.4%, 22.6% and 20.7% of all medications used for sarcoidosis, respectively. The three most commonly first-line drugs for sarcoidosis used were prednisone (355,609 claims for a total cost of US\$ 3,844,683.55), hydroxychloroquine (54,408 claims / US\$ 2,075,303.73) and methotrexate (both injectable and oral; 65,367 claims / US\$ 1,585,008.48).

4.0 Discussion

In this study, we used the 2016-2018 medical claims database from the two main public healthcare systems to conduct the first epidemiologic study of sarcoidosis in the island of Puerto Rico and the largest in a Hispanic ethnic group. Our results indicated that sarcoidosis is not an uncommon disease in Puerto Rico. The annual incidence of sarcoidosis in Puerto Rico was 9.4 per 100,000 population. This occurrence of sarcoidosis is higher than those reported in previous studies on Afro-Caribbean and French multiethnic (incidence ranging from 2.3 to 4.9 per 100,000 per year; 15,16), geographically-isolated Japanese and Korean populations (incidence of 1.01-1.3 per 100,000; 17,18) and Asian, Hispanic and white ethnic groups living in USA (incidence of 3.2, 4.3 and 8.1 per 100,000 per year, respectively; 7). Our estimate is surpassed only by the African American in US (17.9 per 100,000; 7) and Northern Europeans studies (11.5 per 100,000; 19). The incidence and prevalence of sarcoidosis in Puerto Rico between January 2017 and December 2018 showed a significant decrease (Table 1). The reason for the decreasing trend in the number of patients with sarcoidosis may be attributed to the extensive and widespread damage to the healthcare infrastructure caused by the Hurricane Maria in September 2017.

Sarcoidosis have been shown to vary significantly by age and sex (20). In our study, we show that there are dramatic differences in the age distribution and sex of patients with sarcoidosis in Puerto Rico. There were significantly more females than males (67.5% females, $p=0.005$). The frequency of sarcoidosis among women in our study is higher than those reported for Afro Caribbean (59%; 15), French multiethnic (55%; 16), Japanese (1.28%; 17), Korean (58.6%, 18), North Europeans (45%; 19), and USA (64%; 22) female groups. In addition, there is a 10-year difference in age at diagnosis between men and women (male = 55-64-year-old, female = +65-year-old), which is similar to that reported from North European populations (19).

Sarcoidosis is consistently reported to show a monophasic pattern of incidence, with peak between 42 and 55 years of age (3). The peak age in the USA group was 35-45 yrs (22), whereas in Japan the peak showed a biphasic pattern (20-34-yr-old in males and 50-64-yr-old in females;17). In North Europeans, the age at diagnosis in men was 45 compared with 54 in women (19). In Korea, the mean age of patients with sarcoidosis was 48.9 yrs (18). The peak ages of sarcoidosis in our study (mean = 59 years old; male = 55-64-year-old, female = +65-year-old) represent the oldest reported. This finding is strongly influenced by the high proportion of elderly patients living in Puerto Rico (24). The results suggest that sarcoidosis in Puerto Rico is concentrated at a middle to advanced age. The economic impact of sarcoidosis within this group may be more significant than any other age group due to factors such as: loss of working capacity and income, productivity and exacerbations with co-morbidities associated and not associated with the condition itself.

Pulmonary involvement is highly prevalent in sarcoidosis, as it was reported in several studies worldwide (22,23,26,27). However, organ involvement in sarcoidosis have been shown to vary among different geographic and ethnic groups. For example, ocular and cardiac manifestation of sarcoidosis is more frequent among Japanese (17). Skin sarcoidosis is prevalent among African Americans but uncommon among Caucasian Population (22, 25). In our study, the predominant organ involved was the lung with a prevalence of 37%. However, our prevalence was lower than those reported in the USA (95%; 22), Mexico (65%; 26) and Poland (79.2%; 27) studies.

Prior studies had reported that Puerto Rican patients have a high frequency of skin sarcoidosis (5,19,23). However, we did not find that high frequency of skin sarcoidosis among Island Puerto Ricans since our estimate is relatively low (6.6%). According to Soto-Gomez et al. (28), worldwide prevalence of skin sarcoidosis is 25%.

In our study, unspecified sarcoidosis was the second most common sarcoidosis found with a prevalence of thirty-two (32%) of patients. This contrast with a retrospective study made in Poland in which only 5% of patients were diagnosed with unspecified sarcoidosis (27). We can only speculate about the cause of the frequent use of “unspecified sarcoidosis” code in Puerto Rico. One of the possible reasons may be attributed to differences in the level, and expertise of both knowledge and diagnostic techniques on both studies. In the Poland cohort study, all patients were diagnosed or followed at a Tertiary Referral Center dedicated to tuberculosis & Lung Disease care while in our study, all patients under the Puerto Rico Government Health Plan are diagnosed or followed using the Primary Care Provider Healthcare (PCP) system. The new guidelines for the diagnosis of sarcoidosis recommended by the American Thoracic Society on Sarcoidosis (30) may ultimately provide the Puerto Rico Healthcare system and providers with more standardization of diagnostic criteria to better define the condition and thus future studies should have less “unspecified sarcoidosis”.

The goals of therapy in sarcoidosis are to reduce the inflammation of the affected tissues, reduce the impact of granuloma development, and prevent the development of lung fibrosis and another irreversible organ damage (30). The use of corticosteroids is considered the first line of therapy for the treatment of inflammation associated with sarcoidosis (30,31,32). The most prescribed corticosteroid in our study was prednisone (42%). This is slightly lower than the estimates reported by Baughman et al (7) who found that 49.1% of new and 56% of continuing cases of sarcoidosis patients enrolled in a national health plan in US were being treated with the drug. The antimalarial drug hydroxychloroquine (Plaquenil) was the second most used drug in our study (20%), as it was in the study of Baughman et al (7). This agent has been reported to be effective in people who have sarcoidosis of skin, lung and nervous system or a high level of

calcium in their blood. However, our findings contrast with findings from Bradford-Rice (20% vs 4.1% on lower cost patients and 20% vs 6.8% on high cost patients,33). It is known that the prolonged use of prednisone and hydroxychloroquine is associated with the development of glaucoma and cataracts (30) and this may explain the 8.1% in expenses associated with the use of prescription drugs for ophthalmic use found in our study (Table 2). The immunosuppressive agent methotrexate is the third most prescribed drug for sarcoidosis in our study and its use is higher than that reported by Baughman et al. (18% vs 12.5 and 16.8% in new and continuing cases, respectively, 7). Also, there is difference in the utilization of NSAIDs (9.9% vs 25.0% on lower cost patients and 9.9% vs 34.7% on high cost patients, 33). This finding reflects the complexity in the treatment of sarcoidosis in Puerto Rico, as therapy is not yet standardized. Hypertension, genitourinary disorders, and Diabetes mellitus Type 2 are among the most common morbidities in our group of sarcoidosis patients (Figure 3b). The prevalence of hypertension and Diabetes mellitus in our study is similar to that reported from population-based studies in Puerto Rico (34,35). In addition, the frequent use of prednisone in our study may contribute for the high prevalence of these two comorbidities since hypertension and diabetes mellitus is known to be a side-effect of prednisone (30)

The heavy load to the health care expenses and patient well-being associated with the somatic manifestations and psychosocial, economic and comorbid conditions of sarcoidosis are well known (7,8). This can create a significant economic impact to the healthcare resource utilization. We examine the healthcare resource utilization and costs, including sarcoidosis-related drug use on the Island Puerto Rican patients seen during the 2016-2018 period of the study. We found that the distribution of overall healthcare cost in sarcoidosis is skewed towards pharmacy spending. While total annual healthcare cost to the state insurance payers was only \$328.64 per

sarcoidosis patient, the cost of sarcoidosis-related prescription drugs were 52 times greater (\$17,003.35). The mean annual healthcare cost estimate in our study is significantly lower than the drug use estimates of \$19,714 per patient reported by Bradford-Rice et al. in the United States (29). The proportion of costs per patient attributed to sarcoidosis-related drugs in our study represents 98% of the total healthcare cost. The high cost estimate in medications contrasts with those reported by Bradford-Rice et al (29), in which US sarcoidosis patients in the top 20% of health care utilization spent between 6% to 18% in sarcoidosis-related prescription drugs, while patients in the remaining 80% have costs in the range of 20%-26%. The extensive use of medications may be also indicative that both sarcoidosis drug-associated and age-associated comorbidities have a significant impact in the overall cost of sarcoidosis in Puerto Rico.

The findings of our study have some potential bias. The study may not be generalizable since the analysis is concentrated in the economically disadvantaged population in Puerto Rico covered under the Puerto Rico Healthcare system and excluded residents who have private health insurance and those without insurance coverage. Second, data on the incidence and prevalence of sarcoidosis in Puerto Rico might have been overestimated over the study period due to possible inaccuracies in the use of ICD codes assigned by the health care providers to diagnose sarcoidosis and subtypes. Since sarcoidosis may mimic other chronic inflammatory / granulomatous conditions, the risk of misclassification or over diagnosis of sarcoidosis cannot be excluded. We were unable to confirm the sarcoidosis cases through the access of medical records data (i.e., imaging, pathologic results). Third, there is a possibility that we may oversample an older group of subjects in determining the incidence and prevalence of sarcoidosis in Puerto Rico since the population in the ASES database is older than the general population in Puerto Rico.

Despite the limitations, the large sample size obtained by the use of the insurance claims database from the Puerto Rico health insurance and Medicare can be considered as an advantage, since it provided data on a large subset of the population and a first estimates of prevalence and incidence of sarcoidosis in Puerto Rico.

5.0 Conclusions

The data obtained in the present study shows differences in age, sex, and organ involvement compared with other studies worldwide. The demographic profile of sarcoidosis in Puerto Rico presents a patient in the mid-to advanced age, mostly female, and incurring in extremely high costs of medications. Lung and frequent extrapulmonary sarcoidosis characterize the female patient. This study's findings provide health care providers with useful information to better understand the disease's complex and multidimensional nature. The study also revealed the need for accurate characterization of sarcoidosis in the Primary Care System in Puerto Rico to formulate better strategies for the disease's control and treatment.

Keywords: Epidemiology, sarcoidosis, incidence, prevalence, Puerto Rico

Abbreviations: ICD = International Classification of Disease; ASES = Administración de Seguros de Salud de Puerto Rico; PSG = Plan de Salud del Gobierno; PRHIA = Puerto Rico Health Insurance Administration; NSAID = Non-Steroidal Anti-Inflammatory; GLM = Generalized linear model; df = degrees of freedom.

Ethics approval and consent to participate: This study has the approval of the San Juan Bautista School of Medicine Institutional Review Board (Study Protocol IRB # EMSJBIRB-16-2019).

Consent for publication: A written informed consent for publication was obtained from the Administración de Seguros de Salud de Puerto Rico (ASES).

Availability of data and materials: The databases generated and/or analyzed during the current study are not publicly available but are available from the corresponding author upon reasonable request.

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

Funding: This study was supported by partial funds from the San Juan Bautista School of Medicine.

Authors' contributions: RSV: participated in study design, coordination during field work, acquisition of data, creating the first draft of the manuscript, finalizing and drafting of the manuscript. RLT: performed the statistical analysis, creation of tables and figures and interpretation of data. All authors read and approved the final draft of this manuscript.

Acknowledgements: The authors thank the staff of the Planning and Quality Affairs Division Evaluation of the “Administración de Seguros de Salud de Puerto Rico” (ASES) for their valuable contribution to this research. We kindly appreciate Dr Estela S. Estapé for the critical review and comments to the manuscript.

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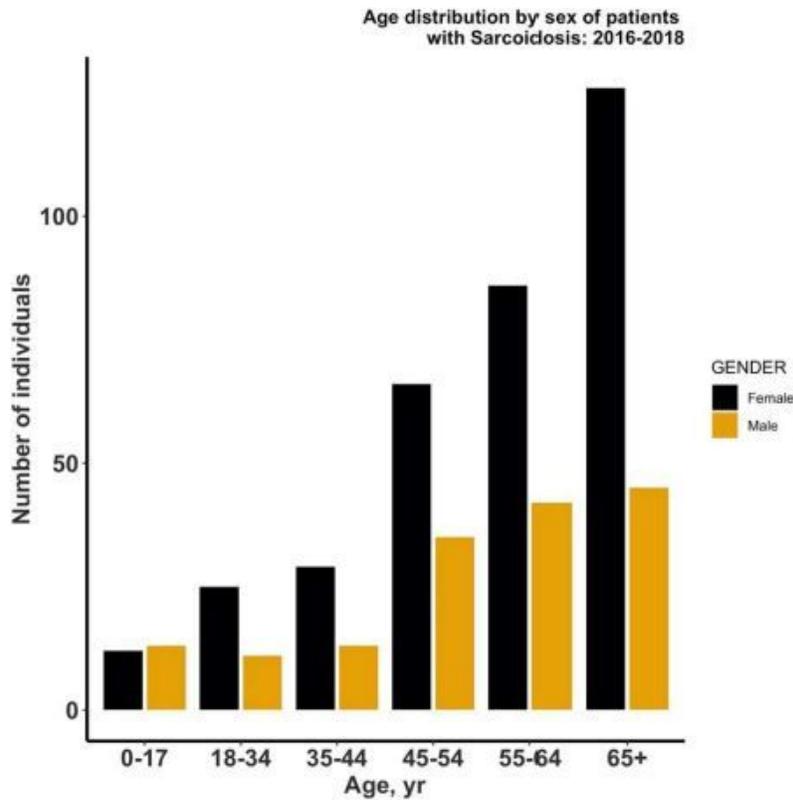
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Figures

A



B

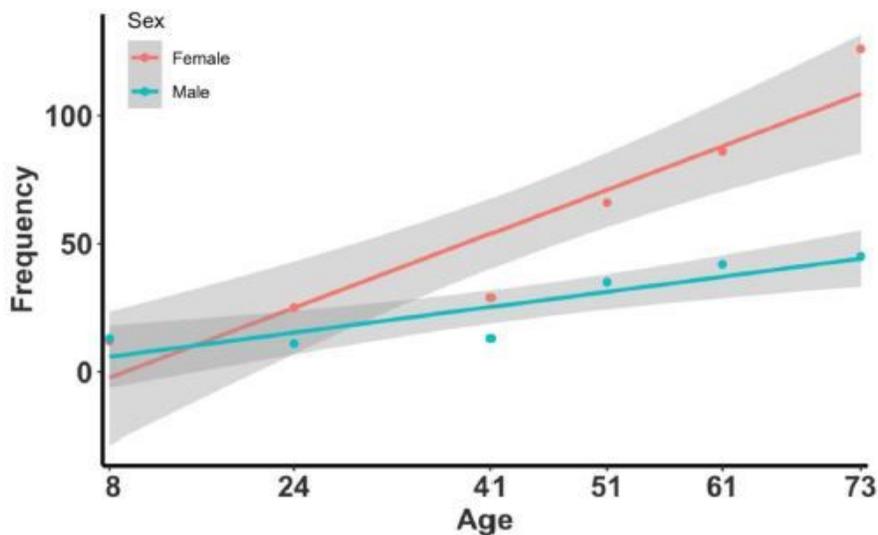
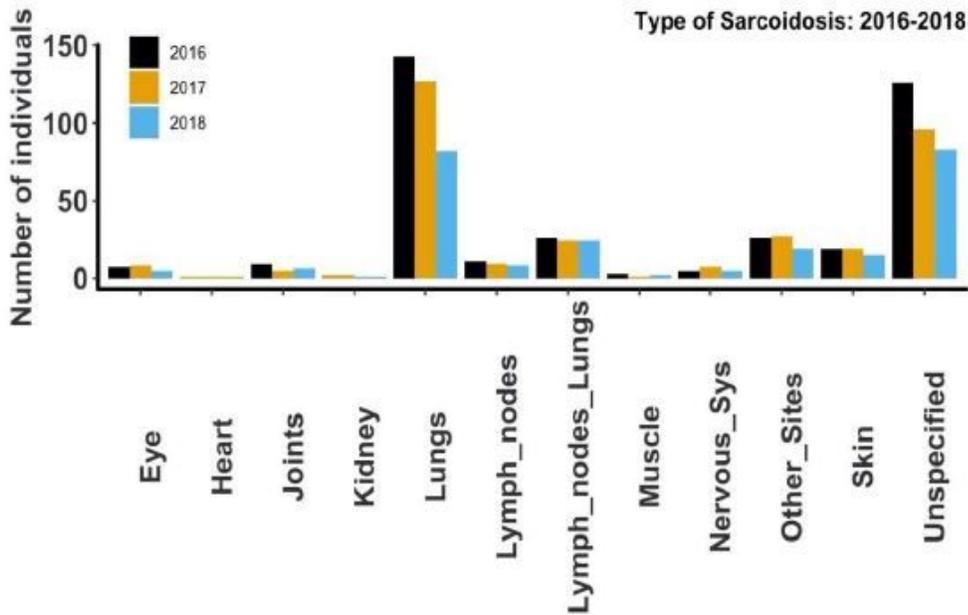


Figure 1

Sarcoidosis occurrence by age and sex in Puerto Rico:2016-2018. A) Frequency of number of patients by age and sex. B) Generalized ordered regression model analysis showing the comparison of the frequency of sarcoidosis patients by age and sex. The rate of change in sarcoidosis frequency in patients is

positively correlated with age categories and is significantly different between males and females ($p < 0.01$).

A



B

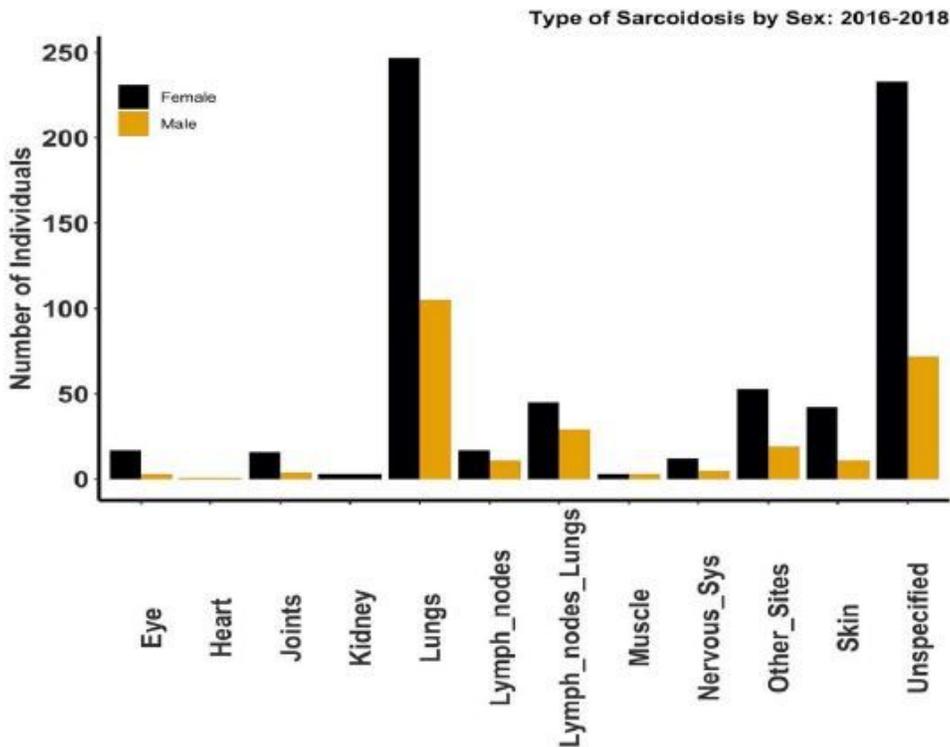
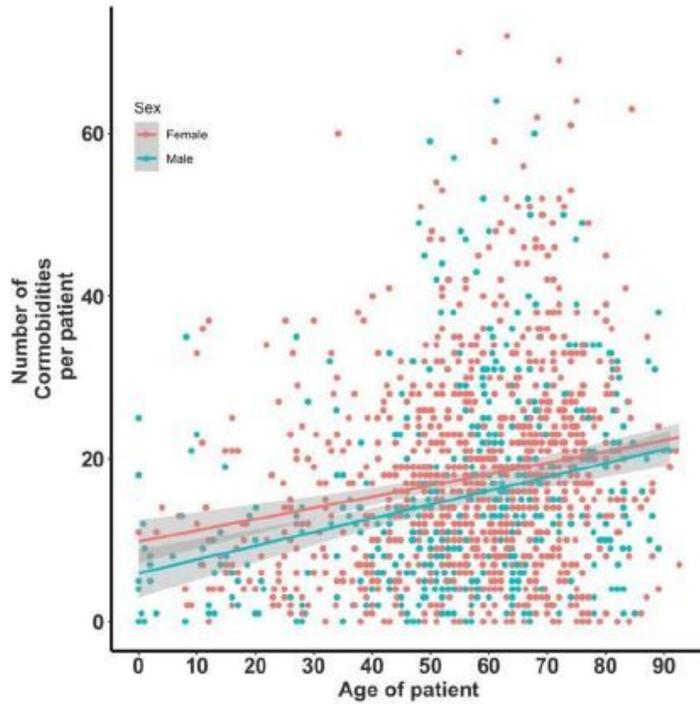


Figure 2

Organ involvement of sarcoidosis in Puerto Rico. A) Number of unique patients per year with specified organ involvement. B) Comparison of patient's sex and the involvement of each organ for all years surveyed.

A



B

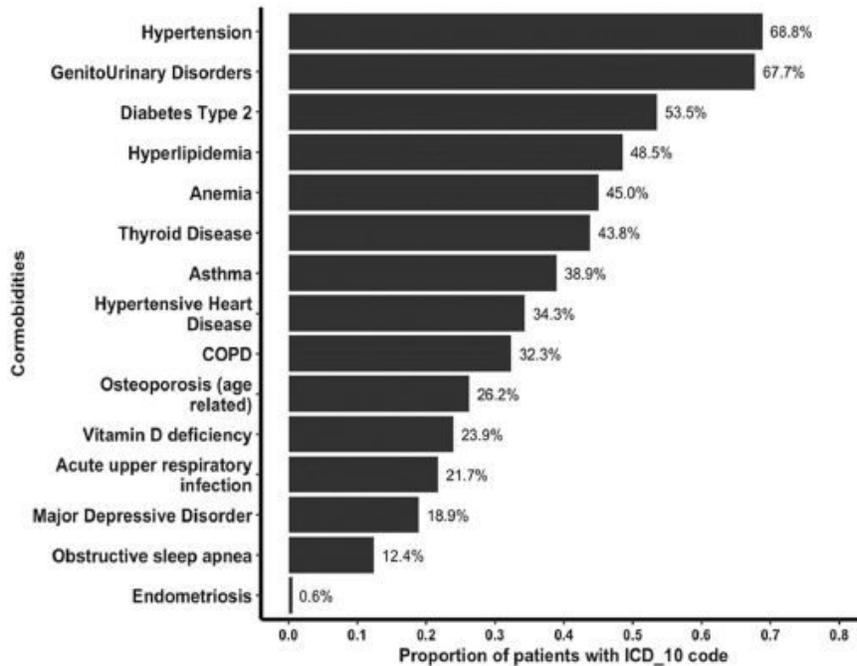


Figure 3

Analysis of comorbidities in sarcoidosis patients from Puerto Rico: 2016-2018. A) Scatterplot and linear regression analysis showing the correlation between age and sex of patient with sarcoidosis and number of comorbidities per patient. The relationship was modeled using linear regression, the slope of the lines is significant ($p < 0.001$). The grey area is the 95% confidence interval of the linear regression. B) The

proportion of unique patients with the most prevalent diseases in sarcoidosis patients according to the groups of ICD-10 classification.

Supplementary Files

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