Predicting Survival in Pulmonary Arterial Hypertension: Time to Combine Markers

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Time to Combine Markers

In recent years, we have witnessed the use of a growing number of surrogate markers in pulmonary arterial hypertension (PAH) to evaluate novel therapeutic options. From the first, large, multicenter study cohort derived from the 1980s National Institutes of Health Registry to the contemporary data of the French Registry and the US REVEAL (Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management), several prognostic markers have been described that are now commonly used to test response to PAH therapy. These markers include functional assessment, exercise capacity, biomarkers quantification, echocardiographic measurements, MRI, and hemodynamic parameters measured by right-sided heart catheterization. Because these measurements reflect different aspects of PAH pathophysiology, their integration in composite scores seems reasonable and even necessary.

In this issue of CHEST (see page 1285), Kane and coworkers present the results of a retrospective study that aims to demonstrate the incremental prognostic value of combining clinical, World Health Organization functional class, laboratory, and hemodynamic variables for PAH evaluation in a large, single-center study of patients with PAH. Recently published studies have applied similar rationale in prospective cohort studies with different prognostic markers, resulting in prediction scores or equations that combine those markers.

In the current study, the authors demonstrate the value added by each different marker, concluding that the integrative analysis of these variables improves prediction of survival. The authors also state that the inclusion of invasive hemodynamic measurements did not significantly improve the prognostic value of the model. This statement, however, should be interpreted with caution. Hemodynamic variables may have a high degree of collinearity with many of the variables incorporated in the different models. Therefore, the conclusion about the prognostic value of invasive hemodynamic measurements may be far-reaching. Nevertheless, the CI for the concordance index was not presented in the study, limiting further conclusions on the comparison between the models built with different variables (eg, different number of patients and events) most likely related to the given availability of said variables to be analyzed. It would also be useful to determine which specific variable from each class (clinical, functional, laboratory, hemodynamic) of marker was included in the multivariate model to calculate the specific valuation.

Even taking these limitations into account, the study is of absolute importance because it reinforces the concept that a patient with PAH should be evaluated as a whole and not according to a single parameter. The 2009 European guidelines for the diagnosis and treatment of pulmonary hypertension presented a panel of markers that could be used for the assessment of prognosis in PAH. To reinforce the integrative analysis of markers, a green zone and a red zone were established with the cutoff values separately determined for each marker present in the panel; thus, a patient would fall in the green zone if each analyzed variable reflected a positive prognosis. If this kind of approach seemed reasonable, Kane and coworkers have proven it valuable.

Another objective of the study was to validate the REVEAL score in a different retrospective study cohort. With regard to this matter, the current study interestingly demonstrates that the REVEAL score may distinguish a high-risk population regardless of functional class, which has been used as the indicator for the therapeutic approach to be followed in PAH. Based on their results, the authors suggest that the REVEAL score might be used as an indicator for more aggressive first-line therapy. Once again, the concept of integrative evaluation of a single patient is highlighted but now for determining the treatment strategy.

The current study stresses the concept of integrative analysis of prognostic markers in PAH based on the baseline evaluation of patients. Future studies...
should examine how the temporal behavior of the different markers over time, as a consequence of different therapeutic interventions, for instance, may influence or confirm a prognosis. It is likely that changes in these markers will prove useful for patient management and treatment decisions, such as choosing the appropriate time for combination therapy or referring a patient for transplantation. The French PAH network currently is conducting a prospective study that aims to evaluate the prognostic value of the changes in different prognostic markers, including invasive hemodynamic measurements, in the follow-up of patients with PAH.

Finally, it is important to highlight that Kane and colleagues’ confirm that survival in PAH is still poor in the modern management era, despite valuable therapeutic advances. One-, 3-, and 5-year survival rates of 81%, 61%, and 48%, respectively, are similar to recently published rates, illustrating that we are far from a cure for PAH and that there is still a lot to be done in the field.

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