Integration of Clinical and Hemodynamic Parameters in the Prediction of Long-term Survival in Patients With Pulmonary Arterial Hypertension

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Pulmonary arterial hypertension (PAH) is a devastating illness characterized by pulmonary vascular remodeling and right-sided heart failure. Despite changes in diagnosis and management since the National Institutes of Health (NIH) registry of the 1980s, disease outcomes, although improved, remain poor. It has long been recognized that mortality in patients with PAH is associated with both the severity of symptoms and the extent of right-sided heart failure. Over time, many factors have been demonstrated to correlate individually with prognosis, including male sex, age, World Health Organization (WHO) functional class, connective tissue disease, and echocardiographic and catheter-derived measures of right ventricular (RV) dysfunction. Therefore, it is
appropriate that multiple factors that pertain to a poor prognosis should be considered while choosing pharmacologic therapy. However, in part because of limited evidence about the incremental prognostic value of clinical and hemodynamic factors in patients with PAH, treatment guidelines for PAH remain predominantly based on functional class.\textsuperscript{21,22} The purpose of the present study was to evaluate survival patterns in patients with PAH and to establish clinical and hemodynamic factors that, when considered together, provide incremental prognostic value in the prediction of survival.

**Materials and Methods**

**Study Population and PAH Definition**

All patients agreed to the use of their data for research purposes, and the study was approved by the Mayo Clinic institutional review board (Committee Expedited Review B-IRB No. 06-005447). The study included all adult patients (\(\geq 18\) years) who fulfilled the contemporary diagnostic criteria for WHO group 1 pulmonary hypertension (PH) (mean pulmonary arterial pressure \(\geq 25\) mm Hg occurring in the setting of increases in precapillary pulmonary resistance) and were first seen (January 1, 1995, to December 31, 2004) at the Mayo Clinic Rochester, a tertiary care referral academic practice with a designated physician-staffed and nurse-staffed specialty PH clinic.\textsuperscript{23,24} For the purposes of this study, to best reflect clinical practice, the time of diagnosis was defined as the date that the diagnosis of PAH was made by the PH treating physician based on clinical assessment, pulmonary function, and radiographic noninvasive, and invasive cardiac testing. The final testing generally, but not always, corresponded to the date of the right-sided heart catheterization (RHC). For example, in some cases, pulmonary function testing (PFT) or ventilation perfusion scanning followed RHC. Five patients diagnosed elsewhere were receiving "PH-specific therapy" at initial evaluation at Mayo Clinic. Two patients were receiving IV epoprostenol (for 1 month and 11 months, respectively), and three were receiving bosentan (for 1, 4, and 11 months, respectively). These five patients were excluded. Of the remaining 484 patients, 115 were taking calcium channel blockers. Complete details on the doses of calcium channel blockers were not available.

**Measurements**

Transthoracic echocardiography was performed according to standard American Society of Echocardiography guidelines.\textsuperscript{5,26}

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RV systolic pressure was determined as four times the square of the peak trans-tricuspid valve systolic regurgitant velocity,\textsuperscript{2} plus the estimate of right atrial pressure (RAP) (based on two-dimensional and Doppler characteristics of interrogation of the inferior vena cava and hepatic veins). The degrees of right atrial and RV enlargement, RV systolic dysfunction, and tricuspid valve regurgitation, and the presence of a pericardial effusion were scored on an ordinal qualitative scale based on visual assessment by an experienced echocardiologist as part of clinical practice (normal or mild, moderate, or severe enlargement or dysfunction). Echocardiograms were not rereviewed as part of this study. Because the RV index of myocardial performance (Tei index) is an integrative measure of both RV systolic and diastolic function, it is reported as a separate parameter, as described previously.\textsuperscript{14,17} The estimated glomerular filtration rate was calculated using the Modification of Diet in Renal Disease.\textsuperscript{25} Basic clinical characteristics, including WHO functional class, echocardiography, and RHC, were available for or performed in all patients. The availability of these measures was as follows: serum hemoglobin levels (\(n = 477\)), glomerular filtration rate (\(n = 474\)), brain natriuretic peptide (BNP) levels (\(n = 80\)), 6-min walk (\(n = 335\)), and PFT (\(n = 394\)). At the end of follow-up (5 years after baseline), medical records provided vital status for 90% of deceased subjects with the status of the remaining 10% of deceased subjects, obtained from the National Death Index.

**REVEAL Score Analysis**

The REVEAL (Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management) risk score is a previously reported ordinal scale calculated as a baseline number of to which qualifiers are added or subtracted based on available data, as follows\textsuperscript{80}:

1. WHO group: +1 point if PAH in setting of connective tissue disease or +2 points if portal hypertension;
2. Demographics: +2 points if subject is male and >60 years of age and/or has renal dysfunction; +1 point if significant renal dysfunction is present (if estimated glomerular filtration rate \(\leq 30\) mL/min/m\(^2\));
3. WHO functional class: −2 points if class I, +1 if class III, and +2 if class IV;
4. Vital signs: +1 if systolic BP \(\leq 109\) mm Hg and +1 if heart rate \(>92\) beats/min;
5. 6-min walk: +1 if distance \(<165\) m and −1 if distance \(\geq 440\) m;
6. BNP levels: +1 if BNP \(\geq 180\) pg/mL and −2 if BNP <50 pg/mL;
7. Pericardial effusion: +1 if present;
8. Diffusion capacity of lung for carbon monoxide (DLco): +1 if DLco <33% and −1 if DLco \(\geq 80\%\);
9. RHC: +1 if RAP \(>20\) mm Hg and +2 if pulmonary vascular resistance >32 Wood units.

**Statistical Analyses**

Statistical analyses were performed using SAS, version 8.2, and JMP, version 7.0 (SAS Institute Inc; Cary, North Carolina). Continuous variables were presented as mean ± SD or median with interquartile range and tested between groups using analysis of variance. Categorical variables were presented as number and percentage, and comparisons were done using Pearson chi analysis. Survival was estimated using Kaplan-Meier methods and compared among groups using the log-rank test. Cox proportional hazards regression models were used to examine predictors of mortality. For all analyses, \(P < 0.05\) was considered statistically significant. We also examined the predictive value of disease characteristics
using the concordance index (c-index). The c-index is a mathematical measure that is equivalent to the area under a receiver operating characteristic curve and helps determine the validity of the model in assessing survival. The c-index may range from 0 to 1, with 1 corresponding to perfect discrimination and 0.5 to what is expected by chance alone. In predicting mortality, we first included WHO functional class. We then included the following characteristics in a sequential fashion: demographic and clinical characteristics, laboratory findings, PFT results, echocardiographic findings, and lastly, RHC measurements. We also examined the c-index using the REVEAL score. For patients for whom data were incomplete, additional categorical variables (test done, test not done) were included. However, because of insufficient BNP or vasodilator testing data (<20%), we did not include these variables in prediction models.

Results

Clinical Characteristics

Clinical, laboratory, and hemodynamic characteristics at the time of diagnosis of the 484 individual subjects with WHO group 1 PH are shown in Table 1. A total of 272 subjects (56%) had idiopathic, familial, or anorexigenic PAH, 114 (24%) had PAH in the setting of connective tissue disease, and the remainder were associated with congenital systemic to pulmonary shunts (n = 45), portal hypertension (n = 51), and HIV (n = 2).

The majority of patients (75%) were women. The mean age was 52 ± 15 years and was similar for men and women. A total of 113 subjects (23%) were ≥65 years of age. The mean disease duration from the onset of symptoms to Mayo Clinic evaluation was 1.8 (SD ± 2) years. More than one-half of the subjects (268, 55%) were WHO functional class III, and 77 (16%) were class IV. Subjects with connective tissue diseases were older, more frequently women, and had worse disease severity markers, including worse functional class, shorter 6-min walk distances, lower hemoglobin, higher BNP levels, and worse hemodynamic parameters than did subjects with idiopathic PAH.

Patterns and Predictors of Survival

Over a median follow-up of 3.2 years (interquartile range, 1.3-5.0 years), a total of 21 subjects (4%) received lung(s) (n = 10) or lung(s)/heart (n = 11) transplant, and their follow-up was censored at the time of transplant. An additional 243 subjects (50%) died. Overall median survival was 4.56 years (95% CI, 3.8-5.1), corresponding to 1-year, 3-year, and 5-year survival rates of 81.1% (95% CI, 77.0-84.7), 61.1% (95% CI, 56.5-65.3), and 47.9% (95% CI,

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Data are presented as mean ± SD, %, or No. (%). BNP = brain natriuretic peptide; cPAH = pulmonary arterial hypertension in the setting of connective tissue disease; DLCO = diffusion capacity of lung for carbon monoxide; GFR = glomerular filtration rate; IPAH = idiopathic/familial/anorexigenic pulmonary arterial hypertension; PA = pulmonary arterial; PAH = pulmonary arterial hypertension; PFT = pulmonary function test; RA = right atrial; RHC = right-sided heart catheterization; RV = right ventricle; RVSP = right ventricular systolic pressure; TDCI = thermodilution cardiac index; TV = tricuspid valve; WHO = World Health Organization.
between 1 mg/dL and 1.4 mg/dL. Enlargement of the right atrium (Fig 1D), RV, and measures of RV dysfunction including RV index of myocardial performance were all significantly associated with a poor outcome (Table 2). Hemodynamic findings at RHC were similarly associated with mortality. Although the mean pulmonary arterial pressure was not significantly associated with mortality, cardiac index and RAP correlated strongly with mortality (Table 2). When adjusted for age, sex, cause of PAH, and WHO functional class (Table 2), estimates of RAP, and the presence of severe right atrial enlargement, RV enlargement or dysfunction or severe tricuspid valve regurgitation all remained as significant predictors of mortality.

**Incremental Prediction of Survival**

Analyses by incremental modeling using the c-index demonstrated that the prediction of mortality in patients with PAH was incrementally improved by incorporating clinical and noninvasive data over that of functional class alone (Fig 2), with the greatest
that also included the per-unit increase in % DLCO, the c-index increased to 0.77. With the addition of echocardiographic measures, the c-index reached 0.82. The increase in c-index was modest (0.84) with the inclusion of RHC measures in the model that already included echocardiographic measures. The c-index with the REVEAL score was 0.71.

Similar modeling was also performed in the sub-group of patients who had idiopathic, familial, or anorexigenic PAH. Here, similarly, the prediction of mortality over 5 years was improved incrementally by incremental benefits observed with the addition of clinical demographics (age, sex, cause of PAH, 6-min walk distance) and echocardiographic measures of RV size, function, tricuspid valve regurgitation severity, estimated RAP, and the presence or absence of pericardial effusion. The first model, which included WHO functional class, had a c-index of only 0.60. Inclusion of age, sex, PAH cause, and 6-min walk distance resulted in a c-index of 0.75. Inclusion of laboratory values (hemoglobin and serum creatinine) improved the c-index to 0.76. In a subsequent model that also included the per-unit increase in % DLCO, the c-index increased to 0.77. With the addition of echocardiographic measures, the c-index reached 0.82. The increase in c-index was modest (0.84) with the inclusion of RHC measures in the model that already included echocardiographic measures. The c-index with the REVEAL score was 0.71.

Similar modeling was also performed in the sub-group of patients who had idiopathic, familial, or anorexigenic PAH. Here, similarly, the prediction of mortality over 5 years was improved incrementally by
incorporating clinical and noninvasive data (c-index 0.85) over that of functional class alone (c-index 0.62). In this group, the c-index with the REVEAL score was 0.70 and with the updated NIH risk equation was 0.66.

Validation of the REVEAL PAH Risk Score

The recently developed PAH risk score described by the REVEAL investigators was also tested in this cohort. Our cohort was largely similar to the REVEAL registry cohort; only 16% of the PAH subjects in this cohort were included in the REVEAL registry. Notable differences were as follows: When compared with the published results of the REVEAL registry, our cohort (excluding those Mayo Clinic subjects in REVEAL) tended to have more severe disease, with a higher proportion having WHO functional class IV (18% vs 6%), shorter mean 6-min walk distances (322 m vs 370 m), and higher mean RAP (13 mm Hg vs 9 mm Hg). This difference in disease severity was reflected in different 1-year survival of 77.3% (95% CI, 72.6-80.9) in our cohort and 91.0% (95% CI, 89.9-92.1) in the REVEAL registry. When applied to this subgroup of our cohort, the mean REVEAL risk score was 6.8 and ranged from 2 to 14. The risk score was proportional to both 1-year (Fig 3A) and long-term mortality (Fig 3B).

Based on WHO functional class, those subjects who were class IV had the worst prognosis (Fig 1B). Using the REVEAL risk score, we determined a cohort of subjects with equivalent risk. Subjects with WHO functional class II-III and a REVEAL risk score $\geq 8$ (n = 100) had a comparable mortality to those subjects who were class IV (n = 76); $P = .43$ (Fig 4A). Although subjects with WHO functional class IV had the worst prognosis, when stratified by REVEAL risk score ($< 8$ or $\geq 8$), survival was better or worse, respectively, than patients with functional class III (Fig 4B).
However, the data reported here demonstrate that incorporation of clinical and test-based information significantly improves the prediction of survival over WHO functional class alone, and thus provide support for management decisions as they pertain to prognosis in PAH not being solely based on functional class.

Our study has some potential limitations. Because the study’s primary aim was to assess the incremental prognostic value of clinical and hemodynamic factors on the prediction of long-term (5-year) survival, patients diagnosed between 2005 and 2009 were not included. BNP levels were available in only a minority of patients (<20%) and so could not be factored into our modeling. It is likely that the addition of BNP data would provide further incremental prognostic information. Data on 6-min walk and PFT were also incomplete. The available echocardiography data did not include measures of cardiac output or formal quantitated measures of RV size and function, apart from those of the RV (Tei) index of myocardial performance. Measures particularly of longitudinal RV systolic function, including those with tissue Doppler and strain-based analysis, likely provide improved accuracy over qualitative assessment. Moreover, whether alternative imaging modalities of RV size and function may provide incremental prognostic value in patients with PAH remains to be better elucidated.

Our study included all sequential patients seen at a high-volume tertiary referral center, akin to those enrolled in the REVEAL registry. However, our cohort included more patients with severe disease. By design, REVEAL is prone to selection bias, including subjects not newly diagnosed. This likely explains the observed illness severity and mortality differences between the cohorts. Furthermore, our cohort preceded that of the REVEAL registry and while in the era of IV prostanoid therapy, also spanned the introduction of oral endothelin antagonists and phosphodiesterase type 5 inhibitors. Therefore, it is plausible that the absence of the availability of oral therapy to all subjects over all study years may have negatively impacted the outcome. Mortality rates in our study were similar to those recently reported in various other single-center and multicenter registries that spanned the era of the introduction of oral PH-specific treatment. However, it is important to recognize that the REVEAL risk score did not include treatment status. The calculation of risk is intended to be based on the “intrinsic” clinical characteristics of the patient. If a medication influences those clinical characteristics, the risk score may be modified accordingly. Data were not available to integrate incremental medication use over time. Despite these differences, this study validates the REVEAL

**DISCUSSION**

The present study expands the available information of survival patterns in a large cohort of patients with PAH and provides new information on which clinical variables provide incremental prediction of survival. The emphasis of this article is on examining the usefulness of integrating the intrinsic characteristics (demographics and measurable clinical parameters) into the estimation of future risk of death in PAH. Our findings indicate that clinical parameters have the highest impact on survival and beyond functional class. Thereafter, the largest additional impact is from echocardiographic findings, with other laboratory and PFT parameters contributing further incremental benefit. Although an important component of the diagnostic evaluation, RHC contributed little to the overall prediction of survival after all other clinical and noninvasive components were included. Current PAH treatment guidelines recommend treatment strategies primarily based on WHO functional class. However, the data reported here demonstrate that incorporation of clinical and test-based information significantly improves the prediction of survival over WHO functional class alone, and thus provide support for management decisions as they pertain to prognosis in PAH not being solely based on functional class.
risk score for 1-year survival in a large PAH group and further demonstrates the usefulness of the risk score in the prediction of mortality over the longer term. Similarly, the updated NIH equation\(^2\) also predicted survival over the longer term, although less accurately than the REVEAL score. Although BNP data were limited, detailed information on laboratory and echocardiographic parameters allowed us to create robust prediction models. Indeed, the relatively simple REVEAL prediction score explained significantly more than that of functional class alone, although less than the more complicated models that incorporated all available data (Fig 2). However, it must be recognized that our study was based on data from only one center and was retrospective, and all parameters were not available in every patient; hence, an independent prospective multicenter validation is encouraged.

### Conclusions

Our findings suggest that routine PAH clinical parameters can significantly enhance prediction of survival over functional class alone. Patients with PAH who are functional class II-III but have a REVEAL risk score > 8 have a risk equivalent to those patients presenting in functional class IV. We propose that these patients be considered for aggressive treatment protocols such as first-line parenteral prostacyclin analog therapy and suggest that this approach be tested in future studies.

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**Author contributions:** Dr Kane had access to the data and takes responsibility for the integrity of the data and the accuracy of the data analysis.  

**Dr Kane:** contributed to study concept and design, analysis and interpretation of the data, and drafting of the manuscript.  

**Dr Maradit-Kremers:** contributed to study concept and design, analysis and interpretation of the data, statistical expertise, and critical revision of the manuscript.  

**Mr Slusser:** contributed to study concept and design, analysis and interpretation of the data, statistical expertise, and critical revision of the manuscript.  

**Mr Scott:** contributed to study concept and design, analysis and interpretation of the data, statistical expertise, and critical revision of the manuscript.  

**Dr Frantz:** contributed to analysis and interpretation of the data and critical revision of the manuscript.  

**Dr McGoon:** contributed to study concept and design, analysis and interpretation of the data, statistical expertise, and critical revision of the manuscript.  

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### References


26. Lang RM, Bierig M, Devereux RB, et al; Chamber Quantification Writing Group; American Society of Echocardiography’s Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr*. 2005;16(12):1440-1463.


