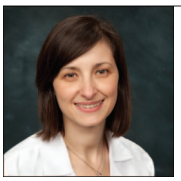
Review of the Latest Published Research



Section Editor
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Summaries and commentaries from the section editors and invited reviewers present a clinical context for practitioners' application of the latest published research relevant to the care of patients with pulmonary hypertension. In this issue, Ioana Preston discusses insights on patient outcomes in Spain in the current treatment era.

Escribano-Subias P, Blanco I, López-Meseguer M, et al; on behalf of the REHAP investigators. Survival in pulmonary hypertension in Spain insights from the Spanish registry. Eur Respir J. 2012 Feb 23. [Epub ahead of print]

This study reports on the incidence, prevalence, and survival in pulmonary arterial hypertension (PAH) and in chronic thromboembolic pulmonary hypertension (CTEPH) among patients diagnosed in Spain between 1998 and 2008 who were included in the Spanish Registry on Pulmonary Arterial Hypertension (REHAP) registry. Diagnostic criteria included a catheterization-based diagnosis, except in the case of patients with Eisenmenger syndrome, with a pulmonary artery pressure (PAP) mean above 25 mm Hg, wedge <15 mm Hg and pulmonary vascular resistance (PVR) >3 Wood units. Exclusion criteria were significant left heart disease or lung disease, and age less than 14 at diagnosis. Thirty-one hospitals participated in the registry, covering 15 of the 17 administrative regions in Spain. Analyses included calculation of incidence, prevalence, and survival; determinants of predictors of survival; and a comparison of actual survival vs predicted survival based on the National Institutes of Health (NIH) equation, the pulmonary hypertension connection (PHC) equation, the French registry, and the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) calculator.

One thousand twenty-eight patients were diagnosed with PAH or CTEPH during the 10-year study period, including 866 PAH patients and 162 CTEPH patients. The PAH patients were younger, had a greater female to male ratio, and had more severe hemodynamic abnormalities compared with the CTEPH patients. PAH etiologies included were idiopathic PAH (30%), congenital heart disease PAH (16%), connective tissue disease PAH (15%), portal hypertension (6%), HIV (5%), toxic oil syndrome (3.2%), and pulmonary veno-occlusive disease (PVOD) (1.5%). The overall estimated prevalence of PAH from 2007-2008 was 16 cases per million population, with an incidence of 3.7 cases per million population. CTEPH was less common, with an estimated incidence and prevalence of 0.9 and 3.2 cases per million population, respectively.

Survival in the overall cohort (PAH and CTEPH) was 87%, 75%, and 65% at 1, 3, and 5 years. Survival rates were surprisingly similar in the idiopathic PAH group (89%, 77%, and 68%) and in the CTEPH group (93%, 75%, and 65%). Only 30% of CTEPH patients underwent pulmonary thromboendarterectomy (PTE), and survival among those patients alive 3 months after PTE surgery was much better—90% at 5 years. Predictors of worse outcome in the multivariate analysis included male gender, later functional class, higher right atrial pressure, and lower cardiac index (CI). Additionally, connective tissue disease and portopulmonary hypertension subtypes had worse outcomes compared with idiopathic PAH patients ($P<0.05$), while congenital heart disease (OR 0.86, 95% CI 0.51-1.46) and HIV PAH (OR 1.05, 95% CI 0.57-1.94) had similar survival compared with idiopathic PAH.

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Survival vs Predicted Survival: Idiopathic PAH (NIH, PHC, and French Equations)

Survival among the idiopathic PAH patients was better at all time points than the survival rate predicted by the NIH registry, and was similar to survival predicted by the PHC equation. Compared with the French equation, and looking only at patients diagnosed since 2004, 1-year survival was significantly better than predicted (94% vs 89%, $P=0.02$), while there was no significant difference at 2 years (78% vs 73%, $P=0.17$).

Survival vs Predicted Survival: PAH (REVEAL Equation)

Looking at the PAH group combined, overall survival was significantly worse than survival predicted by the REVEAL equation. The authors suggested that this may have related to 2 factors: (1) the inclusion of patients from earlier years in REHAP (1998-2008), as REVEAL extends back only to 2003; and (2) the inclusion of incident cases vs the large percentage of prevalent cases in REVEAL (85%), potentially providing overly optimistic survival figures.

Over the last 2 decades a number of registry and cohort studies have been published in idiopathic PAH, CTEPH, and more recently, in pulmonary hypertension in general. These types of studies help inform clinical decision making by providing information on incidence and prevalence and on predictors of survival. This study adds considerably to that literature, based on its large and diverse patient population as well as its comprehensiveness,

as a large percentage of all PAH and CTEPH patients diagnosed in Spain during those years were likely included.

The overall survival rate of 65% at 5 years suggests improved survival since the early 1990s, based on comparisons using the NIH equation, similar to other cohort studies conducted since the availability of advanced PAH therapies. The authors also suggest that survival may have improved since the early 2000s, based on their 1-year survival rate for patients diagnosed from 2004-2008, compared with predicted survival based on the French equation (derived from patients diagnosed from 1999-2003). They go on to suggest that this could relate to either earlier diagnosis and/or better treatment options. However, while the comparison seems valid, a number of other factors could also contribute to the variability in 1-year survival, including unmeasured patient characteristics and other confounders or just chance. Further, it is not clear that this was the best way to approach the question: an alternative would have been to compare patient survival rates in their own cohort by year of diagnosis.

Despite this small concern, the overall study appears to have been well designed and conducted, and has a large number of strengths. The comparisons across the different survival equations in idiopathic PAH and in PAH are particularly interesting, as so far this has been rarely done, likely because 3 of the 4 equations (the PHC, French, and REVEAL) were only published in the last several years. Other strengths of the study include their attention to other forms of PH, including PVOD, PH related to toxic oil exposure, and CTEPH. Interestingly, the incidence and prevalence numbers suggest that CTEPH continues to be quite rare, despite findings from other studies suggesting that CTEPH may develop in as much as 1%-5% of pulmonary embolism survivors.[1-3] Whether this relates to misdiagnosis, lack of referral to pulmonary hypertension centers, or other factors is unclear, but this is unfortunate because patients with surgically accessible disease are among those most likely to benefit from specialty referral; this area may therefore may be one where physician education may be beneficial.

In conclusion, this study provides information on patient outcomes in Spain in the current treatment era. This type of multicenter registry is particularly important in pulmonary hypertension because the prognostic information derived may help with clinical decision making and can be hypothesis generating for the design of future clinical trials. Additionally, regional variations in incidence rates and associations can also help to identify novel risk factors, as with the toxic oil exposure epidemic in Spain.[4]

References

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