The Growing Burden of Pulmonary Hypertension in the Modern Era

A Zebra No More?

See Article by Wijeratne et al.

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Pulmonary hypertension (PH) is a heterogeneous syndrome characterized by elevated pulmonary pressures. Although often suspected based on symptoms of dyspnea and elevated estimates of pulmonary arterial systolic pressures on echocardiogram, PH can only be diagnosed by right heart catheterization demonstrating a mean pulmonary artery pressure ≥25 mm Hg. Clinically, PH can result from various comorbid conditions, including underlying cardiac, pulmonary, thromboembolic, and miscellaneous diseases. PH in the absence of these comorbid conditions constitutes a small subset of PH, known as pulmonary arterial hypertension (PAH).

Over the last several years, determining the incidence and prevalence of PH in population-based studies has proven challenging, in part, because of the lack of specificity of diagnosis codes commonly used in reimbursement system databases. These codes do not align with the current classification system and thus are unable to accurately distinguish disease phenotypes. In addition, proper classification of PH, according to guideline recommendations, requires not only a high clinical suspicion but also extensive targeted testing, which is often not completed in clinical practice.[1] As shown in prior studies, (1) only a minority (<6%) of patients with a diagnosis of PAH complete the entire recommended testing algorithm and (2) nearly one third of patients referred to a tertiary center for PH have a change in their diagnosis after completing the entire workup.[2,3] Thus, the clinical diagnosis of PH at both the population and the individual level has a significant likelihood of inaccuracy that limits the reliability of estimates of disease incidence and prevalence.

In this issue of *Circulation: Cardiovascular Quality and Outcomes*, Wijeratne et al[4] offer an important step to overcome these challenges. The authors report on a large, modern day, population-based cohort study performed in Ontario wherein they describe the incidence, prevalence, prescribing medication patterns, and mortality in essentially all forms of PH, pediatric and adult. The authors used data from the Institute for Clinical Evaluative Sciences, using databases from the Ontario Health Insurance Plan, prescription data from the Ontario Drug Benefit Database, mortality data from the Registered Persons Database and hospitalization data from the National Ambulatory Care Reporting System plus the Canadian Institute for the Health Information Discharge Abstract Database. Although the authors use standard *International Classification of Disease* diagnosis codes to identify patients with various forms of PH as many prior studies have used, they have taken the novel step to validate these diagnosis codes with individual chart reviews in a subset of patients. Thus, the authors are to be complimented not only for accessing and interpreting data from these large, complimentary databases, but also for distilling important and substantially more reliable information from these sources.

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The authors found that from 1993 to 2012, the incidence and prevalence of PH increased significantly. Whereas traditionally considered a rare disease, in this population-based cohort study performed in Ontario, representative of much of North America, the annual prevalence of PH among adults was 127.3 cases/100 000. It is reassuring that this estimate aligns well with a population-based study conducted in Olmsted County, MN, which showed that in some cohorts, up to 20% of the population will have echocardiographic evidence of PH.[5] As shown in both of these studies, PH is a disease commonly associated with left-sided heart disease (World Health Organization group 2 disease), particularly as the North American populations get older, grow more obese, and develop systemic hypertension.[6] These data suggest that PH is becoming an increasingly common disease that will be encountered and treated in community settings, much like heart failure.

It is particularly concerning that the 1-year mortality for WHO group 2 disease was 40.9% and was even higher for PH secondary to hypoxic lung disease (WHO group 3 disease) at 46%. This contrasts dramatically with the 1-year mortality for PAH (group 1 PH), which was 22.8%. Historically, group 1 PH was considered to be the most feared form of PH, but as the authors here show, any diagnosis of PH results in at least a 7-fold increase in adjusted mortality.[7] A recently published single-center registry study from the University Hospital Giessen in Germany showed a similar concerning trend with 1-year survival for group 1 PH of 88.2% compared with 86.7% for group 2 PH and 79.5% for group 3 PH.[8] Although the reasons for this increased mortality in group 2 and group 3 disease remain unknown, these findings highlight the importance of proper diagnosis to appropriately risk stratify patients with PH. Future studies to confirm these important observations will be needed.

The authors also captured important data on prescribing patterns, namely, the observation that pulmonary vasodilator therapies, only approved for group I disease, were commonly prescribed off-label for group 2 and group 3 disease. Given the cost of PAH medications, off-label use adds significant expense to the healthcare system and financial burden to the individual patient without proven clinical benefit.[9] In fact, in recognition of the inappropriate use of PAH-specific therapy and its attendant cost burden, the American Board of Internal Medicine selected use of pharmacological agents to treat PH as 1 of 5 topics on a list of Things Providers and Patients Should Question as part of its *Choosing Wisely* Campaign (www.choosingwisely.org) that aims to tackle the problem of overuse in medicine. This list is designed to facilitate conversations between patients and providers about the need-or lack thereof-of many frequently ordered tests or treatments; inclusion of PH treatment on the list of the 5 most pressing issues in pulmonary medicine highlights the vast knowledge gap in diagnostic evaluation and appropriate treatment for PH.

Within the United States, we need more urgent data to confirm these findings. Already, the Pulmonary Hypertension Association has accredited approximately 50 Centers of Comprehensive Care for PH based on demonstrated excellence in clinical care and research.[10] If the increased prevalence of PH, high prevalence of inappropriate use of PAH-specific medications, and significant mortality associated with group 2 and group 3 PH suggested by Wijeratne et al[4] is confirmed more broadly, there will be an urgent need to expand beyond these centers to educate and train providers how to properly evaluate and manage PH. Awareness programs such as the American Board of Internal Medicine's *Choosing Wisely* campaign, the PHA's *Sometimes It's PH* campaign (www.phaonlineuniv.org), and the PHAware campaigns (www.phaware.global) are important and substantial but expanded and sustained efforts to raise awareness for this disease could be warranted. Based on the data presented in this important study, PH may no longer be a medical zebra, a disease seen only once in a lifetime, but more likely one encountered every day.

FOOTNOTES

Circ Cardiovasc Qual Outcomes is available at http://circoutcomes.ahajournals.org.

DISCLOSURES

Dr Mathai discloses consultancies for Actelion and United Therapeutics. Dr Mathai serves on the Scientific Leadership Council of the Pulmonary Hypertension Association and is a member of the Rare Disease Advisory Panel for the Patient Centered Outcomes Research Institute. The other author reports no conflicts.

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