REGULAR ARTICLE

The Impact of Socioeconomic, Racial, and Ethnic Disparities on Pulmonary Hypertension Diagnosis and Treatment

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Health disparities have a major impact in the quality of life and level of clinical care received in minority populations in the United States. Underrepresented patients with pulmonary arterial hypertension (PAH) may be at risk for worse outcomes. Furthermore, advances in biomedical research have provided extensive knowledge on the genetic role in the pathogenesis of PAH but whether these also impact minorities is incompletely understood. Health disparities in patients with PAH create an enormous barrier in health care delivery. Understanding the contributors to health disparity represent a fundamental step towards personalized medicine and further improvement in PAH care.

INTRODUCTION

Health care delivery disparities are an important consideration for any disease process, as they significantly impact quality of life and outcomes for minorities.[1] Health disparities are defined as significant differences in health care that are closely linked to racial ancestry, social, economic, and/or environmental differences.[2] Today, in the United States, nearly 36% of the population belongs to a racial or ethnic minority group, with this figure likely to increase over the coming years.

Pulmonary arterial hypertension (PAH) is a cardiopulmonary process resulting in right heart failure from elevated pulmonary artery pressures that predominantly affects women and has a median survival of 3 years without treatment.[3] PAH is an interesting disease to evaluate through the lens of health care disparity, as it is rather less common than other cardiovascular diseases but still has a high mortality.[4] Still, the extent of how health disparity affects PAH diagnosis and treatment is understudied.

Information currently available at this intersection is largely from historical cohort studies using registries. Such investigations have demonstrated that age, sex, race/ethnicity, country of origin, medical treatments, and socioeconomic status (SES) may be associated with specific types of PAH, response to therapy, and survival. The scope of this article is to summarize health disparities that exist with PAH, and to shed light on possible areas for improvement.

RACE/ETHNICITY AND PAH

Racial differences in the manifestations of various respiratory disorders have been well documented and it has been suggested that it leads to health care delivery disparities.[5] Still, there is a paucity in the literature of studies describing the impact of race on the prevalence and etiology of pulmonary hypertension. The study of race as it relates to pulmonary hypertension is made particularly difficult because pulmonary hypertension registries lack adequate representation of different races/ethnicities. For instance, when compared to the demographics of the general population, the demographics of patients in the registry to evaluate early and long-term PAH disease management (REVEAL) are quite different. African Americans are relatively overrepresented in the registry (with a prevalence of 12.2% versus 10.9% in the general population). Meanwhile, Hispanics are underrepresented (with a prevalence of 8.9% versus 11.5% in the general population).[6]

More recently the Pulmonary Hypertension Association (PHA) registry has been assessing the adherence to guidelines, treatment patterns, quality of life, and outcomes of patients with PAH and chronic thromboembolic pulmonary hy-

Key Words——health disparities, pulmonary arterial hypertension, socioeconomic status, race, sex
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Disclosure: The authors have no conflicts of interest.

pertension who begin their care at pulmonary hypertension centers accredited by the PHA for their track record in the care of patients with PAH; self-reported race/ethnicity, primary language spoken at home, and various individual indicators of SES are also collected in this registry. The data from this registry suggest that health-related quality of life appears to correlate with socioeconomic measures like education status, and also the clinical PAH measures like right atrial pressure and pulmonary vascular resistance.[7]

High pulmonary artery systolic pressure in heart failure patients is known to be a significant risk factor for hospitalization.[8] Interestingly, racial disparities exist within this metric. In 2017, the CARDIA study found an association between Black race and higher echocardiographically recorded pulmonary artery systolic pressure.[9] Additionally, a study by Yang et al.[10] showed that, after controlling for clinicodemographic covariates, African Americans were associated with a 41% greater risk for PH than Caucasians. The authors further noted that African American patients with PAH were typically younger, and had a higher rate of heart failure, more severe pulmonary hemodynamics, and more prevalent cardio-metabolic/renal disease than Caucasians. However, Medrek et al.[11] have reported that, based on their analysis of the REVEAL registry, race/ethnicity is not a significant predictor of mortality in PAH. These contradictory findings merit further investigation.

Connective tissue disorder disease–associated PAH is one subgroup that shows clear differences in presentation between races/ethnicities.[12] Scleroderma-associated PAH (SSc-PAH) is most common connective tissue disorder associated with pulmonary hypertension (with a prevalence of 5%-12%).[13] There is a suggestion that scleroderma-associated PAH patients tend to be less responsive to therapy and have a worse prognosis than patients with other types of PAH.[14] A retrospective study by Moore et al.[15] found that African American scleroderma patients have more severe pulmonary hypertension and more severe cardiac involvement than non–African American patients. It has also been reported that Hispanic patients are more likely to have portopulmonary hypertension.[16]

Recent investigations suggest that there may be significant differences in health care delivery between races. Parikh et al.[17] demonstrated that adjustment for insurance status dampens the association of race with survival for those with PAH. Al-Naamani et al.[16] reported that Hispanics are less likely to be treated with PAH-specific medication regimens. In addition, Valverde et al.[18] analyzed local epidemiological data of PAH in Latin America and found that the percentage of idiopathic PAH patients in Latin America is higher compared to European studies and the REVEAL registry.

The relationship between race/ethnicity and PAH disease presentation needs to be studied further. It has been suggested that Black and Hispanic patients have more severe disease at the time of presentation.[19,20] Though the exact reason for this remains unclear, many factors have been proposed for this observation. For instance, impaired nitric oxide balance in Black population may predispose this population to vasculopathy.[21] Other investigators have suggested structural differences in the pulmonary vasculature between different races. Kawut et al.[22] proposed that right ventricular mass is lower in African Americans than in Whites. Ventetuolo et al.,[23] on evaluation of 463 single-nucleotide polymorphisms in 10 candidate genes in 2761 genotyped participants, found that polymorphisms in the gene CY1P1B1 were associated with the differences in the right ventricular ejection fraction (RVEF) in Black women. The study also found race-specific differences in the relationship between urinary estrogen metabolites and RVEF: though there was no relationship in Black and Chinese American populations, there was a positive correlation between estrogen metabolites and RVEF in White patients.[23]

The response to PAH-directed therapy is also heterogeneous and may, to some extent, be related to race. Data to support this assertion exist for the endothelin pathway. It has been demonstrated that Black patients had increased circulating levels of endothelin-1 compared with white patients.[24] The cytochrome P450 pathways, which are an important factor in at least endothelin receptor blockers, show a significant racial variation and could help explain the differences in response to these medications.[25] These findings underscore the importance of population-based investigations to better understand PAH genotypes in various ethnicities and races.

SES AND PAH

The interplay between SES and population health is clear. To some extent, SES dictates the type of insurance patients have [26] and may therefore be reflective of a patient's ability to follow up with physicians.[27] Still, of all the measured demographics in health care today, SES is often unreported.[28] SES particularly has a measurable and significant effect on cardiovascular health. This is true even more so for disadvantaged individuals who have many biological, behavioral, and psychological risk factors.[29]

Talwar et al.[30] evaluated patients with PAH using their home zip code as a surrogate for SES. There was an inverse correlation between functional class at the time of initial evaluation and household income.[30] One possible explanation for severe disease at initial presentation and delayed diagnosis in lower SES individuals is that these individuals may have significant barriers to access health care. This presents a problem specifically for PAH, which requires referral to a specialist center and a right-heart catheterization for diagnosis.

Similarly, Wu and colleagues[31] showed that lower SES (as measured by educational level, annual household income, occupation, and medical reimbursement rate) was associated with a higher risk of clinical worsening and mortality for patients with idiopathic PAH. These findings were independent of hemodynamics, demographic variable, and medical treatment characterstics.

A study by Jin et al.[32] stratified patients with connective tissue disorder–associated PAH based on SES. The study found that connective tissue disorder–associated PAH patients with low SES had a much lower 5-year sur-

vival than patients with middle or high SES (75.7% versus 81.4% versus 87.9%, respectively). These results are consistent with those found by Moore et al.,[15] who reported that the hazard of death for patients with scleroderma decreased by 15.5% for every additional $10,000 of household income (independent of race). Examination of SES in systemic sclerosis suggests that higher wealth and more equitable access to health care services may mitigate increased mortality attributable to specific ethnic groups.[33]

Current guidelines and management algorithms do not factor the effect of SES on the disease process. However, from the emerging data it is evident that SES plays an important role in health-related quality of life and clinical outcomes. It will be worthwhile to pay more attention to SES as a major variable in research studies, as it will help identify vulnerable patients with risk factors that are unique to underrepresented minorities in the United States.[4] This also argues for a push towards greater inclusion of different races/ethnicities in various clinical trials of PAH, as is true for a multitude of other disease states as well.[34] There are many reasons as to why underrepresented minority patients do not participate in trials including lack of access to trials and lack of education about the purpose of clinical trials.[35] Language barriers also often preclude minority patients from participating in trials. However, such issues are easily surmountable and should be resolved so that future trials in clinical medicine provide adequate representation to underrepresented minorities.[36]

SEX, AGE, AND GENETIC CONTRIBUTORS TO HEALTH CARE DISPARITIES IN PAH

Sex disparities in PAH cannot be ignored. Although PAH predominantly affects females (females are 1.8 times more likely to be affected by PAH relative to their male counterparts)[6] they remain underrepresented in clinical research.[37] Sex also has an effect on survival; it is well established that females with PAH have better survival compared to males. Interestingly, the survival benefit for females appears to decline with age[38] and correlates with declines in estradiol levels.[39] The discrepancy in incidence and outcomes in men/women is commonly referred to as the PAH-estrogen paradox.

According to Ginoux et al.,[40] the patient age at time of diagnosis of PAH is increasing. They reported that compared to young patients, elderly patients have a longer time to diagnosis, more comorbidities, worse New York Health Association functional class, and a worse prognosis. When compared with younger patients, very elderly patients have a longer delay in access to a regional referral center for pulmonary hypertension.[40] It is also known that patients 65 years of age or older have the worst prognosis.[41,42]

Personalized medicine, also known as individualized medicine, is a rapidly emerging field in which medical treatments are tailored to an individual's genomic characteristics in order to provide more targeted interventions for patient care.[43] While the pathophysiologic cascade in PAH is not completely understood, there have been many advances in the molecular pathways that contribute to the pathology. To date, it has been established that certain genes contribute to hereditary PAH (particularly bone morphogenic protein receptor type II).[44,45] Other genes that may be involved include endoglin,[46] caveolin-1,[47] potassium channel two pore domain subfamily K member 3,[48] and eukaryotic translation initiation factor 2α kinase 4.[49] PAH susceptibility has been linked to common variants of genes encoding prostacyclin and endothelin-1 pathways,[50,51] calcium signaling,[52] sex hormone metabolism,[53] and the endostatin gene.[54] Most of these pathways have not been studied under paradigms that include minorities and therefore may have inherent selection bias.[55]

CONCLUSION

Disparities certainly exist in health care delivery in the context of PAH. Recent investigations have revealed associations between genetics, sex, age, race, SES, and PAH outcomes. Understanding the contributions of these factors, as well as the broader context of health care delivery, represent a fundamental step towards personalized medicine and further improvement in PAH care.

For future research into PAH, integration of SES into the traditional risk prediction models may allow improved management of individuals with high risks for this disease. Education of physicians and other health care providers facilitating PAH awareness, addressing cross-cultural training, and recognizing the risk factors associated with different races, sexes, etc. is crucial.[4] Lastly, refocusing health care laws that advocate for minorities is important.

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