Journal of the American Heart Association

RESEARCH LETTER

Risk Prediction and Right Ventricular Dilation in a Single-Institution Pulmonary Arterial Hypertension Cohort

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Therapies for patients with pulmonary arterial hypertension (PAH) have dramatically expanded. This expansion is welcome but has raised important questions about when to deploy therapies. To inform treatment decisions, risk-assessment tools have been developed and guidelines advocate for formal risk stratification.[1] Risk-scores are heavily weighted in patient and clinician education on treatment escalation (eg, www.pahinitiative.com/pah-information-support).

Nevertheless, discrepancies between physician gestalt and risk scores exist.[2] Divergent impressions arising from gestalt may represent fallibility in subjective decision making, a more comprehensive clinical synthesis, or both. Results from cardiac imaging may contribute to divergent impressions. Cardiac imaging is recommended for guideline-concordant care but not strongly represented in risk-assessment tools.[3] Using a single-institution cohort, we evaluated right ventricular (RV) dilation alongside risk scores to further inform risk stratification. RV dilation was chosen as an approachable example to inform the hypothesis that routinely available clinical information may meaningfully modify impressions from formal risk assessment.

The Servetus (Seattle Right Ventricle Translational Science) study includes a prospective cohort of participants with PAH enrolled and consented at the University of Washington between 2014 and 2016 (institutional review board number 3387). All participants had RV basal diameter measured on echocardiography and completed questionnaires every 3 months for 3 years. Vital status was confirmed for participants who died or did not return questionnaires. REVEAL 2.0 risk scores from the follow-up visit most proximate to the echocardiogram were calculated using established methods (at least 7 variables were used).[3]

In parametric analyses, unadjusted Cox proportional hazards estimated associations between risk scores and hazard of death over 3 years. Proportional hazards were confirmed using the Therneau and Grambsch test of non-zero slope. In complementary analyses, log-rank testing compared survival at 3 years (fixed time point) in nonparametric analyses. Two risk-assessment approaches were used. Standard REVEAL 2.0 risk scores were used in the first set of analyses. The presence of RV dilation was used to further subdivide the large group of high-risk REVEAL participants in the second set of analyses. Analyses were performed using Stata 15.0 (StataCorp, College Station, TX). Data supporting the findings are available from the corresponding author upon reasonable request.

Ninety-two participants were included. Most were on dual-agent PAH therapy (44.6%), and many used 3 agents (20.6%). Participants with a high-risk REVEAL 2.0 score comprised the largest subset (45.7%). The table reports associations between standard REVEAL 2.0 scores and outcomes (Table). Low- and

Key Words: basal diameter ■ echocardiography ■ pulmonary hypertension

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For Sources of Funding and Disclosures, see page 2.

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Table. Survival Using 2 Different Risk Stratification Approaches for Participants With Pulmonary Arterial Hypertension

Risk strata	N	Hazard of death		Survival at 3 years	
		HR (95% CI)	*P* value	Survival	*P* value
Standard REVEAL 2.0 risk score					
Low risk	30	Referent		97%	Referent
Intermediate risk	20	1.5 (0.1–24.1)	0.77	95%	0.77
High risk	42	11.0 (1.4–84.2)	0.02	69%	0.004
Alternative approach					
Low risk	30	Referent		97%	Referent
Intermediate risk	20	1.5 (0.1–24.1)	0.77	95%	0.77
High risk (RVd <5 cm)	26	6.2 (0.7–52.8)	0.10	81%	0.06
High risk (RVd ≥5 cm)	16	21.9 (2.7–176.0)	0.004	50%	0.002

HR indicates hazard ratio; and RVd, right ventricular basal diameter in diastole.

intermediate-risk scores did not differentiate outcomes; however, high-risk scores clearly identified a group with increased risk for poor outcomes.

When the high-risk group was further stratified by RV size, 26 participants had mild or moderate RV dilation (<5 cm) and 16 had severe RV dilation (≥5 cm) defined as the upper quartile of dilation. The high-risk group without severe RV dilation was not statistically different from intermediate- or low-risk groups. The high-risk group with severe RV dilation had worse survival compared with all other groups.

These data reinforce previous work demonstrating that REVEAL risk scores, particularly high-risk scores, predict poor outcomes in prevalent patients with PAH. We add to this by showing that readily available clinical results further delineate risk.

We do not believe these findings undermine the value of formal risk-assessment in routine care. The correct approach to titrating PAH therapy is in flux, and some evidence suggests both high-risk groups (with and without RV dilation) might benefit from aggressive therapy.[4] Conversely, the value of rapid escalation to 3 pulmonary vasodilators including parenteral therapy is not clearly established; side effects are common, and the possibility for harm is present.[5] Given this uncertainty, identifying 2 high-risk subgroups (one with 50% and one with 81% survival) likely crosses thresholds where patients and clinicians might variably choose a more incremental or aggressive approach.

There are clear limitations. This was a small, single-institution cohort. Insufficient power and small cohort size may have contributed to the lack of significance when comparing the high-risk group without RV dilation and intermediate-risk group to the low-risk group. Nevertheless, despite its size, the cohort was well-phenotyped, had several years of follow-up, and demonstrated significant differences in survival and thus adequate power between high-risk participants with and without RV dilation. This underscores the large survival difference between these 2 high-risk groups. There is also no validation cohort. Risk assessment derivation requires large cohorts, careful attention to model specification, and rigorous validation. Our intent was not to develop a competing risk score or specifically focus on RV basal diameter. Instead, we believe these results are an example where routine clinical data may alter clinical gestalt in a manner that is important and not well-captured in current risk scores.

In summary, formal risk-assessment to guide therapeutic escalation is widely promoted in academic and industry-sponsored education. In this real-world single institution cohort, most participants were considered high risk by risk score alone. We provide data that reinforce a paradigm where formal risk assessment is an important decision aid but does not supplant clinical synthesis and decision making.

ARTICLE INFORMATION

Received January 24, 2022; accepted June 13, 2022.

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Sources of Funding

This work was supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under award KL2TR000421.

Disclosures

Dr Rayner received research funding from Bayer Pharmaceuticals. Dr Leary has received research funding from the National Institutes of Health, the American Heart Association, and Bayer Pharmaceuticals; salary support from the Cystic Fibrosis Foundation Therapeutic Development Network; and consulting fees from Bayer Pharmaceuticals. The remaining authors have no disclosures to report.

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