Prediction of Health-Related Quality of Life and Hospitalization in Pulmonary Arterial Hypertension: The Pulmonary Hypertension Association Registry (PHAR)

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To the Editor:

Pulmonary arterial hypertension (PAH) negatively impacts health-related quality of life (HRQoL) and is associated with increased hospitalizations. Therapy is tailored according to the risk of adverse outcome, and several prediction rules for mortality have been proposed. We evaluated whether risk prediction models for mortality were associated with patient-related outcomes. Using the Pulmonary Hypertension Association Registry (PHAR), we hypothesized that higher risk assessment would be associated with worse HRQoL and increased risk for hospitalization.

The PHAR is a prospective registry of individuals with PAH or chronic thromboembolic pulmonary hypertension, enrolled at participating centers throughout the United States. We included individuals age ≥ 18 years with PAH enrolled between 2015 and September 2019, with follow-up to March 2020. Two HRQoL questionnaires are administered at each visit: the Medical Outcome Study Short Form-12 (SF-12) with general physical and mental component scores(1); and the emPHasis-10 (e10), a pulmonary hypertension-specific instrument(2). Using baseline data, we assigned patients into low, intermediate, and high risk categories using COMPERA(3, 4) and REVEAL 2.0(5, 6) prediction rules. The outcomes were HRQoL by SF-12 and emPHasis-10 and the risk of hospitalization. Since hospitalization was an outcome of interest, it was not used in calculating the REVEAL 2.0 score.

We fitted mixed-effects generalized linear regression models with p values for linear trend by risk category. These models were adjusted for potential confounders of PAH risk: age, sex, race/ethnicity, and PAH medications (parenteral therapy and total number of vasodilator medications). We performed a sensitivity analysis imputing the worst-possible HRQoL score for participants who died or were lost to follow-up. Negative binomial regression was used to estimate incidence rate ratio (IRR) for all-cause hospitalization by risk category with an offset term for follow-up time. We then performed sensitivity analysis where death, lung

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transplantation, or loss to follow-up were counted as hospitalizations to account for potential unrecorded events. To estimate the relative risk of hospitalization with death as a competing risk, we calculated subdistribution hazards ratios (sHR) and cumulative incidence functions using Fine-Gray competing-risks regression. These models were then adjusted for the same potential confounders. Statistical analyses were performed using Stata Version 15.1 (College Station, TX).

Of 1,021 participants enrolled in PHAR, 869 were included (**Table**). Using COMPERA 16% were low-, 70% intermediate- and 14% were high-risk. 796 participants had at least seven variables necessary for REVEAL 2.0, which classified 43% as low-, 24% intermediate-, and 32% high-risk patients(6). Higher baseline risk by either method was associated with higher (worse) e10 score at baseline and over time (**Figure 1A**) by COMPERA and REVEAL 2.0 (β=5.81, 95%CI 3.72-7.90 vs β=3.78, 95%CI 1.85-5.71 for intermediate-risk and β=12.12, 95%CI 9.36-14.89 vs β=8.10, 95%CI 6.28-9.91 for high-risk, respectively). Higher predicted risk was also associated with statistically lower (worse) SF-12 physical scores ($p<0.05$) but unclear clinical significance due to small magnitude of difference. Differences in SF-12 mental scores were only noted for COMPERA ($p=0.04$). These associations persisted after multivariate adjustment, and in sensitivity analyses using complete data and when imputing the worst-possible HRQoL score for those who died or were lost to follow-up.

There was 1,255 person-years of follow-up; 281 (34%) participants with follow up reported a hospitalization, 12 (1%) underwent lung transplantation, 102 (12%) died, and 119 (14%) transferred care or were lost to follow-up. Intermediate and high predicted risk by both COMPERA and REVEAL 2.0 was associated with an increased rate of hospitalization (COMPERA - IRR 1.88, 95%CI 1.27-2.77 and IRR 2.34, 95%CI 1.42-3.82; and REVEAL 2.0 - IRR 1.45, 95%CI 1.03-2.03 and IRR 1.88, 95%CI 1.38-2.59). This persisted after multivariable adjustment and in sensitivity analysis where death, lung transplantation and transfer/loss to

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follow-up were counted as hospitalizations. Higher risk was associated with an increased subdistribution hazard ratio for hospitalization for COMPERA and REVEAL 2.0 (intermediate: sHR 2.34, 95%CI 1.53-3.60 vs. sHR 1.35, 95%CI 0.99-1.85 and high: sHR 2.23, 95%CI 1.34-3.72 vs. sHR 1.58, 95%CI 1.20-2.09, respectively). Cumulative incidence functions for hospitalization are shown in the **Figure 1B**.

In a large multicenter national cohort of PAH patients, higher predicted risk of mortality by two methods was associated with worse HRQoL and increased hospitalizations. We observed a larger relative difference in the e10 scores compared to SF-12, suggesting the disease-specific tool may be more sensitive, with an approximate 10-point difference between low- and high-risk groups, similar to the published difference between those with WHO functional class II and III symptoms(2). In contrast, differences in SF-12 scores were smaller and of unclear clinical significance(7).

Our findings support prior reports of the importance of hospitalizations as a prognostic indicator, similar to findings reported in REVEAL(5). Hospitalizations represent a period of potential high morbidity and mortality and are often driven by PAH-related complications(8, 9). While the cause of hospitalization was not available and to account for potential undercounting of hospitalizations, we conducted sensitivity analysis imputing death, transplant or loss to follow-up as hospitalization events which confirmed our findings. Our study was not powered to detect differences between the intermediate and high risk groups, but the subdistribution hazard ratios for these groups were similar, suggesting a lack of discrimination in the higher risk strata - an area for potential improvement.

The multicentered PHAR cohort included a diverse population from centers throughout the country, making generalizability a particular strength. We calculated risk scores with available data in a “real-world” setting and conducted sensitivity analyses assuming the “worst-case” outcome. We only calculated predicted risk from data at baseline; the strength of the

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relationships support the importance of the baseline “risk profile” irrespective of subsequent treatment. Unmeasured or residual confounding could explain the results, however these prediction rules are designed to be used in a “stand-alone” fashion, so even if present, the clinical importance of the findings remains.

In conclusion, we found that higher predicted risk for death by COMPERA and REVEAL 2.0 was associated with worse disease-specific HRQoL, a higher rate of hospitalizations, and increased risk for nonfatal hospitalizations. Improved risk stratification will allow for targeted strategies to improve HRQoL and reduce hospitalizations in these vulnerable PAH patients.

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TABLES AND FIGURES:

Table:

Baseline characteristics (n=869)	Value
Age (years)	55.4 +/- 16.0
Sex	
Male	217 (25.0%)
Female	642 (73.9%)
Other/Unknown	10 (1.1%)
Race/ethnicity	
White non-Hispanic	582 (67.0%)
Black non-Hispanic	107 (12.3%)
Hispanic	97 (11.2%)
Asian	40 (4.6%)
Other	43 (4.9%)
Body Mass Index (kg/m^2) (n=845)	29.4 +/- 7.2
WHO Group I diagnosis	
Idiopathic PAH	344 (39.6%)
Heritable PAH	23 (2.6%)
Drug/toxin induced PAH	103 (11.9%)
Connective tissue disease (CTD) PAH	283 (32.6%)
HIV-related PAH	15 (1.7%)
Portopulmonary hypertension	57 (6.6%)
Congenital heart disease (CHD) PAH	44 (5.1%)
Baseline WHO functional class (n=815)	
I	58 (7.1%)
II	289 (35.5%)
III	411 (50.4%)
IV	57 (7.0%)
Six-minute walk distance (m) (n=744)	340 (253, 425)
EmPHasis-10 score (n=853)	26 (16, 34)
SF-12 physical score (n=854)	34.3 (30.0, 38.5)
SF-12 mental score (n=854)	48.7 (42.2, 54.6)
Baseline right heart catheterization	
Right atrial pressure (mmHg) (n=826)	9.0 (5.0, 13.0)
Mean pulmonary artery pressure (mmHg) (n=843)	49 (40, 58)
Pulmonary artery wedge pressure (mmHg) (n=809)	11.0 (7.0, 14.0)
Cardiac output (L/min) (n=791)	4.0 (3.2, 5.1)
Cardiac index (L/min/m^2) (n=830)	2.2 (1.8, 2.7)
Pulmonary vascular resistance (Wood units) (n=803)	9.0 (6.0, 13.0)
PAH therapy use by drug class	
Phosphodiesterase-5 inhibitor	531 (61.1%)
Endothelin receptor antagonist	374 (43.0%)
Prostacyclin analogue (inhaled)	25 (2.9%)
Prostacyclin analogue (oral)	36 (4.1%)
Prostacyclin analogue (parenteral)	129 (14.8%)
Soluble guanylate cyclase stimulator	20 (2.3%)

Summary statistics are presented as mean +/- SD if normally distributed or as median (IQR) if skewed.

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Figure:

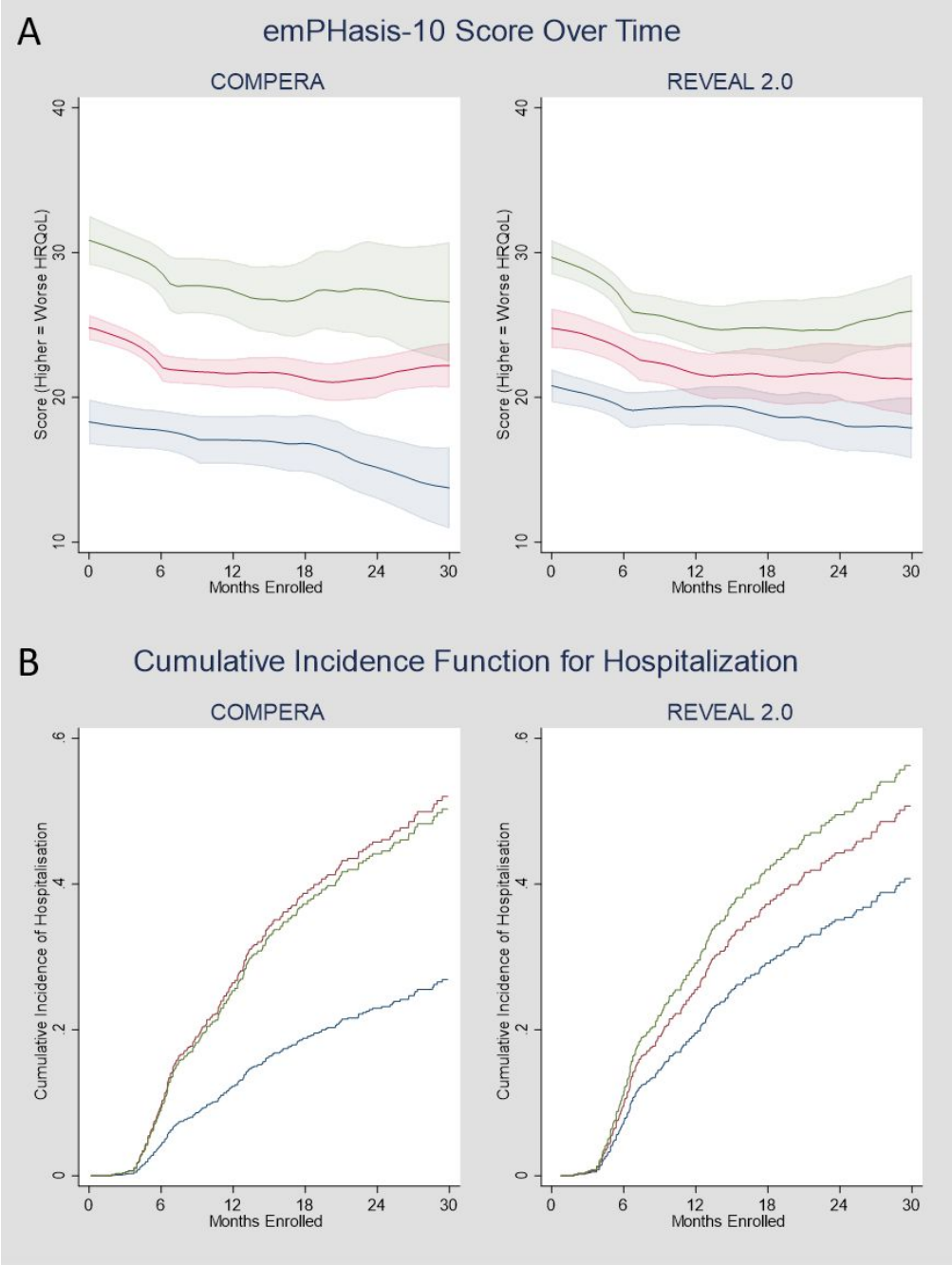

Figure legend: Disease-specific quality of life scores and cumulative incidence of hospitalization over time

A) Local polynomial smoothed plot of emPHasis-10 scores over follow-up time for COMPERA and REVEAL 2.0, with shaded areas representing 95% confidence intervals. Higher scores indicate worse health-related quality of life (HRQoL). B) Cumulative incidence functions for hospitalization over follow-up time for COMPERA and REVEAL 2.0. Groups were stratified by low- (blue), intermediate- (red) and high-risk (green) groups.

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