Researchers revisit pulmonary arterial hypertension survival

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Setting out to determine the survival of patients with pulmonary arterial hypertension (PAH), researchers at the University of Chicago Medical Center and their colleagues also discovered that an equation used for more than 20 years to predict survival is outdated. Accordingly, they developed and recently published a new survival prediction equation that will impact clinical practice and the drug development process.

In PAH, the pulmonary arteries, which carry blood from the heart to the lungs to pick up oxygen, become restricted, forcing the lower right chamber of the heart to pump harder. This leads to shortness of breath, limited exercise capacity, fatigue, heart failure and death. Often the condition goes undetected until it is advanced. Untreated, patients with PAH have a very poor prognosis.

That prognosis is determined using an equation developed by a landmark National Institutes of Health study published in 1987, well before there were any Food and Drug Administration approved therapies for PAH. The first such therapy was approved in 1995; today there are seven.

"Since 1987, great progress has been made in understanding and treating PAH, so a few years ago we decided that it was time to study contemporary survival," said Mardi Gomberg-Maitland, MD, MSc, Associate Professor of Medicine and Director of Pulmonary Hypertension at the University of Chicago Medical Center. "Our results show that survival is vastly improved today. That led us to rework the NIH equation, which has been a standard measuring stick for more than

22 years."

Gomberg and her colleagues at the Medical Center and Northwestern University's Feinberg School of Medicine studied the survival of 576 PAH patients in their registry. Of these patients, 282 had idiopathic, familial, and anorexigen-associated PAH, which matches the conditions of the 187 patients in the pioneering NIH study.

Using the NIH equation, these 282 patients would have been expected to have one-, three- and five-year survival rates of 65%, 43% and 32%, respectively. In fact, their survival rates were much higher: 92%, 75% and 66%, respectively.

"This new formula is important for patients who want to know what, on average, to expect from their disease and for doctors who want to give accurate advice," said Stephen L. Archer, MD, Harold Hines Jr. Professor and Chief of Cardiology at the University of Chicago Medical Center and co-author of the study. "We hope others will test our work. If it is validated by others it could be a very useful tool."

Patients survive longer

The researchers were not able to determine why PAH patients survive longer today than in the 1980s, even though they measured the survival impact of many factors, including pulmonary function, demographics, medications, exercise treadmill, laboratory markers, echocardiography, and hemodynamics as well as the cause of the disease, which includes heart and lung disease, genetics, blood clots, connective tissue disease and other conditions.

None of these factors or causes had a significant impact on survival in multivariate analysis (when tested together statistically)—except hemodynamics. This explains why the new equation only incorporates

hemodynamic parameters.

"Based on this result, physicians should stop drifting away from cardiac catherization, which is the gold standard test to determine exact hemodynamics," Gomberg said. "Providers have been using more echocardiography and less cardiac catherization but we need to reverse that trend because until you know the hemodynamics you can't accurately predict survival and or cure the disease.

"You can estimate hemodynamics with echocardiography but not accurately enough," she added.

Many clinical trials in PAH used the NIH equation to suggest improvement in survival by comparing observed survival rates on a study drug versus survival rates predicted by the NIH equation, the study says. Since the NIH equation understates contemporary survival, it has led to more favorable comparisons of clinical trials testing new drugs to treat PAH, according to Gomberg.

"Our research suggests a reason that the drugs currently approved to treat PAH do not always work as well as we hope—because they were not held to a higher contemporary standard during their development and post-approval," Gomberg said. "The new equation should ameliorate this bias.

"Although some of these drugs dramatically improve the condition of some patients, none of them improves hemodynamics to normal levels," she added. "Therefore, we, as a medical community, have to acknowledge the fact that we have not yet cured PAH."

"This research would not have been possible without the collaboration of the entire PAH team at the University of Chicago and the tireless efforts of two young physician scientists, Thenappan Thenappan, MD,

Cardiology fellow at The University of Chicago, and Sanjiv Shah, MD, a former Cardiology fellow at The University of Chicago and current faculty member at Northwestern," Archer said.

Both are co-authors of the study, along with Gomberg, Archer, Stuart Rich, MD (Cardiology at The University of Chicago), and Lu Tian, ScD, (Preventive Medicine at Northwestern University).

The research team hopes that this report will motivate development of novel agents and epidemiologic research.

More information: Called "Contemporary Survival in Patients with Pulmonary Arterial Hypertension: A Reappraisal of the National Institutes of Health Risk Stratification Equation," the study was published on line December 23, 2009, by the European Respiratory Journal.

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