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The prognostic impact of follow-up assessments in patients with idiopathic pulmonary arterial hypertension

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ABSTRACT: Current guidelines for the treatment of patients with idiopathic pulmonary arterial hypertension (IPAH) recommend basing therapeutic decision-making on haemodynamic, functional and biochemical variables. Most of these parameters have been evaluated as risk predictors at the time of diagnosis. The aim of the present study was to assess the prognostic impact of changes in these parameters after initiation of targeted therapy.

A cohort of 109 patients with IPAH who had undergone haemodynamic, functional and biochemical assessments at baseline and 3–12 months after initiation of pulmonary arterial hypertension (PAH)-targeted therapy, were followed for a median 38 months in order to determine predictors of mortality at baseline and during the course of their disease.

Within the observation period, 53 (48.6%) patients died and four (3.7%) underwent lung transplantation. Kaplan–Meier estimates for transplantation-free survival were 92%, 67%, and 51% at 1, 3, and 5 yrs, respectively. Among baseline variables, 6-min walk distance, right atrial pressure, cardiac index, mixed-venous oxygen saturation (S_{v,O_2}) and N-terminal-pro brain natriuretic peptide (NT-proBNP) were independent predictors of survival. During follow-up, changes in World Health Organization functional class, cardiac index, S_{v,O_2} and NT-proBNP proved significant predictors of outcome. When assigned to prognostic groups, improvements as well as deteriorations in these parameters after initiation of PAH-targeted therapy had a strong impact on survival. Measurements obtained at follow-up had a higher predictive value than variables obtained at baseline.

Changes in established predictors of outcome during the course of the disease provide important prognostic information in patients with IPAH.

KEYWORDS: Pulmonary hypertension, right heart catheterisation, survival, World Health Organization functional class

Idiopathic pulmonary arterial hypertension (IPAH) is a rare chronic disease characterised by progressive remodelling of the pulmonary vasculature which, left untreated, results in increased pulmonary vascular resistance eventually leading to right heart failure and death [1]. In recent years, numerous effective treatments have become available, with continued active research providing optimism for additional future therapeutic options [2–5]. Despite these advances, however, IPAH remains incurable, with many patients requiring combination therapy to achieve or maintain treatment goals [1, 6] and mortality rates remaining high [7, 8]. As a result, increasing emphasis has been placed on accurately assessing prognosis to assist in deciding upon treatment choice, subsequent monitoring and timely referral for lung transplantation.

In recent years, numerous studies have sought to identify reliable outcome predictors in patients with IPAH, ranging from World Health Organization (WHO) functional class, exercise parameters to haemodynamic values and various biomarkers. Earlier research in the National Institutes of Health (NIH) registry over 20 yrs ago identified right atrial (RA) pressure, cardiac index, and mean pulmonary artery pressure ($\bar{P}_{pa}$) at the time of diagnosis as predictors of survival [9]. Several subsequent studies have confirmed in the interim that RA pressure, cardiac index and mixed-venous oxygen saturation (S_{v,O_2}) are powerful and robust independent

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predictors of mortality [8–11]. Furthermore, certain noninvasive prognostic parameters have been widely studied, including WHO functional class, 6-min walk distance (6-MWD) and serum biomarkers, such as brain natriuretic peptide (BNP) and its N-terminal fragment NT-proBNP [8, 11–18]. Based on the available data, best-practice decision-making currently relies upon this constellation of clinical, biochemical and haemodynamic parameters. The current European guidelines for pulmonary hypertension extend their role further, suggesting use of these parameters in categorising patients as stable and satisfactory, or unstable and deteriorating [19].

In addition, numerous attempts have been made to develop risk scores as predictors of outcome based on these variables. Almost all risk scores developed thus far have relied entirely on baseline measurements, *i.e.* at time of diagnosis prior to initiation of pulmonary arterial hypertension (PAH)-targeted therapy [8, 10, 11]. Several bodies of evidence suggest however, that long-term survival of IPAH patients is principally dependent upon their individual response to targeted therapy [12–14]. In the present study, we analysed the prognostic implications of changes in haemodynamic, functional and biochemical parameters during the course of the disease.

METHODS

Setting, patients and treatment

Hanover Medical School is a tertiary referral centre for IPAH patients. Beginning at the time of first diagnostic heart catheterisation, all relevant patient data has been prospectively gathered on an ongoing basis since 1999. Plasma and serum samples were collected during each cardiac catheterisation and frozen at -80°C for future analyses. This approach has been approved by the local institutional review board (Hanover Medical School) and all patients provided written informed consent, which was renewed at each follow-up catheterisation.

For the purpose of the present study, we selected from our database all patients with newly diagnosed IPAH between 1999 and 2009 who had undergone at least one follow-up right heart catheterisation within the first year after PAH-targeted therapy had been initiated. The date of the first post-baseline catheterisation was defined as first follow-up and all other assessments relevant for this study were performed within 24 h of the right heart catheterisation. Functional class assessment and 6-MWD measurement were usually performed on the day before the catheter study and blood samples were obtained during catheterisation. All patients were followed until October 1, 2010.

The diagnosis of IPAH (referred to as primary pulmonary hypertension until 2003) was made in accordance with the standards of the respective time periods [19, 20–22]. Diagnostic workup consisted of echocardiography, pulmonary function testing, chest radiography and ventilation–perfusion scanning. To exclude other forms of PAH, various laboratory studies, chest computed tomography angiography, and/or pulmonary angiography were performed, if necessary. In order to ensure a homogeneous patient population, patients aged <18 yrs and >75 yrs were excluded. In addition, patients fulfilling the criteria for calcium-channel blocker responders [23, 24] were also excluded.

Treatment strategies evolved during the observation period as novel therapies became available. Prior to 2002, inhaled, oral and intravenous prostanoids were the mainstays of treatment. Since 2002, a goal-oriented treatment strategy has been applied using endothelin receptor antagonists, phosphodiesterase-5 (PDE-5) inhibitors and prostacyclin derivatives in predefined, but varying, orders [6].

Handling of data and statistical analyses

Patient data are presented as absolute numbers, percentages, mean±SD or median (interquartile range (IQR)). Changes in functional, haemodynamic or biochemical variables between baseline and the first follow-up were compared by Spearman rank correlation for continuous variables and t-test for WHO functional class. For the purpose of this study, follow-up was defined as the date of the first right heart catheterisation after initiation of PAH-targeted therapy. All other follow-up variables (WHO functional class, 6-MWD, biomarkers) were obtained at the same time point. Statistical calculations were performed with GraphPad PRISM 5.0 for Windows (GraphPad Software, La Jolla, CA, USA), or SPSS 18 (SPSS, Chicago, IL, USA). For all analyses, p-values <0.05 were considered statistically significant.

The combined outcome end-point was death or lung transplantation. The following variables were analysed as possible predictors of adverse outcome based on previously published evidence: WHO functional class, 6-MWD, biochemical variables including serum sodium, creatinine, blood urea nitrogen (BUN), uric acid, γ-glutamyltransferase, bilirubin, C-reactive protein (CRP), and red cell distribution width as well as haemodynamic measurements, *i.e.* RA pressure, $\bar{P}_{pa}$, cardiac index, pulmonary vascular resistance (PVR), stroke volume index, stroke volume/pulse pressure and S_{v,O_2}.

In order to evaluate the predictive value of these parameters at baseline and during follow-up, a sequential approach was implemented. Values obtained at baseline assessment were initially assessed by univariate Cox regression analysis. Identical analysis was performed to assess changes in these variables between baseline and follow-up. All variables with a p-value <0.05 were then tested in stepwise forward Cox regression analyses; variables were entered at a p-value of <0.05 and removed at a p-value of >0.10. In the first model, haemodynamic and biochemical variables were tested separately. A second model, incorporating all statistically significant variables from the univariate analysis, was then tested in multivariate stepwise forward modelling.

All variables identified within the univariate analyses as being significantly associated with survival at both baseline and follow-up were subsequently categorised into risk groups derived from the classification system proposed by the European Pulmonary Hypertension Guideline Group [19]: stable and satisfactory at baseline and during follow-up (group 1); not satisfactory at baseline but stable and satisfactory at follow-up (group 2); stable and satisfactory at baseline but deteriorating at follow-up (group 3); not satisfactory at baseline and unstable or deteriorating at follow-up (group 4). The criteria for classifying WHO functional class and cardiac index as stable and satisfactory or unstable and deteriorating were again adopted from the European guidelines on pulmonary hypertension [19]. Cut-off values for S_{v,O_2} and NT-proBNP were derived from receiver operator characteristic (ROC) analysis. These parameters were assessed with single

and multivariate Cox proportional hazard analysis hazard ratios (HRs) and are given as point estimate and 95% confidence interval (CI). Kaplan–Meier plots were used to illustrate the timing of events during follow-up in relation to the four categories defined above. Group differences in survival of the Kaplan–Meier curves were assessed by stratified log-rank tests (Mantel–Cox).

RESULTS

Data from 109 patients with IPAH were available from the time of diagnosis and 3–12 months after initiation of PAH-targeted therapy (table 1). These patients were selected from a cohort of 232 patients with IPAH treated during the observation period at our centre (123 patients were excluded because they had no follow-up catheter study during the first year after treatment initiation). Baseline characteristics as well as the survival rates of the included and excluded patients were comparable (see online supplementary data). Initial PAH-targeted therapies consisted of prostanoids (23%), PDE-5 inhibitors (47%), and endothelin receptor antagonists (30%). The interval between baseline and first invasive evaluation on therapy varied between 3–6 months in 81 (74%) patients and 6–12 months in 28 (26%) patients. The median follow-up was 38 months (IQR 25–70 months). Within the observation period, 53 (48.6%) patients died and four (3.7%) underwent lung transplantation. Kaplan–Meier estimates for transplantation-free survival were 92% at 1 yr, 81% at 2 yrs, 67% at 3 yrs, and 51% at 5 yrs.

Prognostic importance of baseline parameters

The results of the modelling of the prognostic importance of baseline parameters are presented in table 2.

Functional capacity

At baseline, high WHO functional class (HR 2.3, 95% CI 1.0–5.1; p=0.04) and low 6-MWD (HR 1.2, 95% CI 1.0–1.3; p=0.002) were associated with risk of death in the univariate analysis. In the multivariate model, only low 6-MWD (HR 1.5, 95% CI 1.0–1.8; p=0.04) was an independent predictor of mortality.

Haemodynamics

In the univariate analysis, high RA pressure (HR 1.2, 95% CI 1.0–1.3; p=0.001), low cardiac index (HR 1.7, 95% CI 1.4–2.6; p=0.01) and low S_{v,O_2} (HR 1.2, 95% CI 1.1–1.4; p=0.02) at baseline were associated with poor outcome. All three variables remained statistically significant in the multivariate model (HR for high RA pressure 1.1, 95% CI 1.0–1.3; p=0.001; HR for low cardiac index 1.8, 95% CI 1.4–2.3; p<0.001; and HR for low S_{v,O_2} 1.6, 95% CI 1.2–2.2; p<0.001).

Biochemical variables

In the single model, elevated levels of NT-proBNP (HR 1.3, 95% CI 1.1–1.6; p=0.04), bilirubin (HR 1.1, 95% CI 1.0–1.3; p=0.023), creatinine (HR 1.4, 95% CI 1.2–1.9; p=0.04), uric acid (HR 1.1, 95% CI 1.0–1.6; p=0.01) and CRP (HR 1.3, 95% CI 1.1–1.6; p=0.04) were associated with an increased risk. In the multivariate approach, only NT-proBNP (HR 1.2, 95% CI

TABLE 1 Patient characteristics at baseline and 3–12 months after treatment initiation

Variables	Patients with full data available n	Baseline values	Values at first invasive follow-up 3–12 months after initiation of therapy	p-value
Age yrs	109	55 (42–68)		
Female %	109	78		
WHO functional class	100	3±0.6	3±0.4	0.41
6-MWD m	95	358 (300–432)	399 (330–450)	0.001
RA pressure mmHg	109	7 (3–11)	7 (3–11)	0.88
$\bar{P}_{pa}$ mmHg	109	52 (44–60)	52 (45–60)	0.55
Cardiac index L·min^{-1}·m^{-2}	109	2.0 (1.7–2.6)	2.2 (1.8–2.8)	<0.001
PVR dyn·sec·cm^{-5}	103	961 (675–1257)	940 (601–1188)	0.68
S_{v,O_2} %	109	62 (56–68)	63 (55–69)	0.85
SVI mL·m^{-2}·beat^{-1}	82	27.9 (21–33)	26.3 (19–37)	0.002
Capacitance mL·mmHg^{-1}	73	1.1 (0.7–1.2)	1.3 (0.8–1.7)	0.06
NT-proBNP ng·L^{-1}	84	1292 (300–3510)	1177 (474–2920)	0.02
Bilirubin μmol·L^{-1}	103	15	16 (9–25)	0.14
γGT U·L^{-1}	104	47 (24–95)	56 (31–113)	0.11
Creatinine μmol·L^{-1}	105	80 (68–96)	80 (67–100)	0.67
BUN mmol·L^{-1}	105	6.0 (4.7–7.5)	6.2 (4.5–7.5)	0.79
Uric acid μmol·L^{-1}	104	403 (321–521)	396 (309–487)	0.26
CRP mg·L^{-1}	83	5 (3–6)	5 (3–8)	0.03
RDW %	104	14.9 (13.7–16.1)	15.2 (14.2–17.1)	0.16
S-Na$^+$ mmol·L^{-1}	100	139.7 (138–142)	140.6 (139–143)	0.03

Data are presented as median (interquartile range) or mean±SD, unless otherwise stated. WHO: World Health Organization; 6-MWD: 6-min walk distance; RA: right atrial; $\bar{P}_{pa}$: mean pulmonary arterial pressure; PVR: pulmonary vascular resistance; S_{v,O_2}: mixed-venous oxygen saturation; SVI: stroke volume index; NT-proBNP: N-terminal pro-brain natriuretic peptide; γGT: gamma-glutamyltransferase; BUN: blood urea nitrogen; CRP: C-reactive protein; RDW: red cell distribution width; S-Na$^+$: serum sodium level.

TABLE 2 Results of univariate and multivariate proportional hazards modelling of baseline variables

Variables	Univariate model		Multivariate model	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Functional capacity				
WHO functional class	2.3 (1.0–5.1)	0.04		
6-MWD	1.2 (1.0–1.3)	0.002	1.5 (1.0–1.8)	0.04
Haemodynamic variables				
RA pressure mmHg	1.2 (1.0–1.3)	0.001	1.1 (1.0–1.3)	0.001
$\bar{P}_{pa}$ mmHg	1.0 (0.9–1.1)	0.18		
Cardiac index L·min^{-1}·m^{-2}	1.7 (1.4–2.6)	0.01	1.8 (1.4–2.3)	<0.001
PVR dyn·sec·cm^{-5}	1.0 (0.8–1.1)	0.42		
S_{v,O_2} %	1.2 (1.1–1.4)	0.02	1.6 (1.2–2.2)	<0.001
SVI mL·m^{-2}·beat^{-1}	0.96 (0.9–1.1)	0.11		
Capacitance mL·mmHg^{-1}	0.95 (0.6–1.4)	0.76		
Biochemical variables				
NT-proBNP ng·L^{-1}	1.3 (1.1–1.6)	0.04	1.2 (1.1–1.4)	0.04
Bilirubin μmol·L^{-1}	1.1 (1.0–1.3)	0.023		
γGT U·L^{-1}	1.0 (0.9–1.2)	0.07		
Creatinine μmol·L^{-1}	1.4 (1.2–1.9)	0.04		
BUN mmol·L^{-1}	1.1 (0.9–1.2)	0.06		
Uric acid μmol·L^{-1}	1.1 (1.0–1.6)	0.01		
CRP mg·L^{-1}	1.3 (1.1–1.6)	0.04		
RDW %	1.1 (0.6–1.2)	0.16		
S-Na$^+$ mmol·L^{-1}	1.07 (0.9–1.2)	0.19		

HR: hazard ratio; CI: confidence interval; WHO: World Health Organization; 6-MWD: 6-min walk distance; RA: right atrial; $\bar{P}_{pa}$: mean pulmonary arterial pressure; PVR: pulmonary vascular resistance; S_{v,O_2}: mixed-venous oxygen saturation; SVI: stroke volume index; NT-proBNP: N-terminal pro-brain natriuretic peptide; γGT: gamma-glutamyltransferase; BUN: blood urea nitrogen; CRP: C-reactive protein; RDW: red cell distribution width; S-Na$^+$: serum sodium level.

TABLE 3 Results of univariate and multivariate proportional hazards modelling of changes in variables between baseline and follow-up

Variables	Univariate model		Multivariate model	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Functional capacity				
ΔWHO functional class	2.0 (1.1–3.6)	0.02	1.4 (1.2–2.4)	0.04
Δ6-MWD	0.91 (0.94–1.1)	0.08		
Haemodynamic variables				
ΔRA pressure mmHg	0.98 (0.94–1.0)	0.37		
Δ$\bar{P}_{pa}$ mmHg	0.81 (0.69–1.1)	0.29		
ΔCardiac index L·min^{-1}·m^{-2}	2.1 (1.2–3.9)	0.01	1.8 (1.1–2.9)	0.02
ΔPVR dyn·sec·cm^{-5}	0.94 (0.8–1.2)	0.28		
ΔS_{v,O_2} %	2.1 (1.2–3.6)	0.008	2.2 (1.2–4.2)	0.01
ΔSVI mL·m^{-2}·beat^{-1}	1.3 (0.6–2.8)	0.49		
ΔCapacitance mL·mmHg^{-1}	1.2 (0.8–1.7)	0.5		
Biochemical variables				
ΔNT-proBNP ng·L^{-1}	2.4 (1.3–4.5)	0.003	1.3 (1.2–1.8)	0.007
ΔBilirubin μmol·L^{-1}	1.2 (0.9–1.3)	0.08		
ΔγGT U·L^{-1}	1.4 (0.8–2.5)	0.32		
ΔCreatinine μmol·L^{-1}	1.2 (0.6–2.0)	0.55		
ΔBUN mmol·L^{-1}	1.2 (1.1–1.3)	0.03		
ΔUric acid μmol·L^{-1}	1.3 (0.8–2.3)	0.25		
ΔCRP mg·L^{-1}	1.4 (0.7–2.7)	0.24		
ΔRDW %	0.9 (0.4–1.8)	0.79		
ΔS-Na$^+$ mmol·L^{-1}	1.1 (1.0–1.3)	0.03		

HR: hazard ratio; CI: confidence interval; WHO: World Health Orrganization; 6-MWD: 6-min walk distance; RA: right atrial; $\bar{P}_{pa}$: mean pulmonary arterial pressure; PVR: pulmonary vascular resistance; S_{v,O_2}: mixed-venous oxygen saturation; SVI: stroke volume index; NT-proBNP: N-terminal pro-brain natriuretic peptide; γGT,: gamma-glutamyltransferase; BUN: blood urea nitrogen; CRP: C-reactive protein; RDW: red cell distribution width; S-Na$^+$: serum sodium level.

1.1–1.4; p=0.04) remained an independent predictor of an adverse outcome.

Prognostic importance of changes between baseline and follow-up

The results of the modelling of the prognostic importance of changes between baseline and follow-up are presented in table 3.

Functional capacity

A deterioration in WHO functional class between baseline and follow-up doubled the risk of death (HR 2.0, 95% CI 1.1–3.6; p=0.02), whereas there was no statistically significant association of a decrease in 6-MWD and survival (HR 0.9, 95% CI 0.9–1.1; p=0.08). The same was true when we used a 6-MWD threshold of 380 m. In the multivariate model, deterioration in WHO functional class remained an independent predictor of poor outcome (HR 1.4, 95% CI 1.2–2.4; p=0.04).

Haemodynamics

Changes in RA pressure, $\bar{P}_{pa}$ and PVR from baseline to follow-up were not linked to survival, but deteriorations in cardiac index (HR 2.1, 95% CI 1.2–3.9; p=0.01) and S_{v,O_2} (HR 2.1, 95% CI 1.2–3.6; p=0.008) were significantly associated with a poor outcome both in the single and in the multivariate model (HR for a decline in cardiac index 1.8, 95% CI 1.1–2.9; p=0.02; and HR for a decline in S_{v,O_2} 2.2, 95% CI 1.2–4.2; p=0.01).

Biochemical variables

Increases in NT-proBNP (HR 2.4, 95% CI 1.3–4.5; p=0.003) and BUN (HR 1.2, 95% CI 1.1–1.3; p=0.03) were predictors of mortality in the single model. In the multivariate model, an increase in NT-proBNP remained independently associated with a higher risk of death (HR 1.3, 95% CI 1.2–1.8; p=0.007).

Risk group-assigned changes in variables from baseline to follow-up and outcome

The results of the risk group analysis are shown in table 4 and figure 1.

Cut-off values for categorising patients as satisfactory and stable or unstable and deteriorating for WHO functional class (class I and II *versus* III and IV) and cardiac index ($\geqslant$2.5 L·min^{-1}·m^{-2} *versus* <2.5 L·min^{-1}·m^{-2}) were obtained from

TABLE 4 Criteria for categorising patients as stable/satisfactory or unstable/deteriorating

	Stable/satisfactory		Unstable/deteriorating	
	Group 1	Group 2	Group 3	Group 4
WHO functional class	I–II at baseline and at follow-up	III–IV at baseline, I–II at follow-up	I–II at baseline, III–IV at follow-up	III–IV at baseline and at follow-up
Cardiac index	$\geq$2.5 L·min^{-1}·m^{-2} at baseline and at follow-up	<2.5 L·min^{-1}·m^{-2} at baseline, but $\geq$2.5 L·min^{-1}·m^{-2} at follow-up	$\geq$2.5 L·min^{-1}·m^{-2} at baseline, but <2.5 L·min^{-1}·m^{-2} at follow-up	<2.5 L·min^{-1}·m^{-2} at baseline and at follow-up
S_{v,O_2}	$\geq$65% at baseline and at follow-up	<65% at baseline, but $\geq$65% at follow-up	$\geq$65% at baseline, but <65% at follow-up	<65% at baseline and at follow-up
NT-proBNP	<1,800 ng·L^{-1} at baseline and at follow-up	$\geq$1,800 ng·L^{-1} at baseline, but <1,800 ng·L^{-1} at follow-up	<1,800 ng·L^{-1} at baseline, but $\geq$1,800 ng·L^{-1} at follow-up	$\geq$1,800 ng·L^{-1} at baseline and at follow-up

WHO: World Health Organization; S_{v,O_2}: mixed-venous oxygen saturation; NT-proBNP: N-terminal pro-brain natriuretic peptide.

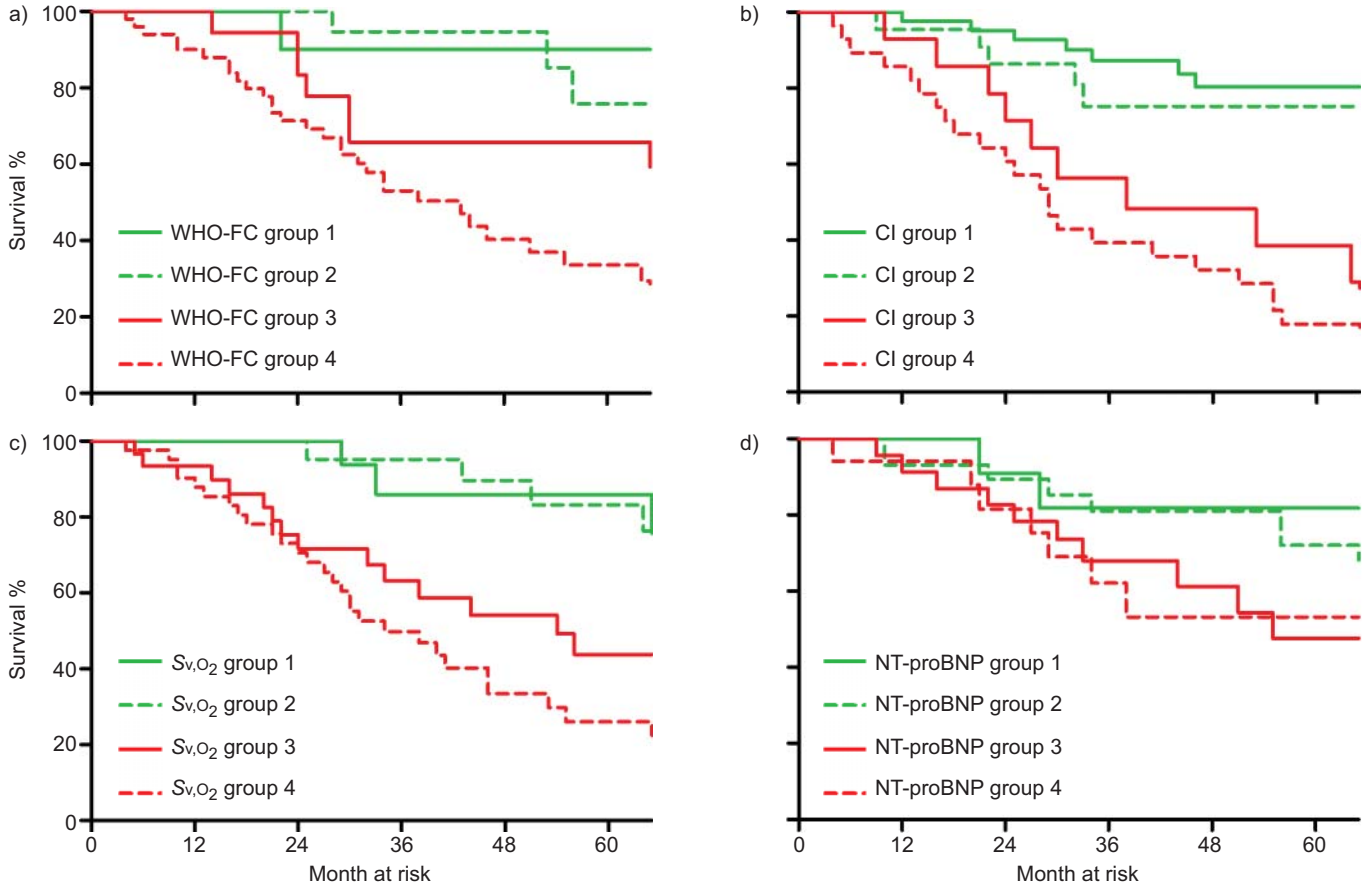

FIGURE 1. Kaplan–Meier estimates of transplantation-free survival according to risk group assignation by a) World Health Organization (WHO) functional class (FC) (group 1: WHO FC I or II at baseline and at follow-up; group 2: WHO functional class III or IV at baseline, I or II at follow-up; group 3: WHO functional class I or II at baseline, III or IV at follow-up; group 4: WHO functional class III and IV at baseline and at follow-up); b) cardiac index (CI) (group 1: CI $\geq$2.5 L·min^{-1}·m^{-2} at baseline and at follow-up; group 2: CI <2.5 L·min^{-1}·m^{-2} at baseline, $\geq$2.5 L·min^{-1}·m^{-2} at follow-up; group 3: CI $\geq$2.5 L·min^{-1}·m^{-2} at baseline, <2.5 L·min^{-1}·m^{-2} at follow-up; group 4: CI <2.5 L·min^{-1}·m^{-2} at baseline and at follow-up); c) mixed-venous oxygen saturation (S_{v,O_2}) (group 1: S_{v,O_2} $\geq$65% at baseline and at follow-up; group 2: S_{v,O_2} <65% at baseline, $\geq$65% at follow-up; group 3: S_{v,O_2} $\geq$65% at baseline, <65% at follow-up; group 4: S_{v,O_2} <65% at baseline and at follow-up); and d) N-terminal pro-brain natriuretic peptide (NT-proBNP) (group 1: NT-proBNP <1,800 ng·L^{-1} at baseline and at follow-up; group 2: NT-proBNP $\geq$1,800 ng·L^{-1} at baseline, <1,800 ng·L^{-1} at follow-up; group 3: NT-proBNP <1,800 ng·L^{-1} at baseline, $\geq$1,800 ng·L^{-1} at follow-up; group 4: NT-proBNP $\geq$1,800 ng·L^{-1} at baseline and at follow-up).

the current European pulmonary hypertension guidelines [19]. As these guidelines do not provide specific target numbers for S_{v,O_2} and NT-proBNP, we determined cut-off values for these variables by ROC analyses (S_{v,O_2} 65%, area under curve 0.69, 95% CI 0.58–0.79, p=0.008; NT-proBNP 1,800 ng·L^{-1}, area under curve 0.72, 95% CI 0.61–0.84, p=0.003). These cut-off values were used to divide patients into four distinct risk groups (table 4).

Cox proportional hazard analyses revealed that risk group-assigned changes in WHO functional class, cardiac index, S_{v,O_2} and NT-proBNP were significantly related to outcome when analysed in the univariate model (HR for WHO functional class 1.6, 95% CI 1.2–2.2; p<0.001; HR for cardiac index 1.8, 95% CI 1.4–2.3; p<0.001; HR for S_{v,O_2} 1.6, 95% CI 1.2–2.2; p<0.001, and HR for NT-proBNP 1.6, 95% CI 1.2–2.1; p=0.003). In the multivariate model, WHO functional class, cardiac index and S_{v,O_2} but not NT-proBNP remained statistically significant (HR for WHO functional class 1.5, 95% CI 1.1–2.1; p=0.03; HR for cardiac index 1.7, 95% CI 1.3–2.3; p<0.001; and HR for S_{v,O_2} 1.5, 95% CI 1.1–2.1; p=0.006).

WHO functional class

Patients presenting in functional class I or II at baseline who remained stable during follow-up (group 1) had survival probabilities of 100%, 90% and 90% after 1, 3, and 5 yrs, respectively. Patients presenting in functional class III or IV at baseline, who improved to functional class I or II during follow-up (group 2) notably demonstrated similar survival rates (100%, 95%, and 76% after 1, 3, and 5 yrs, respectively; p=0.87 *versus* group 1). In contrast, patients presenting in functional class I or II at baseline, who progressed to functional class III or IV during follow-up (group 3) exhibited significantly worse outcomes compared to groups 1 (p=0.02) and 2 (p=0.01) with survival rates of 84%, 66% and 66% after 1, 3, and 5 yrs, respectively. The survival estimates of patients in group 3 did not differ significantly from those in group 4, *i.e.* patients starting in functional class III or IV and failing to improve with therapy (survival estimates for patients in group 4 were 90%, 53%, and 34% after 1, 3, and 5 yrs, respectively; p=0.73 *versus* group 3).

Haemodynamic parameters

Patients with a cardiac index $\geqslant$2.5 L·min^{-1}·m^{-2} at baseline and during follow-up (group 1) exhibited the best outcome (survival estimates 98%, 87%, and 80% after 1, 3, and 5 yrs, respectively), but the survival rates were almost identical for patients starting with a cardiac index <2.5 L·min^{-1}·m^{-2} at baseline that improved to $\geqslant$2.5 L·min^{-1}·m^{-2} during follow-up (group 2 survival estimates 95%, 75%, and 75% after 1, 3, and 5 yrs, respectively; p=0.35 *versus* group 1). Patients with a baseline cardiac index $\geqslant$2.5 L·min^{-1}·m^{-2} that subsequently deteriorated during follow-up (group 3) demonstrated significantly poorer survival (93%, 56%, and 39% after 1, 3, and 5 yrs, respectively; p<0.001 *versus* group 1 and p=0.001 *versus* group 2) which, once again was not significantly different from the survival rates seen in patients with low cardiac indexes throughout (group 4 survival estimates 86%, 39%, and 18% after 1, 3, and 5 yrs, respectively; p=0.49 *versus* group 3).

Similar trends were observed in relation to S_{v,O_2} (fig. 1c). Survival rates in groups 1 and 2 were almost identical (group 1 survival rates 100%, 86%, and 86% after 1, 3, and 5 yrs, respectively; group 2 survival rates 100%, 95%, and 83% after 1, 3, and 5 yrs, respectively; p=0.82), with group 3 survival rates being significantly lower than those of the first two groups (93%, 63%, and 44% after 1, 3, and 5 yrs, respectively; p<0.01 *versus* group 1 and p=0.04 *versus* group 2). Again no significant difference in survival existed between groups 3 and 4 (group 4 survival estimates 88%, 50%, and 26% after 1, 3, and 5 yrs, respectively; p=0.38 *versus* group 3).

NT-proBNP

The prognostic implications of changes in NT-proBNP closely reflected those seen for the haemodynamics. Patients with initial NT-proBNP levels >1,800 ng·L^{-1} that subsequently improved with therapy to values below this threshold (group 2) had almost identical outcomes to patients with persistently low NT-proBNP levels at baseline and follow-up (group 1 survival estimates 100%, 82%, and 82% after 1, 3, and 5 yrs, respectively; group 2 survival estimates 93%, 81%, and 72% after 1, 3, and 5 yrs, respectively; p=0.27). Once more, patients with initially lower NT-proBNP levels at baseline which subsequently increased to >1,800 ng·L^{-1} at follow-up had poor survival rates (group 3 survival estimates 91%, 68%, and 48% after 1, 3, and 5 yrs, respectively; p=0.03 *versus* group 1 and p=0.03 *versus* group 2) and there was no statistically significant difference in survival between group 3 and group 4 (group 4 survival estimates 94%, 62%, and 53% after 1, 3, and 5 yrs, respectively; p=0.63 *versus* group 3).

DISCUSSION

Our results confirm previous reports demonstrating that certain parameters obtained at the time of diagnosis have prognostic value in patients with IPAH. Specifically, this was confirmed for 6-MWD, WHO functional class, RA pressure, cardiac index, S_{v,O_2} and NT-proBNP, which is in line with several other studies [8–11, 13, 14, 16–18, 25]. In addition, our data indicates that response to therapy is at least as important as the disease severity at baseline in terms of long-term outcome. Changes in WHO functional class, cardiac index, S_{v,O_2} and NT-proBNP had a strong impact on survival and this was true for improvements as well as for deteriorations. Patients presenting in a favourable prognostic group at baseline had a poor survival if they showed deterioration at follow-up. At the same time, patients starting in a poor prognostic group turned out to have a favourable long-term course if they achieved the defined stable and satisfactory classification after initiation of PAH-targeted therapy. These findings were highly consistent for changes in WHO functional class, cardiac index and S_{v,O_2}, all of which were found to be independently associated with survival. Our data suggest that individual prognosis may depend at least as much on treatment response as on disease severity at the time of diagnosis.

The present data reinforce some of the treatment goals recommended by European and US guidelines on pulmonary hypertension [19, 26, 27]. One treatment goal proposed in these guidelines is WHO functional class I or II. There is already substantial evidence suggesting that patients achieving this treatment goal have a much better long-term prognosis than patients remaining in functional class III or IV during therapy [13, 14]. However, to the best of our knowledge it has not previously been shown that deterioration in WHO functional class after treatment initiation has prognostic implications, and that the life expectancy of such patients is similar to those

presenting in functional class III or IV at the time of diagnosis who do not show improvement after initiation of PAH-targeted therapy.

Interestingly, while both the European and US guidelines propose a cardiac index $\geqslant$2.5 L·min^{-1}·m^{-2} as a therapeutic target [19, 26, 27], this value was not based on evidence from clinical studies, but rather on the fact that 2.5 L·min^{-1}·m^{-2} is generally considered as the lower limit of normal for cardiac index. Our data provide some preliminary evidence that this treatment goal is justified as patients who maintained or reached a cardiac index $\geqslant$2.5 L·min^{-1}·m^{-2} had a significantly better prognosis than patients in whom this was not the case. Crucially, this observation was also true for patients presenting with a cardiac index <2.5 L·min^{-1}·m^{-2} at the time of diagnosis.

Neither the European nor US guidelines provide specific target values for S_{v,O_2} and NT-proBNP. The cut-off values of 65% for S_{v,O_2} and 1,800 ng·L^{-1} for NT-proBNP in this study were derived from ROC analyses and require independent confirmation. The NT-proBNP threshold of 1,800 ng·L^{-1} was somewhat higher than the cut-off values of 1,400 ng·L^{-1} and 1,500 ng·L^{-1} suggested by FIJALKOWSKA *et al*. [16] and BENZA *et al*. [11], respectively. As in previous studies, S_{v,O_2} turned out to be one of the strongest predictors of survival [9, 25, 28–30] and our results suggest that this is not only true for S_{v,O_2} at baseline, but also for changes in S_{v,O_2} during follow-up. Some authors have used a cut-off value of 60% to distinguish between prognostic groups [31]. The cut-off value of 65% as determined in our study, however, is closer to the normal value (70–75%) and may therefore be a more suitable treatment goal.

Of the four follow-up variables that demonstrated significant links to survival, two (cardiac index and S_{v,O_2}) were derived from right heart catheterisation. This reaffirms existing recommendations to obtain invasive haemodynamic measurements not only at the time of diagnosis but also during the disease course [19, 20, 26, 27, 32].

Our results may have implications for the use of prognostic equations in patients with IPAH. Various groups have proposed risk scores based on haemodynamic and functional variables. THENAPPAN *et al*. [10] modified the original equation derived from the NIH registry [9] and based their prognostic assessments entirely on haemodynamic variables (RA pressure, $\bar{P}_{pa}$ and cardiac index). HUMBERT *et al.* [8] evaluated data derived from the French registry and proposed a new equation based on sex, 6-MWD and cardiac output at diagnosis. BENZA *et al*. [11] used the REVEAL registry to develop a complex equation utilising 11 variables. All of these scoring systems were derived from baseline variables, although BENZA *et al*. [11] suggested that their equation can be used at any time during a patient's disease course. This is probably also the case for other risk scores, but this approach remains to be validated. A conceptual problem that persists in all contemporary risk equations is the fact that they have been derived exclusively from variables obtained at the time of diagnosis. There is preliminary evidence that all of the above-mentioned scores may reliably predict the survival of a cohort of IPAH patients. Individual risk assessment, however, may be problematic when based solely on scoring systems that do not take into account the response to therapy. In our study, approximately 40% of the patients changed their risk category between baseline and follow-up; approximately half of these improved and half worsened. This may explain why risk estimates for the entire cohort provide reliable figures, but it also raises concerns regarding the reliability of individual risk assessments. Relying on baseline parameters without considering the response to therapy places a substantial proportion of patients into the wrong risk category.

There are several limitations to the present study. Sample size (n=109) and number of events (n=57) were limited, although sufficient to perform multivariate assessments. Patient numbers did however prohibit any further subgroup analysis. A substantial proportion of our patients were excluded as they did not fulfil the inclusion criteria. This may have created some bias although the included and excluded patients were comparable in terms of baseline characteristics and survival. By design, the study was retrospective but all relevant data had been collected prospectively so that missing values were a minor problem. The fact that the data came from a single centre may have created additional bias, but it did ensure a homogeneous patient population. Finally, we did not analyse in detail some parameters that have frequently been shown to be of prognostic relevance, such as RA pressure or 6-MWD. Changes in both variables were not significantly linked to survival in the present study, but it is possible that larger series will come to different conclusions.

In summary, we provide evidence that the response to therapy has important prognostic implications in patients with IPAH that need to be taken into consideration for risk assessment and treatment decisions. Our results reinforce the value of right heart catheterisation as a follow-up tool and they provide further support for some of the treatment goals currently suggested by international guidelines.

STATEMENT OF INTEREST

Statements of interest for K. Olsson and M.M. Hoeper can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

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