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Editorial

Sarcoidosis: No longer a benign disease?

Sarcoidosis is a multi-system disease of unknown cause characterized by noncaseating granulomatous inflammation that results in symptoms and organ dysfunction due to persistent inflammation and fibrosis. It predominately affects the lungs in over 90% of patients, but can injure any organ in the body. Sarcoidosis can be a life-threatening disease, particularly in those with pulmonary fibrosis, pulmonary hypertension, or cardiac involvement [1,2]. Opportunistic infections may also play a role in mortality in patients on immunosuppression [2,3]. The disease carries an increased risk of death compared to the general population, especially in Blacks or those in older age groups [4,5].

In this issue, the article by Kearney et al. entitled, "Sarcoidosis Deaths in the United States: 1999–2016" describes mortality rates of sarcoidosis as the underlying cause of death over the past two decades within the National Vital Statistics System (NVSS) death certificate database [6]. This work is an extension of prior studies evaluating trends in earlier time periods within the same database which have shown an age-adjusted (annual) rate of mortality due to sarcoidosis of 2.8 per million population for an underlying cause of sarcoidosis [7], and 4.32 per million for all causes of death among patients with sarcoidosis [8]. The results by Kearney et al. continue to confirm a disproportionately high rate of mortality due to sarcoidosis amongst African Americans and women. In terms of trends, Mirsaeidi et al. found by regression analysis that the overall mortality rate for sarcoidosis as the primary cause of death between 1999 and 2010 remained stable, accounting for the yearly variability in rates over time. Kearney et al. add to these results by finding a change point in the data with an increase in mortality rate between 1999 and 2002, and thereafter remaining stable.

The change-point in 2002 found within the current manuscript provides additive information to prior studies, although the cause of this abrupt increase is unknown. It is important to consider alternative factors besides actual death from sarcoidosis to account for this acute change. First, this rise may be related to changing database factors. For instance, the authors note the change in coding in 1999 requiring ICD-10 for death certificates. This may have led to increased frequency of sarcoidosis coding or education of physicians regarding appropriate coding of cause of death and related co-morbidities, resulting in a "learning curve" over the subsequent few years. ICD-10 mortality coding changes (which do differ from morbidity coding) may affect the manner of documentation for physicians and coders, and prior studies have shown that incidental changes in cause-specific mortality codes can lead to trend changes [9]. Furthermore, as of January 1, 2003, the death certificate format was changed to improve ease of reporting and added items to address issues regarding the new ICD-10 coding. At the same time, changes in race and ethnicity reporting within the death certificate were implemented to comply with newly revised federal Office of Management and Budget (OMB) standards; these new race and ethnicity options may also have affected the race-specific data over that time period [10]. For further study of these potential confounders unrelated to death itself, it would be important for future mortality analyses to include carefully selected control groups to assess whether these variations are applicable to other diseases around similar time periods.

Additionally, it is also important to consider whether this mortality increase across years could be related to diagnostic bias. For example, new imaging techniques such as cardiac magnetic resonance imaging (MRI) or positron emission tomography (PET) may now be revealing sarcoidosis as a cause of arrhythmias or cardiac failure; fatal events that may have been previously misclassified due to lack of available diagnostics. It would be useful to assess if there are disproportionate increases in cardiac-related complications of sarcoidosis that may account for some of the rise over time. Similarly, with the increased use of chest CT imaging and applications, it may be that there is increased recognition of sarcoidosis by incidental findings and more granular imaging methods. To determine whether increasing incidence is accounting for this mortality increase, correlations between incidence and mortality time series could be assessed in future studies. Last, improving awareness of sarcoidosis morbidity by physicians could also partially be contributing to the timely rise in rate, as the American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and Other Granulomatous Disorders Statement on Sarcoidosis was published in 1999 [11], and the largest case control study for sarcoidosis etiology (ACCESS study) was ongoing at that time with recruitment in academic centers across the United States [12].

Although the authors do quantify the increased rate over the time period by specific gender, it is important to emphasize that these estimates were calculated by a difference in rate at two separate isolated time points (1998 and 2016), without regard to the data points in the interim years. Given the variable differences (up and down) in overall mortality rates over the years, a direct comparison of any two isolated data points may produce very different conclusions. This is allegorical to many other time trends, such as the stock market or temperature variations, in which data points fluctuate around a mean trending line, and therefore, conclusions based on these calculations alone may not elicit the entire picture of a best-fit line to assess a true trend. However, it is very valuable to compare the current mortality rates with past analyses, thereby providing an increasingly longitudinal view of sarcoidosis mortality over time. Gideon et al. evaluated sarcoidosis or its complications as the immediate cause of death in the NVSS data from 1979 to 1991 and found that the age-adjusted mortality rate increased from 1.6 per million in 1979 to 2.1 per million in 1991 [3]. Even more remote data showed a mortality rate of 1.0 per million in 1958 [13], which is distinctly different than the more recent rate calculation at 2.8 per million. When visualizing these rates over six decades, there does

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seem to be a potential concerning trend that warrants further study. Future death certificate data will be useful to see if the current steady rate changes.

Despite the current limitations of trends analyses and caution in over-interpretation of yearly variability, in totality, the mortality studies in sarcoidosis reveal a significant contribution of sarcoidosis to death that does not appear to be diminishing. Consistent in all studies are the markedly disproportionate death rates amongst African Americans and women. Both the Black Women's Cohort Study and a Swedish population-based cohort have shown that sarcoidosis carries a higher risk of death than the general population (HR 2.4 and HR 1.61, respectively, with an even higher HR for those receiving treatment [5,14]. These data spur compelling questions regarding potential causes of disproportionate burden. Contributing factors may not only include disease severity or varying degrees of granulomatous inflammation by race or gender, but also, complications of immunosuppression, race and gender-specific co-morbidities, or health care access. An age-related effect may also be playing a role as women may be living longer and dying less of alternative causes than male counterparts, as gender differences seem to be more prominent with increasing age in death certificate data.

Overall, the results of the manuscript by Kearney et al., along with its predecessors, refute common belief that sarcoidosis is a benign entity with no significant health ramifications. Rather, these data show that sarcoidosis can be a mortal danger in a percentage of those afflicted. Mortality studies such as these highlight the need to understand contribution of the disease to lifetime morbidity and health complications, particularly in high-risk populations, in order to design strategic interventions that decrease the burden of disease and avert mortality.

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