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PULMONARY HYPERTENSION (JR KLINGER, SECTION EDITOR)

# Biomarkers and Prognostic Indicators in Pulmonary Arterial Hypertension

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**Abstract** Our understanding of the pathophysiology of pulmonary arterial hypertension (PAH) has increased substantially in the past decades. More accurate diagnosis and increased options for treatment have given researchers the opportunity to better explore the response to medical therapy and prognosis. As a result, the use of biomarkers and prognostic indicators for this devastating disease has been widely investigated. Biomarkers and prognostic indicators have also been more frequently incorporated into the design of new clinical trials. This approach has helped the pulmonary hypertension (PH) community step forward in the search for effective treatments for PAH. However, no single biomarker has shown significant superiority in predicting prognosis or patient response and an integrative approach is necessary to understand which combination of markers should be used in each of the clinical scenarios that characterize the management of PAH.

**Keywords** Biomarkers · Prognostic markers · Natriuretic peptides · Exercise testing · Cardiac magnetic resonance · Pulmonary arterial hypertension

## Introduction

The management of pulmonary arterial hypertension (PAH) has changed greatly in the last 20 years, since the development of new treatments that significantly altered the natural course of the disease [1]. The possibility of combination therapy (using multiple drugs that specifically target different pathophysiological pathways) has also improved the treatment management of PAH patients [1–3]. However, intuitive it may seem, these treatment strategies call for proper efficacy assessment. For most comparison studies, survival would be the ideal primary endpoint. However, it is difficult to show small changes in survival benefit in low-prevalence diseases such as PAH. Furthermore, scientists have been challenged by different responses to treatments in patients who share the same diagnosis and clinical profile. This has prompted the need to seek reliable prognostic indicators, both at time of diagnosis and during the course of treatment [4].

Due to the expense and invasive nature of pulmonary artery catheterization and the limited prognostic abilities of most hemodynamic values, the use of surrogate markers would be helpful for assessing a patient's prognosis and monitoring response to treatment. A surrogate marker should be a reliable substitute for a relevant event, keeping a steady tracking with the frequency of such event as an epidemiologic and a therapeutic response marker [1]. Depending on its strength, it may also be used as part of a screening algorithm or diagnostic investigation in specific high-risk populations. Many surrogate markers have been described in PAH, from exercise testing to imaging procedures, to circulating proteins [4]. In this article, we aim to discuss the usefulness and relevance of the most commonly used biomarkers and prognostic indicators in PAH (Table 1).

Pulmonary hypertension may be a consequence of numerous changes in the cardiorespiratory system that results in increased pulmonary arterial pressure. These changes can include primary changes in the pulmonary vessels, left heart dysfunction, chronic hypoxia, pulmonary thromboembolism, and inflammation [5]. The characterization of such changes is

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**Table 1** Most used biomarkers and prognostic indicators in PAH

| Variable | Indicator of better prognosis |
|---|---|
| Functional class | I or II |
| Quality of life | SF-36 with PCS >32 baseline or >38 follow-up |
| Echocardiography/CMR | Normal/near-normal RV size and function |
| | TAPSE >1.8 cm |
| | RVEF >35 % |
| Hemodynamics | RAP <8 mmHg |
| | CI >2.5 to 3.0 L/min/$m^2$ |
| 6MWD | >380 to 440 m |
| Serum markers | Near normal NT-proBNP/BNP[a] |
| | Undetectable troponin |
| | Normal renal function |
| CPET | Peak VO2 >15 mL/min/kg |
| | $EqCO_2$ <45 L/min/L/min |

*6MWD* 6-min walk distance test, *CPET* cardiopulmonary exercise test, *CMR* cardiac magnetic resonance, *Peak VO2* peak oxygen consumption, *RV* right ventricle, *RAP* right atrial pressure, *CI* cardiac index, *TAPSE* tricuspid annular plane systolic excursion, *RVEF* right ventricular ejection fraction, *SF-36* Short-Form 36 Health Survey questionnaire, *PCS* physical component score

[a] Threshold level might differ depending on the methodology used for the measurement

the basis for the adequate classification of a patient with pulmonary hypertension and, ultimately, for the appropriate treatment [6]. PAH is defined by the presence of mean pulmonary arterial pressure ≥25 mmHg with pulmonary artery occlusion or left heart filling pressure <15 mmHg, therefore a precapillary pattern, in the absence of pulmonary parenchymal or thromboembolic disease [1] [7] [8]. The vascular remodeling process that is characteristic of PAH affects predominantly small pulmonary arteries decreasing vascular compliance and increasing pulmonary vascular resistance [9], hence increasing right ventricular afterload. The dysfunctional right ventricle is eventually responsible for most of the clinical and functional limitations seen in PAH and is the main cause of death in this population (Fig. 1) [10].

## Prognostic Indicators

### Functional Class

The modified New York Heart Association Functional Class (NYHA FC) has been found to be an important predictor of survival in PAH. The WHO modification of the NYHA FC uses a scale of I to IV, where I is no symptoms, II is dyspnea with normal activity, III is dyspnea with less than normal activity, and IV is dyspnea with any activity or while at rest. Over the years, many papers have confirmed, in different degrees of strength, the role of FC as a baseline and follow-up surrogate marker for prognosis. The greater the FC (from I to IV), the worse the prognosis [11]. The potential weakness of FC is that it is a subjective measure determined by the clinician and has poor interobserver reliability [12]. There is also considerable variation related to gender, age, and ethnicity. Patients with FC I or II have a better prognosis than those with FC III or IV, both at diagnosis and follow-up [13•], reinforcing the importance of early diagnosis in a condition with high mortality rate such as PAH [14].

### Quality of Life Assessment

PAH is known to have a significant impact on patient quality of life [15]. The assessment of health-related quality of life is an attempt to decrease the mentioned subjectivity of functional class determination addressing the impact of the disease on daily life through a more comprehensive evaluation. There are several instruments to evaluate health-related quality of life in PAH, some generic and one specifically developed for PAH [16] [17]. A recent study demonstrated that the Short-Form 36 Health Survey questionnaire (SF-36) was a valuable tool to demonstrate treatment response after specific intervention in PAH and was also associated with survival. Patients presenting a physical component score >32 at baseline or higher than 38 at the follow-up presented better prognosis compared to patients that did not reach these levels [18•]. These data suggest that quality of life assessment might provide significant information in the daily management of PAH patients.

### 6-Minute Walk Distance Test

The 6-minute walk distance (6MWD) is a relatively simple, reproducible, reliable, and safe test for PAH patients. Over the years, it has been used as primary endpoint for several seminal

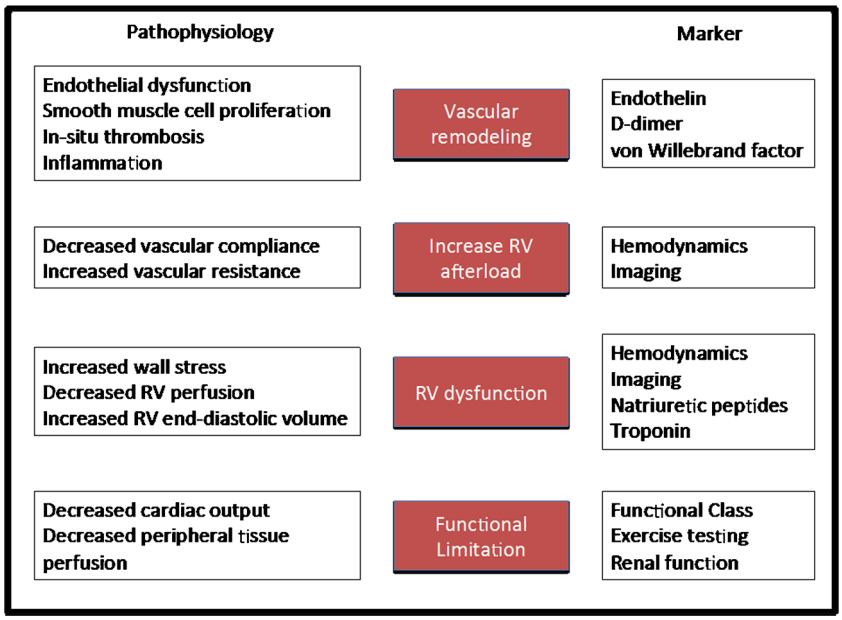


**Fig. 1** Main prognostics indicators in PAH according to pathophysiology

PAH studies and it bears a significant correlation with exercise capacity, hemodynamics, and survival [4]. However, it has been a matter of debate if one should consider the absolute distance walked or a patient's change from baseline after treatment as the better parameter to be taken into consideration [19]. In a meta-analysis of clinical trials in PAH, Savarese and colleagues demonstrated that changes in 6MWD after therapeutical intervention were not associated to short-term clinical events. A different meta-analysis also failed to demonstrate an association between the changes in 6MWD and the short-term course of PAH patients [20••]. Furthermore, some populations have different 6MWD performances for the same diagnosis, FC, and even hemodynamics that may, in part, be explained by selection bias and/or sociocultural differences [8]. Nevertheless, there is consensus that patients who walk between 380 and 440 m have better prognosis [4]. In summary, 6MWD is an important marker of exercise capacity in PAH; although the validity of improvements in response to treatment is questionable, there appears to be specific thresholds that should be considered as treatment goals [4].

## Cardiopulmonary Exercise Testing

Cardiopulmonary exercise testing (CPET) is an effective way of evaluating maximal exercise capacity in patients with PAH through determination of peak oxygen consumption, which is related to survival [21]. The VO2 reflects the integration of cardiac function, muscular efficacy, and ventilator capacity, offering a valuable insight of the resultant PAH impact on a subject's overall heath. Patients who present a VO2 <10 mL/kg/min have poor prognosis, and those with a VO2 >15 mL/kg/min have a better prognosis. CPET has also been used as a guide to goal-oriented therapy, reflecting changes over time according to the treatment response [22].

## Echocardiography

Transthoracic echocardiography (TTE) is a widely available tool in PAH clinics worldwide. Over the years, some parameters have been investigated and used to establish prognosis, both at the time of diagnosis and during follow-up. The first parameter associated with poorer prognosis was the presence of pericardial effusion. A recent study, evaluating 200 consecutive cases of PAH, demonstrated that patients with pericardial effusion at baseline had worse hemodynamic profiles and were more prone to present with underlying connective tissue disease. Moreover, the persistence of pericardial effusion after treatment was an independent marker of decreased survival [23].

Some parameters of right ventricle (RV) function such as the tricuspid annular plane systolic excursion (TAPSE) and RV measurements (RV strain or area) have also been shown to predict patient outcome. Forfia et al. demonstrated that low TAPSE (<1.8 cm) was associated with a worse hemodynamic profile and, most importantly, worse outcome, suggesting that longitudinal shortening of the RV is a significant marker of right ventricular dysfunction [24]. However, the use of echocardiography for obtaining prognostic indicators in PAH is limited by the ability of the ultrasound sonography and reader to properly obtain and interpret the proper images. Depending on the patient's body habitus, adequate imaging may not always be possible. Thus, echocardiographic assessment of RV function is best used as one of several markers of disease severity or response to treatment.

### Cardiac Magnetic Resonance

Cardiac magnetic resonance (CMR) may provide the best assessment of RV structure and volumes [25] and has been increasingly used as a research tool to predict outcome and assess response to treatment. Over the course of the disease, there are several changes in the structure and function of the RV that can be assessed by CMR. Moreover, some of these structural and functional markers are independently associated with survival, suggesting that right ventricular remodeling is an independent process that should be considered in the course of the disease.

Van de Veerdonk et al. demonstrated that the presence of decreased right ventricular ejection fraction (<35 %) was associated with worse survival, independently of the baseline hemodynamic profile, suggesting that the right ventricular response to the increased afterload is an important predictor of outcome in PAH [26].

Van Wolferen et al. also demonstrated that patients with low stroke volume index and elevated right ventricular end-diastolic volume determined by CMR had worse survival. Furthermore, during follow-up, these markers remained independently associated with survival [27]

Beyond the RV, CMR also allows the dynamic evaluation of the pulmonary arteries. Jardim et al. demonstrated that the changes in the cross-sectional area of the main pulmonary artery during the cardiac cycle were directly related with the acute response to vasodilators [9], suggesting that the capacitance of the vascular system was an important variable to be assessed.

Although all these data suggest that CMR should have widespread use in PAH, the high costs and limited availability of the test still impair such recommendation.

### Hemodynamics

Invasive hemodynamic evaluation is of paramount importance in PAH; not only is it necessary for proper diagnosis, but the measurements obtained provide some of the most significant prognostic markers. Since the first registries, cardiac index and right atrial pressure have strongly reflected the burden of the disease to the individual [28]. Contemporary registries have reinforced the role of hemodynamic assessment as a determinant of long-term prognosis in PAH [29] [30]. Notably, patients presenting with mixed oxygen saturation >65 %, cardiac index >2.5 L/min/$m^2$, and right atrial pressure <8 mmHg have a favorable prognosis.

Furthermore, invasive hemodynamic measurements play a prominent role in the determining the lung allocation score for the selection of PAH patients who are candidates for lung transplantation [31].

## Biomarkers

### Uric Acid

Serum uric acid (UA) is the final product of purine degradation and may be elevated in different conditions of impaired oxidative metabolism. Serum UA levels correlate with hemodynamic measures in patients with PAH as well as exercise capacity. Two different studies also demonstrated that higher levels of UA are associated with poorer prognosis. The larger study addressing the significance of UA in PAH enrolled 90 idiopathic pulmonary arterial hypertension (IPAH) patients (35 males and 55 females), diagnosed through right heart catheterization, and followed them for a mean of 31 months. UA levels were higher in the IPAH group, as compared to an age-matched control group, and significantly correlated to disease severity, increasing in proportion to the NYHA functional class or pulmonary vascular resistance and decreasing in proportion to cardiac output, without significant difference between genders [32]. During follow-up, UA decreased in response to pulmonary vasodilator treatment and was independently associated with mortality. It is important to consider that serum UA levels are also affected by renal impairment or the use of diuretic therapy, which may prevent the extrapolation of these findings to some patients [33] [34].

### Troponins

Troponins are proteins that are involved in the process of cardiac muscle contraction, modulating calcium-mediated actin, and myosin interaction. Many different mechanisms are associated with cardiac troponin release, including increased wall stress and myocardial ischemia. Torbicki et al. evaluated 56 pulmonary hypertension (PH) patients (51 PAH and 5 patients with chronic thromboembolic PH) and found that patients with detectable troponin T levels had worse exercise capacity as assessed by 6MWD and worse 24-month prognosis. Interestingly, troponin levels became undetectable during the course of successful treatment but relapsed with disease progression [35].

More recently, Heresi et al., using a more sensitive assay for detection of troponin I, demonstrated that patients with detectable troponin I had lower 6MWD and more severe functional impairment. Also, 36-month transplant-free survival was significantly lower in patients with detectable troponin I (44 vs 85 %). Of notice, detectable levels of troponin I were found in 25 % of the evaluated patients, a much higher proportion compared to previous studies addressing the role of troponin in PH. If troponins are considered to be "late markers" of disease severity, it is possible that high-sensitivity assays for troponin could improve the prognostic capabilities of this class of biomarkers [36].

### Endothelin

Endothelin-1 is a potent endogenous vasoconstrictor and smooth muscle mitogen that is overexpressed in the setting of PH. ET-1 is mainly produced by endothelial cells, with the pulmonary circulation as the most important site of production and clearance. Two different receptors for ETs have been identified, ET receptor A (ETA) and ET receptor B (ETB). In the pulmonary vessels, ETA is expressed on pulmonary smooth muscle cells, and ETB is expressed on pulmonary endothelial and smooth muscle cells. Activation of ETA or ETB on pulmonary vascular smooth muscle cells induces pulmonary vasoconstriction and smooth muscle cell proliferation. Rubens et al. demonstrated that plasma levels of ET-1 correlate with hemodynamic measurements with higher levels being associated with higher pulmonary vascular resistance and mean pulmonary artery pressure and with lower cardiac output and 6MWD. In another study, an elevated ratio of ET-1 and ET-3 (another isoform of endothelin that might be involved in the clearance of ET-1) also correlated with hemodynamic measurements and was associated with poor prognosis [37].

Although ET-1 is recognized as one of the targets for the currently available therapies, the concept of using ET levels as guidance to therapy has not been appropriately tested.

### D-Dimer and von Willebrand Factor

Prothrombotic mechanisms have long been implicated in the pathogenesis of PAH. From endothelial dysfunction to direct platelet activation, many different pathways have been described in this setting [38].

The plasma D-dimer level is a marker of microvascular thrombosis established for the evaluation of patients with suspected acute pulmonary embolism. In the setting of PAH, D-dimer levels have been demonstrated to be higher than in controls and also to correlate with disease severity, although both studies included a remarkably small number of patients [39].

Plasma von Willebrand factor (vWF) is a glycoprotein synthesized in endothelial cells with a direct role in platelet aggregation and adhesion to injured sites. It has been demonstrated that vWF is not only elevated in PH, but also correlates with decreased survival [40]. Also, a different study demonstrated that improved proteolysis of vWF occurred in a small sample of patients under vasodilator treatment with prostacyclin and paralleled the improvement in pulmonary hemodynamics [41].

### Natriuretic Peptides

Type B natriuretic peptide is synthesized and released from the cardiac atria and ventricles as a pro-hormone and cleaved into active type B natriuretic peptide (BNP) and the N-terminal fragment referred to as (NT)-proBNP. Natriuretic peptides decrease intravascular volume by increasing systemic vascular permeability and inducing a natriuretic diuresis. They also relax vascular smooth muscle cell via increasing intracellular cGMP synthesis. Both effects act to reduce blood pressure and ventricular preload [42].

In PH, BNP levels increase in proportion to the degree of right ventricular dysfunction, as demonstrated in different forms of PH. Nagaya et al. demonstrated that BNP positively correlated directly with NYHA functional class, mean pulmonary arterial pressure, and pulmonary vascular resistance and correlated inversely with cardiac output. Moreover, lower baseline and posttreatment levels of BNP were associated with improved survival [43].

Leuchte et al. demonstrated that BNP levels correlate with exercise capacity at baseline [44] and after treatment [45]. The NT-proBNP fragment is more stable in plasma than BNP and has been described as a marker of PH in patients with systemic sclerosis. Plasma NT-proBNP has been shown to correlate with disease severity [46] as well as with treatment response [47] and with acute hemodynamic response to nitric oxide, in the setting of PAH [48].

Fijalkowska et al., evaluating 55 PH patients (36 IPAH), demonstrated that lower baseline levels of NT-proBNP were associated with better survival [49]. Leuchte et al. also addressed the potential confounding bias imposed by the presence of renal impairment on the accuracy of NT-proBNP as a hemodynamic surrogate in PH [45]. They found that NT-proBNP does not correlate with pulmonary hemodynamics in the presence of renal insufficiency but remains a prognostic indicator while BNP does not, suggesting that NT-proBNP might be superior to BNP as a prognostic marker in patients with renal impairment. A question that still remains is whether BNP or NT-proBNP is a useful biomarker in the early phases of PH. Considering that elevated levels of these peptides are a consequence of ventricular overload, they might also be considered as "late" markers of PH severity, in a similar manner to the troponins.

## Renal Function

The hemodynamic impairment characteristic of PAH creates a condition of chronic low tissue perfusion, predisposing to different systemic organ failures. Renal function, particularly, is an independent predictor of mortality in PAH [50]. Shah et al. demonstrated in a large cohort of PAH patients that the presence of a serum creatinine >1.4 mg/dL was associated with a hazard ratio of 2.54, compared to patients with levels <1.0 mg/dL. More recently, the REVEAL registry also demonstrated that renal insufficiency was independently associated with a worse prognosis in PAH [51]. Interestingly, hyponatremia has

also been associated with worse outcome in patients with PAH (Hassoun P et al.).

## Conclusions

There is substantial evidence that several biomarkers and prognostic indicators can help to establish prognosis at time of diagnosis in PAH and help to assess the response to treatment. Many biomarkers currently used in the management of PAH have stood the test of time, having been confirmed as relevant surrogate markers for disease progression or recession. Because no particular biomarker appears to be superior to another, it is likely better that multiple biomarkers be used together to achieve the best assessment of disease severity and prognosis. Although presently available biomarkers do not obviate the need for right heart catheterization, they play a useful role in helping to assess prognosis and response to pharmacologic treatment. We believe that in the following years, new clinical trials and novel pathophysiological studies will strengthen the relevance of each of the discussed methods and discover new biomarkers that will help in the management of this devastating disease.

#### Compliance with Ethics Guidelines

**Conflict of Interest** Carlos Jardim declares no conflict of interest. Rogerio Souza reports personal fees from Actelion, Bayer, BMS, and GSK.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance


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