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Prognostic biomarkers in pediatric pulmonary arterial hypertension

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Abstract: Pulmonary arterial hypertension (PAH) is a progressive life-threatening disease of the pulmonary vasculature. Despite the introduction of targeted therapies, prognosis remains poor. In pediatric PAH, reliable prognostic biomarkers are needed to inform clinicians on disease progression and risk of mortality, in order to be able to assess the need for escalation of medical therapy, consider surgical options such as Pott's shunt and listing for (heart)-lung transplantation. This review provides an overview of prognostic biomarkers that are considered to carry potential for the clinical management of pediatric PAH. These include conventional physiological biomarkers [resting heart rate, heart rate variability (HRV), a child's growth], biomarkers of functional status [World Health Organization functional class, 6-minute walk distance (6MWD), parameters derived from cardiopulmonary exercise testing (CPET), daily physical activity level], electrocardiographic biomarkers, circulating serum biomarkers (natriuretic peptides, uric acid, neurohormones, inflammatory markers, and novel circulating biomarkers), and multiple hemodynamic biomarkers and imaging biomarkers [echocardiography and cardiac magnetic resonance (CMR)]. In recent years, many potential prognostic biomarkers have become available for the management of PAH in children. As the available prognostic biomarkers reflect different aspects of the disease process and functional implications, a multi-marker approach appears the most useful for guiding therapy decisions and improve outcome in pediatric PAH.

Keywords: Biomarkers; outcome; pediatric pulmonary arterial hypertension (pediatric PAH); prognosis

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Introduction

Pediatric pulmonary arterial hypertension (PAH) is a progressive life-threatening disease of the pulmonary vasculature (1). In the past decades, major advances in treatment options for adults with PAH have been achieved, with currently 12 approved PAH targeted drugs (2). Nevertheless, it remains a devastating disease without a cure, with unsatisfactory high mortality rates. This is especially the case for children (3). Although randomized controlled trials (RCT's) demonstrating efficacy in

childhood PAH are lacking, these PAH targeted drugs are generally used in infants and children with PAH (4).

In the current era with an increased number of available PAH targeted drugs, one of the major challenges for clinicians is to tailor optimal treatment regimens for the individual child with PAH (5). Children with PAH present at different stages of disease and at different levels of risk for disease progression and mortality. Prognostic biomarkers are needed to inform clinicians on disease progression and risk of mortality and to guide decisions on how and when to

use the available treatments, when to escalate therapy, and when to consider surgical options such as Pott's shunt and listing for lung-transplantation.

According to the recently harmonized definition by regulatory authorities, a biomarker is "*a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention*" (6). These include biochemical biomarkers in serum or plasma, but also functional, clinical, hemodynamic and imaging markers. The updated definition adds that a biomarker is not a direct assessment of how a patient feels, functions, or survives and therefore not of direct clinical meaning for a patient (6).

Prognostic biomarkers are a subtype of biomarkers that can be used to identify patients with greater likelihood of having a disease-related outcome event such as lung-transplantation or death in PAH (6). For this type of biomarkers, clinical or epidemiological studies are required to show a strong association with such endpoint events (7). Prognostic biomarkers are essential for risk stratification, informing treatment decisions in the management of chronic progressive diseases such as PAH and will therefore be reviewed in this report.

A common misconception regarding prognostic biomarkers is that their demonstrated association with mortality justifies their use for the evaluation of treatment efficacy, either in clinical management or in randomized clinical trials (7,8). However, only few prognostic biomarkers are useful for this purpose. Treatment efficacy is ideally measured by directly clinically meaningful outcomes (i.e., direct assessments of how patients feel, function or survive). Alternatively, surrogates that substitute for these directly clinically meaningful outcomes might be used (7). Surrogates are intrinsically part of the causal pathway of the disease, which can be validated by testing whether influences on the final clinically meaningful outcomes are causally explained by influences on the surrogate (7). A treatment goal represents a special use of validated surrogates, for which achieving predefined target levels of the measurement during treatment has been demonstrated to translate into improved disease outcome (9-11).

As pediatric PAH is a progressive disease with poor outcomes despite the available treatments, prognostic biomarkers are essential for risk stratification informing treatment decisions. This report reviews prognostic biomarkers in pediatric PAH, that are currently considered useful for the assessment of disease progression and outcome and may thereby aid in treatment decisions for

individual children with PAH. Since prognostic biomarkers provide a pool of candidate surrogates that might play a role in evaluating treatment efficacy and a goal-oriented treatment strategy, we also comment on their potential as treatment goals when this is applicable.

Conventional physiological biomarkers

Heart rate

In the general population, resting heart rate carries prognostic value (12). Increased resting heart rate reflects neurohormonal activation and is an independent modifiable predictor of all-cause mortality in heart disease (13,14). In PAH, increased right ventricular afterload leads to impairment of ventricular stroke volume, via sympathetic activation leading to an increased heart rate to maintain cardiac output (15,16). Although heart rate obviously is not a disease specific parameter, the degree of heart rate increase has been shown to predict outcome in adults with PAH (17,18). Also in children, heart rate has been reported to correlate with outcome, although heart rate was not the primary marker under study and patient age might have confounded the results in these cohorts (19,20).

A more reliable non-invasive way to evaluate autonomic dysfunction based on heart rate, is assessment of heart rate variability (HRV) (21,22). Impaired HRV is a predictor of mortality in the general population, and impairments can be due to chronic increased sympathetic nervous system activity or due to stretching of the sinoatrial node in situations of atrial overload (21). Lammers *et al.* have evaluated HRV in children with PAH, by analyzing holter registrations for parameters reflecting the degree of fluctuations of heart rate around its mean value (22). The authors found all HRV parameters to be predictive of death or lung-transplantation. A similar study conducted by Latus *et al.* confirmed associations of HRV with disease severity and hemodynamic parameters in a different cohort (21). These studies in pediatric PAH underscore the potential of HRV as a prognostic biomarker, and their results might find clinical applications in the upcoming digital biomarker era when wearable technology and telemonitoring are expected to be rolled out on a larger scale.

Height and weight

A disease aspect that exclusively applies to the pediatric age, is the impact of the disease on growth. In childhood,

growth is a marker of disease severity that may be predictive for outcome (23). Z-scores for weight and height are decreased in children with PAH and the degree of decrease has been shown to be associated with mortality (24). A study that pooled data from four prospective international registries of children with PAH, has found pediatric PAH to be associated with impaired growth, especially in younger patients and in those with concomitant congenital heart disease (CHD) (25). In addition, the degree of growth impairment was found to be independently associated with disease severity and disease duration. Moreover, catch-up growth over time was associated with a favorable clinical disease course, suggesting standardized height to be a simple and useful biomarker to monitor children over time. Increased caloric expenditure and altered metabolic demands may play an important role in growth impairment in PAH. Unraveling the mechanisms of growth failure, potential effects of treatment on growth and evaluating whether nutritional interventions may modify outcomes are important areas of future research.

Other conventional physiological measurements

In addition to heart rate and growth measurements, other conventional physiological measurements have anecdotally been shown to correlate with outcome in PAH, including transcutaneous oxygen saturation and blood pressure (3,26,27). Limited disease specificity and inconsistency regarding reported prognostic value in pediatric PAH currently hamper their usefulness as prognostic biomarkers for monitoring patients over time.

Biomarkers of functional status

World Health Organization functional class (WHO-FC)

WHO-FC is routinely applied in many expert centers for pediatric PAH and has been shown to be a strong predictor of mortality (28). Despite the disadvantages of being a potentially subjective measurement due to dependency on the observation and impression of caregivers, it has been demonstrated to be a robust and useful prognostic biomarker. Its applicability has been questioned in the youngest children, as it is a subjective measurement, especially in young children due to dependency on the observation and impression of caregivers. However, WHO-FC has been repeatedly demonstrated to be a powerful

prognostic biomarker in pediatric PAH, also in the youngest patients (28).

WHO-FC was not originally designed for children and infants and characterization of “ordinary physical activity” has to be adjusted to the child’s age, similar as in the elderly. To address pediatric-specific aspects of PAH including growth and development, in 2011 the Pediatric Task Force of the Pulmonary Vascular Research Institute (PVRI) proposed the Panama “Pediatric Functional Class” with modifications according to developmental abilities and skills in different age ranges (29). In a single center retrospective chart review study, Balkin *et al.* demonstrated a high inter-observer agreement when scoring the Panama Functional Class (30). Although the authors were not able to demonstrate the prognostic value of Panama Functional Class at time of diagnosis, serial associations with morbidity and mortality increased during follow-up. Prospective longitudinal multicenter validation of the Panama Functional Class will be required before it can be recommended as prognostic biomarker.

6-minute walk distance (6MWD)

The 6-minute walk test is a standardized submaximal exercise test measuring the distance a patient is able to walk over a time frame of 6 minutes (31). 6MWD has been reported to correlate with mortality in adults with PAH and has long been used as an endpoint in treatment efficacy trials in adults (32). In young children, 6MWD is limited due to developmental restrictions: infants are not able to walk and developmental capabilities and motivational issues may affect the test results. 6MWD was not identified as a predictor of mortality in cohorts that included many children below the age of 7 (28). However, in pediatric cohorts consisting of patient that are sufficiently able and old enough to perform this test reliably (e.g., >7 years), 6MWD was demonstrated to be a strong predictor of outcome (22,33). Improvement of 6MWD following treatment initiation or escalation likely reflects improved exercise capacity and quality of life and thus efficacy of treatment (34). It is unclear, however, whether such treatment-induced improvements reflect decreased mortality risks in children with PAH (10). The 6MWD is regarded to reflect patients exercise tolerance, and thus a clinically meaningful endpoint, and this has lead the pediatric task force of the 6th World Symposium on Pulmonary Hypertension to recommend achieving to

improve 6MWD as a treatment goal (4).

Cardiopulmonary exercise testing (CPET)

CPET is a noninvasive method to comprehensively assess exercise capacity, and in expert hands it is a reliable method to assess the degree of exercise intolerance (34). Three measurements shown to be prognostic biomarkers in both adults and children are (I) peak oxygen consumption and (II) the relationship between minute ventilation and carbon dioxide output (VE/VCO_2) also called ventilatory efficiency slope and (III) peak systolic blood pressure (34-37). Even more than is the case with 6MWT, the feasibility of CPET in children depends on developmental and motivational factors. Moreover, CPET requires considerable experience and expertise hampering standardization. The first RCT in pediatric PAH used peak oxygen consumption measured by CPET as the primary endpoint (38). In this pediatric trial, only half of the included children appeared physically and developmentally able to perform CPET, illustrating the limitation of CPET biomarkers in a pediatric population.

Daily physical activity level

Portable electronic accelerometers can accurately and continuously monitor physical activity in the home setting, providing extensive information on exercise capacity that might go far beyond a 6MWT or CPET in a hospital setting (39). A pilot study from Zijlstra *et al.* demonstrated the feasibility of objective physical activity level assessment by accelerometry in children with PAH of various ages (40). Moreover, this pilot study showed that physical activity measured by accelerometry was significantly lower in children with PAH when compared to age-matched controls and correlated with disease severity and time to a clinical event. These findings suggest that continuously measured physical activity level can serve as a prognostic biomarker. Daily physical activity level, as measured by wearable accelerometers, is now under investigation as a potential end point in both adult and pediatric PAH trials (clinicaltrials.gov Identifier NCT03078907). If confirmed, this technique holds promise as a cost-effective monitoring tool for both clinical practice and future treatment efficacy trials (41).

Electrocardiographic biomarkers

Routine electrocardiography (ECG) is non-invasive and

can be performed repeatedly during the disease course of patients with PAH. The ECG of patients with PAH can show signs of right atrial enlargement, RV hypertrophy and right axis deviation, although this is not the case in all children with PAH (42-44). In adults with PAH, increased P wave amplitude in lead II, the presence of a qR-pattern or increased R wave amplitude in lead V1 are associated with worse hemodynamics and decreased survival (45,46). Treatment-induced changes of ECG parameters reflecting RV hypertrophy are associated with concurrent changes in hemodynamics and survival (47-49), providing clues that ECG biomarkers can serve as adjunct prognosticators for risk stratification and for monitoring the disease over time.

Although age-dependent references have to be carefully taken into account in children, recent data suggests that serial ECG's could also have a supporting role in the follow-up of pediatric PAH. In a retrospective study of children with idiopathic PAH, RV hypertrophy ECG parameters were shown to correlate with hemodynamics and to differ between survivors and non-survivors (survival free of Potts shunt or transplantation) (50). Larger scale longitudinal outcome studies are indicated to determine the clinical value of ECG parameters as potential prognostic biomarkers in pediatric PAH.

Circulating serum biomarkers

Circulating serum biomarkers have the advantage of being investigator-independent and easy to obtain through peripheral blood samples (4). Several circulating biomarkers have been investigated in children with PAH.

Natriuretic peptides

Natriuretic peptides are synthesized in cardiomyocytes in response to increased muscular wall stress (51). After cleavage of Pre Pro B-type Natriuretic Peptide (BNP), Pro BNP is split in active BNP and inactive, more stable N-terminal BNP (NT-proBNP). Serum levels of BNP and NT-proBNP have been shown to be closely linked to RV function, the main determinant of clinical outcome in PAH (52).

In pediatric PAH, both biomarkers are associated with disease severity, as associations have been demonstrated with WHO functional class and 6MWD (53-55). It has been demonstrated that changes in NT-proBNP during clinical management also correlate with serial changes in disease severity (53). Both BNP and NT-proBNP are also associated with invasive hemodynamics measurements,

and their value as robust prognostic biomarkers has been demonstrated in multiple studies (28). In clinical practice, NT-proBNP is preferred over BNP, as it is more stable with a longer half-life and carries a stronger predictive value for right heart failure and mortality. NT-proBNP was found not only to be associated with mortality at time of diagnosis, but also at different time points during the course of the disease (10,56). Moreover, serial changes in NT-proBNP over time have been demonstrated to reflect changes in long-term outcome, strongly suggesting that NT-proBNP can function as a surrogate for mortality and can be used to evaluate treatment efficacy (56).

Uric acid

Hyperuricemia is a common finding in cardiovascular disease, including pulmonary hypertension (57-60). Increased levels of uric acid can result from several mechanisms, with increased activation of xanthine oxidase caused by oxidative stress or tissue hypoxia being the most likely in the setting of vascular and cardiac dysfunction (61,62). It has been speculated that elevated uric acid levels are not only a consequence of pulmonary hypertension, but that it may also have a secondary role in the pathogenesis, contributing to progression of disease (63). Its role in the pathophysiology (irrespective of whether or not being pathogenic), makes uric acid a suitable candidate in the quest for prognostic biomarkers in PAH.

In both adults and children, increased uric acid levels have been shown to be associated with increased mortality (36,54,60,64). In the pediatric age group, uric acid has been comprehensively studied, and it has been demonstrated that uric acid levels carry prognostic value, not only at time of diagnosis, but also during the full course of the disease (65). Moreover, a gradual incline of uric acid over time was found to be associated with increased mortality, a finding that indicates that uric acid is useful as prognostic biomarker but can also be valuable in the evaluation of treatment efficacy. Closely monitoring uric acid levels and their profile over time provides important information on the course of the disease and may aid in clinical decision-making in the management of pediatric PAH. In adults with PAH, the use of uric acid serum levels is limited due to the frequent presence of comorbidities that affect purine metabolism such as gout, renal dysfunction and insulin resistance, decreasing its specificity (61,66). Since these comorbidities are significantly less frequent in children, uric acid serum level is an appropriate prognostic biomarker specific in the

pediatric population.

Biochemical markers of neurohormonal activation

Sympathetic nervous system activity is increased in PAH (67). Ciarka *et al.* showed that the degree of sympathetic nervous system activation, directly measured by microneurography, is an independent predictor of mortality in adults with PAH (68). Serum levels of catecholamines such as norepinephrine and epinephrine are believed to reflect the degree of sympathetic nervous system activation, and have been shown to be increased in a subset of patients with PAH. Norepinephrine levels have been suggested to be associated with outcome in both children and adults with PAH (28,69), but for epinephrine the prognostic value is less clear (54). The small sample size in which the catecholamines are studied so far (hampering extensive multivariable or longitudinal modeling), currently limits conclusions regarding its usefulness as potential prognostic biomarkers.

Because of the central involvement of endothelin-1 (ET-1) in vascular remodeling and hence in the pathophysiology of PAH, ET-1 has long been considered a potential candidate prognostic biomarker in several cardiovascular diseases including PAH (70). Despite promising associations with disease severity in adults with PAH, ET-1 has not been adopted as a biomarker into clinical PAH practice (71). The main reasons are a lack of disease specificity, contradictory study findings and unpredictable treatment effects. A study on ET-1 in pediatric PAH did not show associations with disease severity or mortality, arguing against a potential role for ET-1 as a prognostic biomarker in PAH (72).

Inflammatory markers

In view of the important role of inflammation in the pathobiology of PAH, there is growing interest in inflammatory markers as potential prognostic biomarkers. For instance, circulating cytokines including interleukin-6 have been suggested to correlate with hemodynamic disease severity measurements in children with idiopathic and associated PAH and were demonstrated to identify patients at risk for various adverse outcome events (73). In a small experimental study using a proteomics approach, serum amyloid-A4 (an acute phase marker released in response to inflammatory stimuli), was higher in children with idiopathic PAH with poor outcome profile (defined as death, initiation of intravenous prostacyclin) compared to those with a more favorable outcome profile (74). Using a

similar approach, serum levels of apolipoprotein-A1 have also been suggested to correlate with disease severity and outcome in 83 children with idiopathic and CHD-associated PAH (36). Plasma growth differentiation factor 15 is a stress responsive cytokine that has been shown to be elevated in children with CHD-associated PAH compared to controls, and to correlate with disease severity and hemodynamic measurements (75). Galectin-3 is secreted by immune cells that regulate inflammation, fibrogenesis, cell proliferation and tissue repair and high levels have been suggested to predict PH and correlate with echocardiographic disease severity measurements in children with ventricular septal defects (76). Although promising from a pathobiological perspective, all these inflammatory markers are not yet in routine clinical use and further investigations including prospective validations are warranted.

Other circulating serum biomarkers with potential prognostic value

Of the serum biomarkers, natriuretic peptides, uric acid, neurohormones and inflammatory markers have been studied most extensively in pediatric PAH and have therefore been discussed. There is a large set of other potential biomarkers under investigation of which some have also been suggested to carry prognostic value in pediatric PAH. Among others these include: markers of myocyte stress or injury (e.g., cardiac troponins, soluble ST2, midregional pro-adrenomedullin), markers of oxidative stress (other than uric acid), markers of RV extracellular matrix remodeling (e.g., matrix metalloproteinases and its tissue inhibitors), and several markers derived from high-throughput “omics” technologies (e.g., genomics, transcriptomics, proteomics and metabolomics) (36,75,77,78). As some of these hold much promise as prognostic biomarkers in pediatric PAH, their usefulness requires further confirmation in well-defined and phenotyped cohorts of children with PAH.

Hemodynamic biomarkers

Cardiac catheterization is required to define PAH at time of diagnosis, and yields several hemodynamic biomarkers with prognostic value (4). The conventional hemodynamic biomarkers that have most frequently been shown to be associated with outcome in pediatric PAH include mean right atrial pressure, cardiac index and pulmonary vascular resistance index (28). Also, pulmonary-to-systemic arterial pressure ratio (mPAP/mSAP) is associated with mortality (19).

In addition to this, acute response to vasodilator testing has consistently been shown to be associated with improved survival (79,80). A comparison of several clinically used responder criteria in the TOPP registry has shown that transplant-free survival of responders according the so-called Sitbon criteria was superior, whereas children identified by alternative criteria had no better outcome compared to non-responders (80). Apitz *et al.* suggested a relationship between pulmonary endothelial function (by vasodilator response to acetylcholine administered in segmental arteries) and clinical outcome, indicating its potential as prognostic biomarker (81).

Cardiac catheterization in childhood requires sedation or general anesthesia and is accompanied by a, compared to adults with PAH, relatively high mortality risk of 0.6% and a risk for major complications of 1–3%, especially in young infants and those children in high WHO-functional class (82–84). Cardiac catheterization is the gold standard diagnostic modality in PAH, but the associated risks makes it less suitable for regular serial follow-up that is needed to monitor the disease over time.

Imaging biomarkers

Echocardiography

Echocardiography is a generally accessible non-invasive tool without the need for sedation or anesthesia and is well tolerated by children. This imaging modality not only allows for an assessment of the cardiac anatomy and morphology, but also allows for functional assessment of both ventricles and the pulmonary vasculature in pediatric PAH (85). However, accuracy and reproducibility of the measurements is limited due to operator-dependent acquisition and interpretation variability.

A wide range of echocardiographic measurements have been evaluated in adults and children with PAH, and a number of these qualify as prognostic biomarkers.

The tricuspid annular plane systolic excursion (TAPSE) measured in M-Mode in 4-chamber view reflects the degree of excursion of the tricuspid annulus towards the apex (86). This measurement of longitudinal RV function has been demonstrated one of the most robust predictors of disease severity and outcome (independent from age), and is one of the few prognostic biomarkers for which it was demonstrated that treatment-induced improvements are associated with improvements in survival (10,87).

The right-to-left ventricular dimension ratio, which is

measured in the parasternal short-axis view at the level of the papillary muscles and combines information on the pressure-load induced RV enlargement with the degree of septal shift compressing the LV, has also been demonstrated to carry prognostic value (87,88). The reported prognostic value of echocardiographic variables measuring functional properties of both the RV and the LV, supports the emerging recognition that ventricular interdependency is an important determinant of outcome in PAH. Pulmonary artery acceleration time has been shown to be associated with disease severity and invasive hemodynamics, but has not been shown to carry prognostic value in children with PAH (89). An increased systolic to diastolic duration ratio as measured by echocardiography reflects the decrease in diastolic and increase in systolic duration due to increased RV afterload and has been linked to mortality in a child with PAH, but could not be consistently reproduced in other pediatric cohorts (87,90).

More advanced echocardiographic techniques have also been suggested to be valuable in the assessment of children with PAH. Right ventricular free wall longitudinal strain assessed by speckle tracking echocardiography has been shown to be decreased in children with PAH, and to be associated with clinical outcomes (91-94). This assessment is suggested to be better reproducible with lower inter-/intra-observer variability compared to other echocardiographic variables and better suited for serial follow-up (92,95,96). Other emerging echocardiographic techniques that are explored in pediatric PAH include 3D-echocardiography and 4D flow profiles (94,97). Follow-up studies in larger well-defined cohorts of children with PAH are expected to yield essential information on the usefulness of these new echocardiographic measurements as prognostic biomarkers.

Cardiac magnetic resonance (CMR)

CMR imaging is a safe and non-invasive imaging modality and yields reliable and reproducible measurements of right ventricular and pulmonary arterial structure and function. Compared to echocardiography, images are more reproducible, and 3D measurements within the complex anatomical right ventricular configuration allow for better assessments of volumes and tissue masses.

Conventional CMR measurements that have been shown to be associated with disease severity and mortality in both children and adults with PAH include the following: RV volumes, RA and RV dimensions, RV mass, RV ejection fraction, LV stroke volume and tricuspid regurgitation

fraction (20,98,99). These measurements may be used as prognostic biomarkers. In adults with PAH, changes in RV functional CMR measurements have been shown to correlate with outcome, suggesting that such measurements might serve as survival surrogates and can be used in defining treatment goals. This remains to be demonstrated for children with PAH.

In addition to conventional measurements, CMR allows for the assessment of a wide range of cardiovascular functional properties, including systemic and pulmonary blood flow profiles, global and regional myocardial mechanics, interventricular (dys-)synchrony, pulmonary arterial wall dynamics and RV to pulmonary arterial interaction assessments (99,100). All of these may hold promise for the evaluation of the severity of PAH and the adaptive capacity of the heart, both in adults and children. CMR feature tracking techniques are emerging as accurate and reproducible ways for the comprehensive evaluation of myocardial fiber deformation, yielding parameters such as strain, strain rate and mechanical dispersion (101). These CMR biomarkers are under current investigation in cohorts of children with PAH.

It has been argued that CMR is not feasible in small children without sedation or anesthesia as they cannot hold their breath, however, acquisition of real time sequences during free breathing has recently been shown to be feasible even in the youngest awake children (20,102). Disadvantages of CMR are that it requires specific expertise and that this modality is not yet generally available on a global scale. However, in view of the extensive and expanding possibilities, CMR is progressively establishing its role in the evaluation of children with PAH.

Clinical implications

The reviewed prognostic biomarkers reflect different aspects of the disease process and functional implications of the disease. In day-to-day clinical practice, assessment of disease severity and evaluation of treatment efficacy is not based on the result of one of the reviewed prognostic biomarkers, but on the interpretation of the composite result of multiple clinical measurements that also include parameters reflecting how patients feel and function (that might not carry direct prognostic value in terms of mortality risk).

During serial editions of the World Symposia on PH (WSPH), the pediatric task force has proposed (and updated) a WSPH pediatric risk assessment tool in which a set of “risk criteria” are defined on the basis of expert

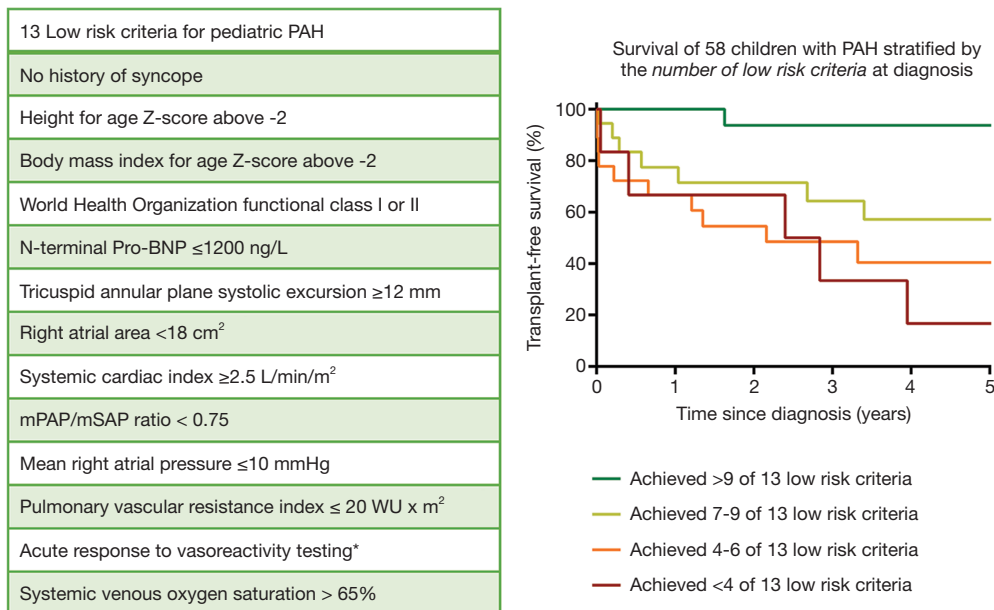


Figure 1 Survival of a cohort of 58 children from the Dutch National Network for Pediatric Pulmonary Hypertension with idiopathic or heritable pulmonary arterial hypertension stratified by the counted number of low risk criteria (103). *, vasodilator response according to Sitbon criteria. PAH, pulmonary arterial hypertension; BNP, brain natriuretic peptide; mPAP/mSAP, ratio of mean pulmonary arterial pressure to mean systemic arterial pressure.

consensus supported by the emerging evidence from observational studies (4). The prognostic value of this risk assessment tool has recently been evaluated in a national cohort of pediatric patients with PAH (103). The results demonstrated that the number of low-risk criteria, as defined in the WSPH pediatric risk stratification tool, present at diagnosis indeed accurately predicted the risk of mortality in children with idiopathic or heritable PAH. To illustrate, the recommended low risk criteria are listed in *Figure 1*. Reaching or preserving a low-risk profile during follow-up was associated with improved survival, suggesting that this low-risk state could be strived for as a multidimensional treatment goal in pediatric PAH.

Concluding remarks

Assessment of prognosis is key in designing an optimal and personalized treatment strategy for the individual child with PAH. In recent years, multiple potential prognostic biomarkers have become available for the management of PAH in children. As the available prognostic biomarkers reflect different aspects of the disease process and functional implications, a multi-marker approach appears the most

useful for guiding therapy decisions and improve outcome in pediatric PAH.

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