Symposium: Pulmonary hypertension in the elderly  
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Which prognostic factors should be used in pulmonary arterial hypertension in elderly patients?

Bahri Akdeniz
Department of Cardiology, School of Medicine, Dokuz Eylul University, Mithatpasa Street, Balcova/Izmir, Turkey. E-mail: bahri.akdeniz@deu.edu.tr

Abstract
In recent times, the prevalence of pulmonary arterial hypertension (PAH) is more commonly seen among elderly populations. The increased prevalence of hypertension, diabetes, obesity, arterial stiffness, as well as diastolic dysfunction, may cause endothelial dysfunction and affect pulmonary vasculature. Furthermore, older patients have certain differences in clinical characteristics and outcomes. In this article, the special characteristics of aging in PAH patients have been reviewed, while the risk predictors of elderly patients are also discussed.

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1 Introduction
Pulmonary arterial hypertension (PAH) is still an incurable and fatal disease, despite the improvements in treatment modalities over the last decade. According to the National Institute of Health (NIH) registry report of 2 decades ago,[1] estimated median survival of patients with idiopathic PAH (IPAH), familial PAH, and anorexigenic-associated PAH was 2.8 years after diagnosis, with 1, 3 and 5-year survival rates of 68%, 48%, and 34%, respectively. The treatment goals of patients with PAH are achieving a low risk status and a low mortality risk. The survival rate of PAH has improved at this time; 1 year survival rate was 91% in prevalent patients in the REVEAL registry with a 3-year survival rate of 58.2% in pulmonary hypertension connection (PHC) cohort.[2,3] Factors determining survival in PAH are important for clinical management. Several prognostic factors have been described in clinical trials and registries.[4–9] These factors are based on certain demographic, functional, laboratory, and hemodynamic parameters.

PAH is now more frequently diagnosed in elderly patients compared to previous decades. Pulmonary artery systolic pressure (PAPs), similar to arterial pressure, was shown to be increased with age in subjects from the general community. Other physiological changes developed in the elderly including left ventricular diastolic dysfunction, arterial stiffening, and reduced lung capacity increase the complexity of clinical findings and prognosis. The increased prevalence of hypertension and diabetes due to aging maybe caused by endothelial dysfunction and also contributes the development of pulmonary hypertension. Prognostic risk factors in elderly patients with PAH have not been investigated previously. In this article, prognostic factors in all age groups with PAH were reviewed, and then certain special situations pertaining to elderly patients are also discussed.

2 Epidemiology and properties of pulmonary hypertension in the elderly
The phenotype of PAH has changed in recent decades. These include changes in age, sex, co-morbidities, and survival. Registry data indicate that the mean age of patients diagnosed with PAH has increased from 36 years two decades ago to 50–55 years at present.[4–7] Additionally, the proportion of elderly patients at the time of diagnosis has increased, with 9% of patients older than 70 years, and 12.8% older than 65 years.[6] The possible explanations of this changing picture may be due to aging of populations, the increase in life expectancy and the increased awareness of PAH.[10] Routine use of Doppler echocardiography to screen patients admitted to unexplained dyspnoea and syncope may also play an important role in diagnosing elderly pulmonary hypertension (PH) patients.

In an epidemiologic study, PAPs was shown to increase with age. It was influenced by increased pulse pressure and left heart filling pressures, suggesting that age associated blood vessel stiffening and diastolic dysfunction contribute to changes in pulmonary artery pressure.[11] William Osler’s
axiom that “Man is as old as his arteries” referred specifically to arterial stiffening. It may postulate that the possible mechanism for the association of arterial and pulmonary hypertension could be an exaggerated endothelial response to vasoconstrictor stimuli, both systemic and pulmonary circulation. Additionally, pulmonary vasculature may be affected by age-associated arterial remodelling, leading to pulmonary vascular stiffening and increases in PAPs.

PH associated with heart failure with preserved ejection fraction (HFpEF) is an increasingly recognized cause of PH in older adults. Consequently, many co-morbid conditions such as hypertension, diabetes, left ventricular diastolic dysfunction, arterial stiffening and sleep apnoea syndrome may coexist in elderly PH patients. Additionally, aortic sclerosis is common in the elderly and is associated with an increased risk of death from cardiovascular causes even in the absence of hemodynamically significant obstruction of the left ventricular outflow. Pulmonary hypertension is also associated with aortic sclerosis in the elderly. Insulin resistance (IR) has been implicated in inflammation, endothelial dysfunction and vascular disease and is strongly associated with adverse clinical outcomes. Unrecognized glucose intolerance and IR are common in PAH. However, there was no correlation between IR or glucose intolerance and prognostic markers in PAH.

Obesity and metabolic syndrome or related comorbidities may play a role in the development of PAH. Unrecognized glucose intolerance is common in pulmonary arterial hypertension. Even in non-obese humans with IPAH, the prevalence of insulin resistance is nearly 50% suggesting a link between glucose dysregulation and IPAH. The correlation of weight loss and hemodynamic improvements with the reduction of insulin resistance, improved exercise tolerance and functional class and reduced PAP has been reported after bariatric surgery in patients with IPAH.

Alveolar hypoxia and hypoxic pulmonary vasoconstriction is thought to be the main mechanism responsible for the development of PH in obesity hypoventilation syndrome. The increased incidence of systemic hypertension with HFpEF feature may contribute the development of pulmonary vasculopathy. On the other hand, obesity may cause restrictive physiology, possibly due to fatty deposition. This situation may contribute to the excessive increase at pulmonary arterial pressure, as well as right atrial pressure. Severe tricuspid regurgitation, mimicking constrictive pericarditis physiology, may cause similar condition.

Aging also affects the respiratory system, with reduced static elastic recoil of the lung, as well as increased chest wall stiffness. These changes cause decreased vital capacity and increased air trapping. Normal aging could either lead to an over-diagnosis of PH or an underestimation of PAH in this population. The main problem in the diagnosis of PH in an elderly patient lies in the discrimination of potential pulmonary vascular disease from the expected consequences of aging and from the frequent causes of PH secondary to left heart failure or lung disease. Endocrine factors may affect pulmonary vasculature. Renal function declines markedly due to aging, even in the absence of renal disease. Decreasing renal function may also contribute to the elevation of pulmonary pressure in elderly people.

Older patients have some differences in terms of their clinical characteristics and outcomes. Older patients with PAH are more likely to be diagnosed with a more advanced stage of the disease, have lower exercise capacity and present with multiple co-morbidities. They also have a lower survival rate compared with younger patients. Despite increasing prevalence in recent years, IPAH is less frequent among elderly PH patients. In a study, connective tissue disease was found to be the most frequently encountered reason of PAH in the elderly. Age at disease onset is a risk factor for PAH in scleroderma. PAH was found to be twice as frequent in elderly scleroderma patients compared to younger patients. Thus, the higher frequency of scleroderma and late diagnosis in the elderly may contribute to the poor prognosis in patients with PH. PH due to left heart disease and mixed disease are also common, while idiopathic PAH is unusual in this cohort. Older patients have lower exercise capacity and functional capacity, although better hemodynamic parameters including reduced mean PAP and pulmonary vascular resistance.

Table 1. Prognostic surrogates in PAH.

| Risk equations | Biomarkers | Hemodynamics | Imaging | Exercise capacity |
|----------------|------------|--------------|---------|------------------|
| NIH registry, French National Registry, PH connection registry, REVEAL registry equation | BNP, NT-proBNP, cardiac troponin, uric acid, DLCO | RAP, CI, PVR, PA capacitance, MVO2, SBP | CMR: RV stroke volume and mass, RVEF, RVEDV | 6MWD Cardiopulmonary exercise testing |
| Echoangiography: pericardial effusion, RV size | TAPSE, Tei index | Functional classification | 6MWD: 6-minute walk distance | Cardiopulmonary exercise testing |
| Right atrial pressure; RV: right ventricular; RVEF: right ventricular ejection fraction | SBP: systolic blood pressure | | | Cardiopulmonary exercise testing |

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3 Prognostic factors

To date, several prognostic factors in PAH have been described in clinical trials and registries.[23-25] These factors are often used to make decisions about the treatment strategy of the disease. Older age was also associated with a two-fold increase in mortality.[23] Both COMPERA and UK and Ireland PH registries revealed lower survival rates in older patients,[19-21] although it is unknown whether the causes of death differed between the younger and older patients. The presence of multiple co-morbidities may mask the symptoms of PAH and could account for late diagnosis of PAH in elderly patients and poorer survival rates.

4 Functional capacity

Functional capacity (FC) is regarded as being the most important factor for predicting mortality. FC class IV has been found to be a major risk factor for mortality in the REVEAL registry.[23] Functional class III is also an important, but weak predictor of survival. The median survival time is 6 years among FC I or II patients, compared with 2.5 years and 6 months for FC III and FC IV respectively.[24-26] However, there are several limitations regarding the evaluation of functional capacity. Determination of FC is a low-cost but subjective measure; the evaluation varies from physician to physician. Indeed, inter-observer variability may be observed, especially when differentiating between FC II and III. Additionally, deterioration of functional class may be due to reasons other than worsening of PAH. Other intervening or chronic disorders frequently encountered in the elderly, including anaemia, diastolic dysfunction, arrhythmias, pneumonia, rheumatologic problems, should be considered while evaluating functional capacity.

5 Exercise capacity

Six minute walking distance (6MWD) is routinely used for evaluating exercise capacity in PAH patients. Baseline exercise capacity is an important factor for predicting survival in REVEAL registry; 6MWD thresholds of greater than 440 m are associated with longer survival, and lower than 165 m with increased mortality.[23] Based on this data, the latest ESC guideline divided patients into three risk groups according to 6MWD.[27] Although reproducible, inexpensive, and simple to perform, the 6MWD has several limitations, in that it is effort-dependent and susceptible to motivational factors, especially in FC I and II patients. In addition, older patients have reduced exercise capacity, displaying lower 6MWD values, probably due to more co-morbidities.[9] Older patients with PAH are diagnosed with a more advanced, severe disease; older patients generally have a more severe functional class.[7] Rheumatologic knee and hip disease, neurologic problems and disability may even prevent walking, resulting in an inability to use this test with elderly patients. 6MWD can, however, be predicted adequately using a clinically useful model in healthy elderly subjects.[19] Using the Borg dyspnoea index and pulse O2 saturation may increase the prognostic yields of this test. Additionally, results of the 6MWD may be interpreted more adequately if expressed as a percentage of the predicted value.

Although 6MWD and other end points are considered potential surrogates for assessing the survival rate of patients with PAH, the change in 6MWD at the follow-up or after treatment was not found to affect survival. Cardiopulmonary exercise testing is considered to be the reference standard for functional assessment and maximal oxygen consumption (peak VO\textsubscript{2}) with proven value in assessing heart failure. However, the greater cost and numerous technical difficulties may reduce the use of this test for routine clinical practice.

6 Hemodynamic parameters

Right heart failure is the most frequent cause of death in PAH. Hemodynamic parameters obtained by right heart catheterization may give important information about prognosis in PAH. Right atrial pressure (RAP), cardiac index (CI), and mean pulmonary artery pressure (mPAP) were described as important predictors of survival in the 1st NIH registry.[3] Pulmonary vascular resistance (PVR) was found to be an important prognostic factor in most of the registries.[14] However, in contrast to the NIH registry, mean pulmonary artery pressure was not an important predictor of survival at rest in other registries. An inverse association between mPAP and mortality has been reported, and likely signifies worsening right ventricular function that leads to eventual decrease in the level of mPAP.[29,30] When adjusted for all other risk factors making up the final multivariable model, only an elevated mean RAP (> 20 mmHg) within the year preceding study enrolment, along with a markedly increased pulmonary vascular resistance (> 32 W), were independent risk predictors.[19] None of the PAH patients whose RAP < 10 mmHg died within one year.[30] A cut-off value of the cardiac index of greater than 2.5 L/min per square meters, or less than 2.0 L/min per square meters has been proposed as a determinant of good or poor prognosis; mean right atrial pressure as found to deliver the most reliable evidence for mortality in a systematic review that studied all hemodynamic variables.[31]
Although mean PAP was not found to be a prognostic risk factor for survival in the REVEAL registry, the prognostic value of systolic PAP estimated from the tricuspid regurgitant jet measured by echocardiography was shown to predict 5 year survival in patients with scleroderma in the EUSTAR cohort.[35] Hemodynamic impairment (mean PAP and PVR) appears to be less severe in older patients.[33] A possible explanation is that younger patients tend to have a right ventricle (RV) capable of preserving cardiac output at higher PVR than older patients; this ability of the right ventricle to generate high pressure falls with increasing age, resulting in older patients becoming symptomatic at lower PVR levels.[9] Despite this less severe hemodynamic impairment, older patients have a lower physiological reserve to cope with this disease than younger patients.[5]

7 The type of PAH

The type of PAH is extremely important for survival. The congenital PAH group has the best prognosis; possibly due to younger age presentation and greater RV adaptation. Scleroderma associated PAH had a poor survival rate and these patients often show less response to treatment than patients with idiopathic PAH.[33] In the REVEAL registry, portopulmonary hypertension and family history of PAH also serve as a poor prognosis.[5] Hereditary PAH with mutations in the bone morphogenetic protein receptor type 2 gene has been associated with more rapid disease progression, greater hemodynamic compromise at diagnosis, and earlier disease presentation, when compared to non-carriers of the mutation.[34] However, genetic screening is not recommended, due to low penetrance rate and the presence of multiple genetic variants.

8 Echocardiography and other imaging methods

The most important echocardiographic predictor in PAH is the presence of pericardial effusion (PE). The presence of pericardial effusion has been found to be an independent predictor of mortality in almost all registries. PE is known to flow back into the right atrium through lymph and venous drainage. However, when right atrial pressure increases, this backflow is limited, and this may cause pericardial effusion.[35] PE has been found to be associated with RAP in most registries. However, it may develop as a result of serositis in patients with connective tissue diseases (CTD) in the absence of increased right atrial pressure.[35] When patients were stratified by the underlying diseases, the presence of pericardial effusion was a significant predictive factor for IPAH cases, although no statistically significant difference was observed for CTD-PAH cases.[35] Echocardiography during exercise provides additional information: a marked increase of PAPs (> 30 mmHg) during exercise reflects better RV function and is associated with a better long-term outcome than when there is a modest increase or no increase.[36] Patients with PAH may have an unexpected deterioration due to progressive right heart failure. Monitoring RV volumes may predict clinical worsening despite an apparent stable condition. A gradual increase in RV end-diastolic volume and RV end-systolic volume and a decline in RV ejection fraction were shown in deteriorated patients; however, there were no such changes in the stable patients.[35,36] Other echocardiographic parameters reflect right ventricular function: tricuspid annular plane systolic excursion (TAPSE), right ventricular velocity in tissue Doppler, and right ventricular fractional area change (RVFAC) have been investigated for the prediction of survival in PAH. Inter-observer variability and/or conflicting results of these echo parameters prevented the wide use of these for ascertaining the prognostic risk factor in PAH. TAPSE reflects the RV longitudinal motion of RV. Values for TAPSE of less than 1.8 cm were associated with significantly worse survival at 1 and 2 years in patients with PAH.[37] However, it is influenced by the degree of tricuspid regurgitation, so it is excluded from the prognostic predictors list in the latest guidelines, despite having previously been present.[22]

Cardiac magnetic resonance (CMR) may give detailed information about RV function and RV volumes. Compared with echocardiography, CMR has low inter-observer variability, making it a better tool for assessing changes in RV volumes, size, and function over time, and with follow-up of patients after therapies.[38] Other important information about hemodynamic parameters, including stroke volume, cardiac output, pulmonary artery distensibility and stiffness, alterations in RV morphology, and patterns of fibrosis with disease progression can also be ascertained by CMR. However, routine use of this imaging modality is not particularly practical.

9 Biomarkers

Despite the challenges of identifying novel non-invasive markers or surrogates of the disease, the study of specific biomarkers for the detection of disease progression in PAH continues to be an active area of investigation. Evaluation of RV function is important for risk estimation. Elevated plasma brain natriuretic peptide (BNP) and N-terminal pro-BNP level are indicators of wall stress. These markers
have been found to be risk predictors in the prognosis of heart failure. Elevation of these markers were shown to correlate well with other important prognosticators reflecting advanced disease, including RAP, PVR, CI, 6MWD, and RV enlargement in patients with PAH. These two biomarkers are regularly used, both at baseline and with medical therapy, and they predict survival. The cut-off value discriminating poor survival was 180 mg/dL. An increase of Nt-ProBNP was shown to be associated with a poor prognosis and the greatest reduction in that has a strongest association with survival in PAH. BNP concentrations were significantly increased with aging. Measurements of BNP may provide prognostic information in elderly patients. Serum uric acid levels independently predict survival in patients with IPAH, and levels proportionally increase with greater severity of the disease and functional impairment. However, uric acid levels are less specific for PAH due to its being affected by multiple disease conditions, including renal failure or other hypoxemic states.

10 Survival equations

Prognostic equations have been developed from multivariable analyses in four registries (US REVEAL, Pulmonary Hypertension Connection Registry, French registry, and UK registry). Since the initiation of the 1st NIH registry, a number of equations have been created. From the retrospective analysis of risk predictors of the NIH registry, a regression equation was derived to estimate survival using three baseline hemodynamic parameters (mRAP, mPAP, and CI). However, this equation increased the risk of death compared to the observed survival rates of other analyses obtained from many clinical trials. The observed survival estimates with modern therapies appear to be significantly better. The PHC registry analyzed 576 patients with IPAH, familial, and anorexigenic associated PAH from 1991 to 2007. From this analysis, a new regression survival equation was developed that uses the same three hemodynamic variables as the NIH equation, albeit with different coefficients. This equation has been more evidently associated with actual observed survival rates in other published PAH cohorts compared to the previous NIH registry.

In the REVEAL registry, several risk factors were independently associated with increased mortality: elevated PVR, etiology of PAH, FC, a family history of PAH, renal insufficiency, RAP, resting SBP and HR, 6MWD, BNP, the presence of pericardial effusion on echocardiography, and percent predicted of DLCO. The REVEAL equation has thus been modified into an uncomplicated risk calculator, which is practical for clinicians.

11 Conclusions

The proportion of elderly patients is gradually increasing in the PAH population. The expected consequences of aging and frequent causes of PH secondary to left heart failure or lung disease may potentially contribute to pulmonary vascular disease in these patients. Regular assessment of risk factors in patients with PAH is, therefore, strongly recommended. Older patients have specific differences in terms of their clinical characteristics and outcomes. These patients have inherently lower exercise capacity, as well as better mPAP and PVR, possibly due to decreased right ventricular function. As a result, these parameters may be used carefully in elderly patients for risk calculation. These patients are also less responsive to PAH specific therapy compared to younger ones. Large scale studies or registries are needed to investigate the prognostic risk factors in elderly PAH patients.

References

1. Rich S, Dantzker DR, Ayres SM, et al. Primary pulmonary hypertension. A national prospective study. Ann Intern Med 1987; 107: 216–223.
2. McLaughlin VV, Suissa S. Prognosis of pulmonary arterial hypertension: the power of clinical registries of rare diseases. Circulation 2010; 122: 106–108.
3. Humbert M, Sitbon O, Yaici A, et al. Survival in incident and prevalent cohorts of patients with pulmonary arterial hypertension. Eur Respir J 2010; 36: 549–555.
4. Humbert M, Sitbon O, Chaouat A, et al. Pulmonary arterial hypertension in France: results from a national registry. Am J Respir Crit Care Med 2006; 173: 1023–1030.
5. Badesch DB, Raskob GE, Elliott CG, et al. Pulmonary arterial hypertension: baseline characteristics from the REVEAL Registry. Chest 2010; 137: 376–387.
6. Frost AE, Badesch DB, Barst RJ, et al. The changing picture of patients with pulmonary arterial hypertension in the United States: how REVEAL differs from historic and non-US Contemporary Registries. Chest 2011; 139: 128–137.
7. Ling Y, Johnson MK, Kiely DG, et al. Changing demographics, epidemiology, and survival of incident pulmonary arterial hypertension: results from the pulmonary hypertension registry of the United Kingdom and Ireland. Am J Respir Crit Care Med 2012; 186: 790–796.
8. Hurdman J, Condiffe R, Elliot CA, et al. ASPIRE registry: assessing the Spectrum of Pulmonary hypertension Identified at a Referral centre. Eur Respir J 2012; 39: 945–955.
9. Hoeper MM, Huscher D, Ghofrani HA, et al. Elderly patients diagnosed with idiopathic pulmonary arterial hypertension: Results from the COMPERA registry. Int J Cardiol 2013; 168: 871–880.
10. Lador F, Herve PA. Practical approach of pulmonary hyper-
tension in the elderly. *Semin Respir Crit Care Med* 2013; 34: 654–664.
11 Lam CSP, Borlaug BA, Kane GC, et al. Age-associated increases in pulmonary artery systolic pressure in the general population. *Circulation* 2009; 119: 2663–2670.
12 Thernappan T, Shah SJ, Gomberg-Maitland M, et al. Clinical characteristics of pulmonary hypertension in patients with heart failure and preserved ejection fraction. *Circ Heart Fail* 2011; 4: 257–265.
13 Gharacholou SM, Karon BL, Shub C, Pellikka PA. Aortic valve sclerosis and clinical outcomes: moving toward a definition. *Am J Med* 2011; 124: 103–110.
14 Otto CM, Bonne K, Lind MS, et al. Association of aortic-valve sclerosis with cardiovascular mortality and morbidity in the elderly. *N Engl J Med* 1999; 341: 142–147.
15 Naderi N, Boobejane P, Bakhshandeh H, et al. Insulin resistance in pulmonary arterial hypertension is it a novel disease modifier? *Res Cardiovasc Med* 2014; 3: e19710.
16 Zamanian RT, Hasmann G, Sook S, et al. Insulin resistance in pulmonary arterial hypertension. *Eur Resp J* 2009; 35: 318–324.
17 Pugh PE, Newman J, Williams B, et al. Hemodynamic improvement of pulmonary arterial hypertension after bariatric surgery: potential role for metabolic regulation *Diabetes Care* 2013; 36; e32.
18 Janssens JP, Pache JC, Nicod LP. Physiological changes in respiratory function associated with ageing. *Eur Resp J* 1999; 13: 197–205.
19 Van der Brugggen C, Spurijit, O, Trip P, et al. Cardiac function in idiopathic pulmonary arterial hypertension patients with a severely reduced diffusion capacity. *Eur Resp J* 2015; 46: PA2465.
20 Pugh ME, Sivarajan L, Wang L, et al. Causes of Pulmonary hypertension in the elderly. *Chest* 2014; 146: 159–166.
21 Rose JA, Minai OA, Cleveland JM, et al. Impact of age on pulmonary arterial hypertension studies, 2010; 122: 164–172.
22 D’Alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with primary pulmonary hypertension: results from a national prospective registry. *Am Intern Med* 1991; 115: 343–349.
23 Humbert M, Sitbon O, Chouaat A, et al. Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. *Circulation* 2010; 122: 156–163.
24 McGoon MD, Benza RL, Subias PE, et al. Pulmonary arterial hypertension epidemiology and registries. *J Am Coll Cardiol* 2013; 62: 51–59.
25 Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Rev Esp Cardiol* (Engl Ed) 2016; 69: 177.
26 Troosters T, Gosselink R, Decramer M. Six minute walking distance in healthy elderly subjects. *Eur Resp J* 1999; 14: 270–274.
27 Sitbon O, Humbert M, Nunes H, et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. *J Am Coll Cardiol* 2002; 40: 780–788.
28 Adachi S, Hirashiki A, Nakano Y, et al. Prognostic factors in pulmonary arterial hypertension with Dana Point group 1. *Life Sci* 2014; 118: 404–409.
29 Swiston JR, Johnson SR, Granton JT. Factors that prognosticate mortality in idiopathic pulmonary arterial hypertension: a systematic review of the literature. *Resp Med* 2010; 104: 1588–1607.
30 HachullaE, Cleson P, Airo P, et al. Value of systolic pulmonary arterial pressure as a prognostic factor of death in the systemic sclerosis EUSTAR population. *Rheumatology (Oxford)* 2015; 54: 1262–1269.
31 Kuhn K, Byme D, Arbgast PG, et al. Outcome in 91 consecutive patients with pulmonary arterial hypertension receiving epoprostenol. *Am J Respir Crit Care Med* 2003; 167: 580–586.
32 Rosenzweig EB, Morse JH, Knowles JA, et al. Clinical implications of determining BMPR2 mutation status in a large cohort of children and adults with pulmonary arterial hypertension. *J Heart Lung Transplant* 2008; 27: 668–674.
33 Miller AJ, Pick R, Johnson PJ. The production of acute peri-cardial effusion. *Am J Cardiol* 1971; 28: 463–466.
34 Grunig E, Tiede H, Enymayew EO, et al. Assessment and prognostic relevance of right ventricular contractile reserve in patients with severe pulmonary hypertension. *Circulation* 2013; 128: 2005–2015.
35 Forfia PR, Fisher MR, Mathai SC, et al. Tricuspid annular displacement predicts survival in pulmonary hypertension. *Am J Respir Crit Care Med* 2006; 174: 1034–1041.
36 Di Giugliano L, Dore R, Vespri V, et al. Pulmonary hypertension role of computed tomography and magnetic resonance imaging. *Ital Heart J* 2005; 6: 846–851.
37 Doust JA, Pietrzak E, Dobson A, et al. How well does B-type natriuretic peptide predict death and cardiac events in patients with heart failure: systematic review. *BMJ* 2005; 330: 625.
38 Blyth KG, Groenning BA, Mark PB, et al. NT-proBNP can be used to detect right ventricular systolic dysfunction in pulmonary hypertension. *Eur Resp J* 2007; 29: 737–744.
39 Vong Nooerdegraaf A, Vesterhof N, et al. Right ventricular ejection fraction and N Terminal pro BNP are both indicators of wall stress in pulmonary hypertension. *Eur Resp J* 2007; 29: 622–623.
40 Wallén T, Landahl S, Hedner T, Saito Y, Masuda I, Nakao K. Brain natriuretic peptide in an elderly population. *J Intern Med* 1997; 242: 307–311.

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Nagaya N, Uematsu M, Satoh T, et al. Serum uric acid levels correlate with the severity and the mortality of primary pulmonary hypertension. *Am J Respir Crit Care Med* 1999; 160: 487–492.

D’Alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with primary pulmonary hypertension: results from a national prospective registry. *Ann Intern Med* 1991; 115: 343–349.

Humbert M, Sitbon O, Chaouat A, et al. Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. *Circulation* 2010; 122: 156–163.

McLaughlin VV, Sitbon O, Badesch DB, et al. Survival with first-line bosentan in patients with primary pulmonary hypertension. *Eur Respir J* 2005; 25: 244–249.

Thenappan T, Shah SJ, Rich S, et al. Survival in pulmonary arterial hypertension: a reappraisal of the NIH risk stratification equation. *Eur Respir J* 2010; 35: 1079–1087.

McLaughlin VV, Suissa S. Prognosis of pulmonary arterial hypertension: the power of clinical registries of rare diseases. *Circulation* 2010; 122: 106–108.