The Evolution of Risk Assessment in Pulmonary Arterial Hypertension

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ABSTRACT: Pulmonary arterial hypertension (PAH) is a chronic debilitating disease that carries an unacceptably high morbidity and mortality rate despite improved survival with modern therapies. The combination of several modifiable and nonmodifiable variables yields a robust risk assessment across various available clinical calculators. The role of risk calculation is integral to managing PAH and aids in the timely referral to expert centers and potentially lung transplantation. Studies are ongoing to determine the role of risk calculators in the framework of clinical trials and to elucidate novel markers of high risk in PAH.

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a progressive and debilitating disease mediated by complex mechanisms of vasoconstriction, smooth muscle cell hypertrophy, endothelial cell proliferation, and thrombosis. These maladaptive changes lead to increased vascular resistance, increased right ventricular (RV) strain, and eventual RV failure.[1] Although there have been considerable insights into the disease and momentum in the field over the past few decades, it remains an incurable and highly morbid disease.

In 1984, the landmark National Institutes of Health (NIH) registry established median survival to be 2.8 years from initial diagnosis, with survival rates of 68%, 48%, and 34% at 1, 3, and 5 years, respectively.[2] This pioneering data comprising 194 patients with idiopathic, drug-induced, or mixed connective tissue disease offered the first insight into features that could potentially predict survival. Investigators used this untreated population to identify hemodynamic, functional, medical history, and pulmonary function variables that portended worse outcomes.[3]

The first PAH-specific therapy, intravenous epoprostenol, was approved by the US Food and Drug Administration about a decade after the initial registry study. It subsequently sparked a revolution of pharmacotherapy in PAH and remains the only class of medication backed by survival data.[4] As sophisticated treatment options have emerged, risk assessment has become an integral part in monitoring disease progression. Although survival is improved in the modern era, the decision to escalate therapy and/or refer to a center of expertise hinges on the accurate assessment of a patient's risk of dying from this disease.

Since there is no single variable that can precisely capture the patient with heterogeneous PAH, clinicians use a combination of variables that are known to hold prognostic data and have broad clinical applications. Older metrics, such as right atrial pressure and 6-minute walk distance (6MWD), have stood the test of time while novel markers are constantly being examined. The 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) outlines this multivariable approach, and other modern-era registries, such as REVEAL (Registry to Evaluate Early and Long-Term PAH Disease Management), have built on the NIH backbone to refine this concept.[5,6] The following review explores the evolution and development of current risk assessment tools and acknowledges limitations and future directions.

DEMOGRAPHICS

Gender has played an important role in the risk profile of PAH since the first registry studies. While women certainly have a greater disease burden, it seems they have better survival than men.[7] Several studies have explored this paradox.[8-10] Estrogen is the obvious target to explain this discordance and has been shown to protect against pulmonary vasculopathy and improve RV function.[11]

Age is another risk that has a complex relationship with gender. An interesting pooled data analysis involving 1,211 patients demonstrated that men < 45 years tended to have more severe hemodynamic parameters, but this effect was attenuated with age.[12] Conversely, the observational REVEAL study identified age > 60 years as a significant predictor of risk for males (HR 2.2; CI 1.6-3).[6] Looking deeper, a substudy stratified the REVEAL cohort by age and found that older males had poorer survival and in general worse hemodynamics.[13]

There have been important observations regarding race and ethnicity in the era of ancestry data and genetic deconstruction. An important publication from 2020 explored this relationship using self-identified data while also incorporating ancestry analysis.[14] Groups were categorized as self-reported non-Hispanic White (NHW), non-Hispanic African American (NHAA), and Hispanic. Correlating this with ancestry data, the NHW group was 97% European, the NHAAs were 82% African, and the Hispanic population was 85% European, 36% Native American, and 7% African. Interestingly, the Hispanic population was associated with a significantly improved transplant-free survival, a finding that was echoed in larger analyses using the US National Inpatient Sample database. Native American status also was shown to have a protective effect, and perhaps this piece of ancestry explained the improved survival in the Hispanic population as well. Conversely, there have been studies using national registries of death certificates suggesting that Black women had the highest mortality rates among patients with PAH.[15] This was also noted in the 2020 study, and admittedly there has been no comprehensive analysis to potentially account for this data. Considering that the heart failure literature has demonstrated a role for race-specific therapies to improve outcomes, this would be an important first step in understanding potential biological differences in therapy response among races.

In all major registries, patients with connective tissue disease (CTD) had poorer outcomes compared to other subtypes. The REVEAL registry had the unique advantage of having nearly 25% of all PAH patients with some type of CTD, and this large-scale data allowed for meaningful conclusions to be drawn regarding survival. Patients with systemic sclerosis had the worst 1-year survival among the CTD subtypes, while those with lupus and rheumatoid arthritis did considerably better. All patients with CTD carried a higher risk profile, with lower diffusing capacity for carbon monoxide and higher brain natriuretic peptide (BNP) at enrollment.[16]

FUNCTIONAL CLASS

The World Health Organization (WHO) functional class (FC) is the most widely used assessment of exercise capacity in PAH. Graded on a scale of I to IV, with IV being the most advanced disease, this subjective evaluation is based on the degree of limitation perceived with activities of daily living (Figure 1).[17] The WHO FC system is incorporated in most risk calculators, yet there is a large range of inter-rater agreement among clinicians.[18] To establish a more uniform approach to this assessment, investigators have sought to correlate health-related quality of life scores with FC. In a recent publication, 1,745 patients with PAH completed a 10-field questionnaire designed to assess PH-specific psychological and physical morbidity. Moderate correlations were seen with the WHO FC, and quality of life scores could be used to further substratify patients with WHO FC III. This is an important step in establishing a more objective and rigorous assessment of functional capacity.[19]

Six-minute walk distance (6MWD) has been widely used across different disease states as a quick and reproducible measure of exercise capacity. This metric emerged as an early tool in the risk stratification of PAH and was the primary end point of most PAH trials.[20] Among the first group of patients treated with epoprostenol for 12 weeks, the eight who died at the end of the study had significantly lower 6MWT compared with the 73 who survived (195 m vs 305 m, $P < .003$).[4] Although 6MWD was used as a surrogate for survival, cutoffs were variable and largely unsubstantiated. REVEAL investigators examined the role of 6MWD in prognostication and concluded a few salient points. First, survival seemed to be lowest in those patients with a baseline 6MWD < 165 m and highest in those with a baseline > 440 m. Next, a worsening of 6MWD over time was significantly associated with worse

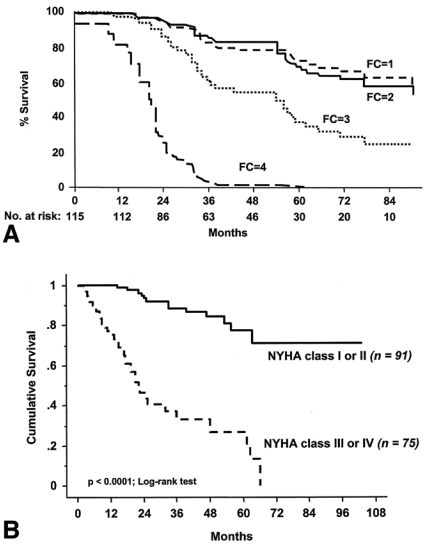

Figure 1.
(A) Subsequent survival in patients with idiopathic pulmonary arterial hypertension (IPAH) stratified by functional class after 1-year epoprostenol treatment 1: $P < .001$ for functional class III vs. functional class IV and for functional class III vs functional class I and functional class II.[30] (B) Survival in patients with IPAH treated with intravenous epoprostenol according to New York Heart Association (NYHA) functional class. After 3 months of treatment with epoprostenol, survival rates for patients reclassified in NYHA functional class I or II (solid line) were 100%, 93%, and 88% at 1, 2, and 3 years, respectively, as compared with 77%, 46%, and 33% for patients persisting in NYHA functional class III or IV (dashed line) ($P < .001$ by the Cox-Mantel log-rank test). Reproduced with permission of the © Elsevier Science & Technology Journals; J Am Coll Cardiol 2004;43(12 Supple S):40s-47s.[17]

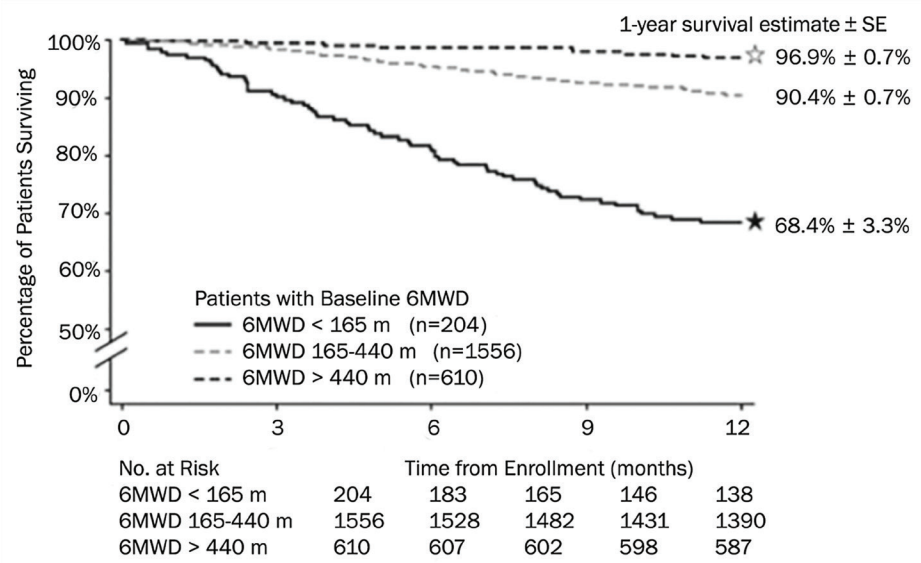

Figure 2.
Kaplan-Meier survival estimates based on 6-minute walk distance (6MWD) thresholds at 165 m and 440 m and all possible 6MWD thresholds. One-year survival estimates are shown for patients with a baseline 6MWD < 165 m (black solid), 165-440 m (gray dashed), and > 440 m (black dashed). Stars mark the 1-year survival estimates for patients with a 6MWD of > 440-m threshold (white star) and patients with a 6MWD ≤ a 165-m threshold (black star) and show the relationship between the two figures. Reproduced with permission of the © Elsevier Science & Technology Journals; J Heart Lung Trans. 2015;34:362-368.[21]

survival. Finally, improved or stable 6MWD did not translate to improved survival (Figure 2)—an interesting observation given that, up to this point, all clinical trials relied heavily on improvement in 6MWD as an end point.[21]

Although 6MWD is a robust prognostic tool, it provides only limited clinical information about the complex cardiopulmonary interplay during exercise. Cardiopulmonary exercise testing (CPET) has the power to reveal marked abnormalities in this interplay, and certain CPET variables have been determined to have strong independent prognostic value. One of the established pitfalls of the 6MWD is its submaximal value when testing younger patients, who may be able to walk long distances despite having advanced RV failure. Maximal CPET can provide a precise evaluation in this scenario and offer a more rigorous approach to exercise capacity, especially in the younger population. Peak volume of oxygen (VO_2), exercise duration, VE/VCO_2 slope, and systolic blood pressure have all been shown to be independent predictors of survival.[22]

Although CPET is the most comprehensive exercise tool for PAH patients, it is not widely accessible and requires expertise with regard to performance and interpretation. Conversely, exercise treadmill testing is widely available and thus is a logical choice for community centers to properly risk stratify without needing expensive equipment. In a large cohort of patients with PH (63% WHO group I), reduced exercise capacity on a treadmill test was associated with worse hemodynamics and was an independent predictor of mortality.[23] Whichever method of exercise testing is employed, the PH patient's functional capacity must be assessed routinely as a correlate of risk.

LABORATORY PARAMETERS

Over the years, several laboratory parameters—including markers of cardiac function, renal function, inflammation, and metabolism—have emerged as strong prognostic indicators for PAH. Active BNP or the inert N-terminal proBNP (NT-proBNP) are surrogates of cardiac function and therefore play a logical predictive role in PAH given the resultant RV failure.[24] BNP and NT-proBNP correlate to several hemodynamic metrics, including right atrial (RA) pressure, mean pulmonary artery pressure (PAP), pulmonary vascular resistance (PVR), and cardiac index.[25,26] Serial measurements can be a very useful directional trend to track prognosis.[27] Along these lines, soluble suppression of tumorigenicity 2 (ST2) has been shown to have prognostic usefulness in heart failure. Recent studies also support this marker as being associated with higher pulmonary pressures, vascular resistance, and lower 6MWD. Along with NT-proBNP, ST2 elevations are associated with an increased risk of death and should be incorporated in survival models.[28]

In the REVEAL registry, renal insufficiency was strongly associated with worse survival, and a ≥ 10% decline in glomerular filtration rate (GFR) from baseline over a 1-year period had a significantly increased risk of both death and the composite of all-cause hospitalization and death. This isolated measure was able to predict survival independently of any functional class data or 6MWD.[29]

Inflammatory markers such as C-reactive protein, platelet activation, and uric acid also have been linked with poor outcomes,[30,31] and the protein coding gene *NEDD9* (Neural Precursor Cell Expressed, Developmentally

Down-Regulated 9) has emerged as another promising marker of fibrosis in the pulmonary vasculature. In a recent multicenter retrospective observational study, *NEDD9* was significantly increased in patients with PAH. Interestingly, it was not found to be elevated in other forms of PH. Elevated levels correlated with established hemodynamic parameters or poor prognosis and tracked with clinical events. Although more rigorous prospective trials are needed, *NEDD9* may be an important biomarker in PAH.[32]

ECHOCARDIOGRAPHY

Echocardiography (echo) is the most widely used tool to quantify RV function. Right atrial pressure, RV dimension, fractional area change, RA size, tricuspid annular plane systolic excursion, and the Tei index are among some of the load-dependent measures that have been independently validated in research settings.[33] While no one measurement can determine the state of the RV, a combination may provide a composite view. Echo-estimated RA pressure elevation in addition to RA enlargement has been shown to independently predict transplant-free survival in a modern-era cohort with PAH.[34] A tricuspid annular plane systolic excursion < 1.8 cm, obtained through an M-mode of the free RV wall, predicts decreased 2-year survival.[35] RV fractional area change (FAC) is calculated by a direct measurement of the RV in end systole and end diastole. In clinical practice, this is often an imprecise measurement given the difficulties of capturing a dilated RV by 2-dimensional echo. The Tei index, also called the myocardial performance index, incorporates systolic and diastolic time intervals to provide a global view of ventricular function.[36]

Echocardiography is easily reproducible and widespread, thus making it an attractive option for tracking disease progress and reverse remodeling with therapy. A recent publication found that in a cohort of PAH patients treated with upfront triple therapy, there was a decrease in right-sided atrial and RV areas and an increase in FAC proportionally to hemodynamically derived PVR improvement. This robust data correlated echocardiographic data to invasive hemodynamics and warrants further studies to tie this to a prognostication model for tracking disease.[37]

MAGNETIC RESONANCE IMAGING

For decades predating vasodilator therapy, magnetic resonance imaging (MRI) was recognized as a powerful tool to image the RV in PAH.[38] As temporal and spatial resolutions improved, clinicians gained insight into the complex interplay between the left and right ventricles. Increases in RV mass shown on MRI has been shown to correlate directly to elevated pulmonary pressures.[39]

In addition to mass and volume analysis, flow measurements are an accurate and reproducible tool for quantification of pulmonary artery flow and lung perfusion, which are decreased in PAH patients. MRI-derived values provide excellent quantification of both right and left ventricle stroke volume and are superior at calculating shunt fraction.[40] In a large meta-analysis of MRI studies in PAH, RV ejection fraction was the strongest predictor of mortality.[41]

Recently introduced four-dimensional flow analysis is emerging as the preferred method for assessing pulmonary circulation. Using this technology, subtle changes in pulmonary blood flow can be detected in PAH patients, and improvements in flow can be used to track therapeutic success.[42]

The concept of ventricular-arterial uncoupling emerged in the 1980s to describe the transfer of energy from ventricular contractility to the arterial afterload. Ventricular contractility is described by the term end-systolic elastance (Ees), which is a load-independent measure. Arterial afterload is encompassed in the term arterial elastance (Ea), which combines mean and pulsatile pressures in a way to describe the afterload to the ventricle. Importantly, Ea can be easily calculated through end-systolic pressure divided by stroke volume, and it is accurate in various afterload conditions.[43] The ratio of Ees/Ea—an ideal unitless ratio—completely captures the ventricular-arterial coupling phenomenon and has been established at 1:2.[44] RV-PA uncoupling can be preserved in a compensated RV even with severely elevated pulmonary pressures. As the disease advances, this ratio drops, with the lowest tertile being the most decompensated state. These measurements are derived from invasive RV pressure-volume loops. In recent years, data suggests that RV stroke volume measured by MRI divided by RV end systolic volume is comparable, if not superior, to invasively derived Ees/Ea in predicting RV dysfunction.[45]

A more promising application of MRI in RV imaging lies in the ability to demonstrate improvement with vasodilator therapy. In early 2020, the REPAIR trial (effects of macitentan on markers of RV function) showed that open-label macitentan therapy was associated with improvements in RV stroke volume as detected by MRI.[46] This has raised important consideration for using MRI-based end points in clinical trials to precisely track disease progression with therapy.

HEMODYNAMICS

Hemodynamic assessment offers the first insight into risk stratification in a newly diagnosed PAH patient. The NIH registry identified several parameters associated with poor survival, including elevated mean RA pressure, decreased cardiac index, and elevated mean PAP.[3] In the 2010 REVEAL registry, PVR > 32 WU emerged as the strongest

DETERMINANTS OF PROGNOSIS (ESTIMATED 1-YEAR MORTALITY)	LOW RISK < 5%	INTERMEDIATE RISK 5%-10%	HIGH RISK > 10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope[c]
WHO functional class	I, II	III	IV
6MWD	> 440 m	165-440 m	< 165 m
Cardiopulmonary exercise testing	Peak VO_2 > 15 mL/min/kg (> 65% pred.) VE/VCO_2 < 36	Peak VO_2 11-15 mL/min/kg (35-65% pred.) VE/VCO_2 slope 36-44.9	Peak VO_2 < 11 mL/min/kg (< 35% pred.) VE/VCO_2 slope ≥ 45
NT-proBNP plasma levels	BNP < 50 ng/L NT-proBNP < 300 ng/L	BNP 50-300 ng/L NT-proBNP 300-1,400 ng/L	BNP > 300 ng/L NT-proBNP > 1,400 ng/L
Imaging (echocardiography, CMR imaging)	RA area < 18 cm^2 No pericardial effusion	RA area 18-26 cm^2 No or minimal pericardial effusion	RA area > 26 cm^2 Pericardial effusion
Hemodynamics	RAP < 8 mm Hg CI ≥ 2.5 L/min/m^2 SvO_2 > 65%	RAP 8-14 mm Hg CI 2.0-2.4 L/min/m^2 SvO_2 60-65%	RAP > 14 mm Hg CI ≥ 2.5 L/min/m^2 SvO_2 < 60%

Table 1.
European Society of Cardiology/European Respiratory Society Guidelines risk assessment 2015. WHO: World Health Organization; 6MWD: 6-minute walk distance; BNP: brain natriuretic peptide; NT-proBNP: N-terminal proBNP; CMR: cardiac magnetic resonance; VO_2: maximal oxygen uptake; VE/VCO_2: minute ventilation/carbon dioxide production; RA: right atrial; RAP: RA pressure; CI: cardiac index. Reproduced with permission of the © 2021 European Society of Cardiology & European Respiratory Society. European Respiratory Journal, 46(4):903-75.[5]

hemodynamic variable with a more than fourfold increase in hazard ratio. Mean RA pressure (RAP) also predicted survival, albeit not as strongly as PVR.[6] The European PAH registries have similarly identified hemodynamic risks based on expert consensus, and these are represented in the 2015 ESC/ERS pulmonary hypertension guidelines. RAP, cardiac index, and venous oxygen saturation are all included in these guidelines. Of note, mean PAP has never been shown to predict mortality since the initial NIH study.

Most clinicians use their "clinical gestalt" to discern hemodynamic parameters signifying poor RV function. A recent study presenting accumulated data from 10 clinical experts identified 26 different variables that they perceived as having the most effect on survival in patients with PAH. Concurrently, a Cox regression analysis was performed on baseline hemodynamic parameters in nearly 3,000 patients with PAH from several contemporary clinical trials. The parameters determined to have the most "weight" were cardiac index, RA pressure, and mean PAP. However, in taking the aggregate of the clinical trial data, the hemodynamic parameters most predictive of survival included stroke volume, stroke work index, and stroke work.[47] This suggests that clinical gestalt alone may underestimate the mortality prediction when comparing evidence-based predictors. This and other such suggestive research would lend nicely to the development of machine-learned patient risk stratification tools.

ANCILLARY TESTING

Lung mechanics are substantially altered in pulmonary hypertension. This is mediated through complex phenomenon, including increased dead-space ventilation, increased ventilatory requirement, and decreased cardiac output response to exercise. Of several possible lung function parameters studied, the diffusing capacity for carbon monoxide (DLCO) emerged as an important marker of disease. In one experience of newly evaluated PAH patients, about three quarters had a DLCO < 80% predicted.[48] Despite good inspiratory volume and correction for hemoglobin, this decreased DLCO could only be explained by reduction in the pulmonary alveolar capillary bed. This concept fits with the pathological description of PAH—that is, the muscularization of smaller pulmonary arteries, medial thickening, and a reduction in peripheral vascular bed. Based on the recognition that DLCO is implicated in survival, a larger study further demonstrated the existence of DLCO quartiles, the lowest (< 40%) of which is associated with poor prognosis.[49] Further exploration in the REVEAL registry determined that a percent predicted DLCO of under 32% considerably added to the risk profile.[50]

In consideration of the older PAH population, it would be remiss to discount the effect of common comorbid conditions on the diagnosis, treatment, and prognosis of PAH. In the presence of conditions such as systemic hypertension and diabetes, the polypharmacy and interaction between PAH-specific drugs and systemic vasodilators must

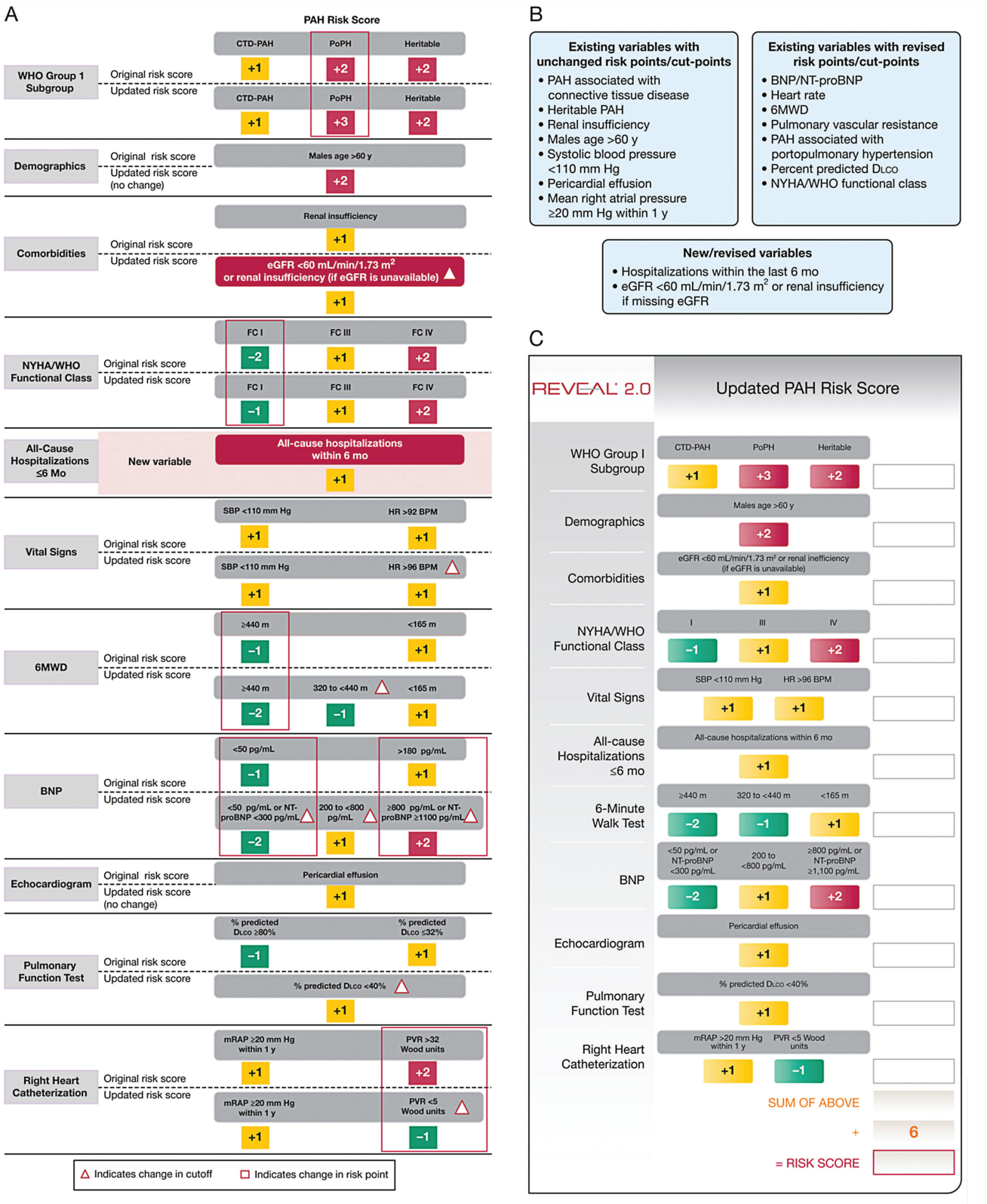

Figure 3.
REVEAL 2.0 Updated Risk Score Calculator. Risk score ranges from 0 (lowest) to 23 (highest). Reproduced with permission (open access).[60]

RISK ASSESSMENT STRATEGY AND RISK GROUP	# PATIENTS (%)	KAPLAN-MEIER ESTIMATED MORTALITY AT 1 Y (%)(95% CI)	HR (95% CI) COMPARED WITH LOW-RISK GROUP	C-INDEX (95% CI), THREE-CATEGORY/ ORIGINAL
REVEAL 2.0 (N = 2,529)				
Low (score ≤ 6)	1,073 (42.4)	1.9 (1.1-2.7)	N/A	0.73 (0.71-0.75)/ 0.76 (0.74-0.78)
Intermediate (score 7-8)	692 (27.4)	6.5 (4.7-8.4)	2.73 (2.2-3.4)	
High (score ≥ 9)	764 (30.2)	25.8 (22.7-28.9)	8.09 (6.6-9.9)	
REVEAL LITE 2 (N = 2,529)				
Low (score ≤ 6)	960 (38.0)	2.9 (1.8-3.9)	N/A	0.70 (0.68-0.72)/ 0.73 (0.71-0.75)
Intermediate (score 7-8)	883 (34.9)	7.1 (5.4-8.8)	2.27 (1.8-2.8)	
High (score ≥ 9)	686 (27.1)	25.1 (21.9-28.4)	6.35 (5.2-7.8)	

Table 2.
REVEAL 2.0 v REVEAL Lite 2; Hazard ratios and concordance indexes for estimation of 1-year mortality. Reproduced with permission (open access).[59] C-index: Harrell's concordance statistic; HR: hazard ratio; CI: confidence interval; N/A: not applicable

be carefully analyzed. Obesity is a highly prevalent condition in the PAH community and has been associated with increased mortality.[51] Not only will the presence of obesity confound available prognostic tools such as the 6MWD, but it may also contribute to PAH severity.

The turn of the century saw the widespread application of genetic studies in the evaluation of disease. Genetic sequencing in family clusters led to the discovery of a heterozygous germline mutation of bone morphogenic protein receptor type 2 (BMPR2), a member of the transforming growth factor-B (TGF-B) superfamily. This early data drove the revision of the classification system during the 3rd World Health Symposium in 2003. Mutations in the *BMPR2* gene are implicated in 70% to 80% of familial cases and 10% to 20% of idiopathic cases.[52,53] In an analysis of individual participant data of this mutation, patients present at a younger age with more severe disease and are at an increased risk of death or transplantation.[54]

On a larger scale, genome-wide association studies (GWAS) are used to test whether certain alleles or genetic variants are commonly found in disease. In a study of 1,198 patients, a single-nucleotide polymorphism (rs11157866) in the G-protein alpha and gamma subunits gene was significantly associated with a combined improvement in functional class and 6MWD at 12 and 18 months and marginally significant at 24 months.[55] The largest GWAS to date included 11,744 individuals, of whom 2,085 were diagnosed with PAH. This analysis linked three genetic regions to PAH—two near the *SOX17* gene and the other within the *HLA-DPB1* gene. In addition to providing a robust link, it was noted that specific variants of the *HLA-DPB1* gene correlated differently with patient survival. Particularly, one variant (C/C genotype) carried a survival of 13.5 years, although the T/T genotype carried a median survival of 7 years. Further research is needed to understand how genome studies can be used to predict prognosis in this clearly heterogeneous population.[56]

HISTORICAL PERSPECTIVE OF RISK ASSESSMENT

The NIH-derived risk tool of patients with idiopathic PH was published in the pretherapy era of the 1990s and laid the groundwork for future risk score development. The advent of pulmonary vasodilator-specific therapy created the need for an updated risk assessment. Several registries across the world emerged as important contemporary corelates, with three major European contributions—the FPHN (French Pulmonary Hypertension Network), the German COMPERA registry (Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension), and SPAHR (Swedish PAH Registry).[5,57] There has been a great deal learned from this collective experience of more than 3,000 patients. Based on expert opinion, a set of readily available clinical, hemodynamic, and imaging variables were used to stratify patients into low, intermediate, or high-risk categories. The ESC/ERS have mirrored their guidelines to reflect these high-risk variables (Table 1).[5]

All three of these international registries varied in complexity and assigned a uniform grade to various prognostic parameters. In addition, most of the 3,000 patients were incident cases of heritable, idiopathic, or drug-induced PAH. The achievement of a low-risk profile certainly offered reassurance of favorable survival in the first year. This was an important development in risk stratification because it established a uniform approach to these highly complex patients.

That complexity, however, prompted further discussion as to the appropriate role of simplified algorithms in risk assessment. The aforementioned registries used expert opinion assessment of high-risk categories rather than a statistical model to validate risk. In addition, the PAH groups were

exclusively idiopathic, heritable, or drug induced and thus the applicability across all subtypes should be taken into consideration. Furthermore, rather than a weighted grade for each variable, there was one fixed value placed on the presence or absence of each parameter. This implies that all parameters hold equal importance in risk stratification. With the evolution of registry data, we have learned that some variables do indeed have more weight than others, and efforts to maintain easily accessible modifiable variables may erroneously exclude the contribution of so-called "nonmodifiable" variables, such as the presence of mixed connective tissue disease or male gender.

REVEAL (The Registry to Evaluate Early and Long-term PAH Disease Management) yielded the first comprehensive US-based risk assessment combining several modifiable and nonmodifiable factors. Recently updated as REVEAL 2.0, this score was built on a registry with prevalent *and* incident cases, with the added benefit of allowing for serial assessments to define risk as a movable target. Like the prior risk assessment tools, patients can be categorized as low, intermediate, or high risk.[58] It is important to note that REVEAL 2.0 showed a greater degree of risk discrimination compared with the ESC/ERS-based risk assessment strategies. In clinical practice, however, there have been several barriers to implementing rigorous risk calculation. Partially to blame are the number of parameters involved (12 clinical and functional parameters would need to be calculated for every patient visit) and the need for repeat hemodynamic assessment. To mitigate some of these factors and potentially expand the role of risk assessment in clinical practice, investigators have developed an abridged format of scoring called the REVEAL Lite 2 calculator, which uses only six modifiable and noninvasive variables. A recent analysis of this assessment method showed that it approximates the more involved 13-variable REVEAL 2.0 at discriminating low, intermediate, and high risk for 1-year mortality (Figure 3, Table 2).[59,60]

Whichever risk tool is used, clinicians strive to achieve the low-risk category using available pharmacotherapy. As the field of risk assessment progresses, there has been an increasing trend to simplify the variables and scoring calculations. While this may hold merit to increase the utilization of risk scores, it is important to keep in mind that the weighting of many variables is essential on an individual patient level to discriminate and calibrate between available tools. The physician making decisions on medical therapy must keep in mind that an algorithm with statistical significance in predicting mortality on a heterogeneous population may not perform well on an individual level. When applied in a PAH practice, a risk calculator may enhance the consistency of treatment approaches and improve timely referral to lung transplantation.

FUTURE DIRECTIONS

The basic assumption of any risk calculator is that all possible contributors of risk are already established, yet insight into RV biology and the complexities of the pulmonary vasculature is rapidly evolving. There are numerous neurohormonal and physiological processes underlying PAH that are not captured in current risk scores. Additionally, genome-wide association studies are hotly underway to tackle the genetic underpinnings of disease severity.

The greatest use of risk scores is in their ability to guide management and escalate therapy. Another promising role is in clinical end point management. For decades, clinicians relied on 6MWD as a primary end point for most large therapy trials. The clinical risk score can serve as an important treatment end point and also stratify patient risk during recruitment and randomization. This may fortify enrollment by making sure a heterogenous risk profile is recruited while also identifying patients who will benefit most from a certain intervention.

There is much to be learned from the collective experience in this complex field. The risk assessment of the patient should take a uniform approach and constantly evolve with our current understanding.

KEY POINTS

- Although mortality has improved significantly in the post-therapy era, pulmonary arterial hypertension remains a chronic debilitating disease.
- Routine assessment of risk should be used in clinical practice to aid in decision making regarding medication escalation and referral for advanced therapy options.
- Several modifiable and nonmodifiable variables have been shown to alter risk, and the combination of these are used in modern risk calculators.
- There are important strengths and pitfalls to available risk calculators; the aim should be to strike a balance in simplification to increase utilization while also maintaining accuracy in risk prediction.
- Further research is needed to elucidate novel markers and to define the role of risk scores in clinical trials.

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