Predicting survival in pulmonary arterial hypertension in the UK

Wai-Ting Nicola Lee*, Yi Ling*, Karen K. Sheares#, Joanna Pepke-Zaba#, Andrew John Peacock* and Martin Keith Johnson*

ABSTRACT: Contemporary prognostic equations in pulmonary arterial hypertension (PAH) derived from US and French cohorts may not perform as well in the UK as a locally derived scoring scheme. The aim of the study was to develop and validate a UK risk score to predict prognosis in PAH.

Baseline mortality predictors identified by multivariate Cox analysis in 182 incident PAH patients were used to derive the Scottish composite score (SCS). Its prognostic performance in an independent UK cohort was compared with the French registry and Pulmonary Hypertension Connection (PHC) registry equations using Brier scores (BS).

The SCS based on age, sex, aetiology, right atrial pressure, cardiac output and 6-min walk distance predicted survival in the validation cohort (hazard ratio (HR) 1.7 per point increase; p<0.001) and provided further prognostic stratification in World Health Organization (WHO) functional class III patients (HR 1.8 per point increase; p<0.001). It was more accurate than the French registry equation in predicting 1-yr survival (BS: 0.092 *versus* 0.146; p=0.001) and 2-yr survival (0.131 *versus* 0.255; p<0.001). There was no significant difference in BS between the SCS and PHC registry equation.

The SCS predicts survival and can be used to supplement WHO functional class in prognostication.

KEYWORDS: Prognosis, pulmonary hypertension, survival

Pulmonary arterial hypertension (PAH) remains an incurable disease associated with high morbidity and mortality despite expansion of effective pharmacological therapy in the last decade [1]. As accurate prognostication is an integral part of disease management, considerable efforts have been made to identify prognostic factors and develop algorithms to predict patient outcome for clinical use. The first prognostic equation based on pulmonary haemodynamics (right atrial pressure (Pra)), mean pulmonary artery pressure (mean Ppa) and cardiac index at diagnosis) was derived from the National Institutes of Health (NIH) registry study of 194 patients with primary pulmonary hypertension (now classified as idiopathic, heritable and anorexigen-associated PAH) from 32 centres across the USA two decades ago before the advent of PAH-specific drug therapy [2]. It has become obsolete but continues to be used as a benchmark for patient outcome without targeted therapeutic intervention. Survival analysis of a contemporary PAH cohort from the Pulmonary Hypertension Connection (PHC) registry treated in a single centre in Chicago (IL, USA), including demographics and functional measures, identified the same haemodynamic variables as the NIH equation and these were used to derive a new equation based on a similar methodological approach [3]. Another prognostic equation based on sex, 6-min walk distance (6MWD) and cardiac output (CO) has been developed from the French registry including incident and prevalent patients diagnosed up to 3 yrs prior to study entry [4, 5]. These two contemporary equations only apply to patients with idiopathic, familial and anorexigen-associated PAH whereas the equation developed from the Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management (REVEAL) included all patients in World Health Organization (WHO) Group I PAH [6]. Due to its large sample size, a greater number of variables were incorporated in the prediction model compared with the French registry and PHC registry equations (13 *versus* three variables).

This article has supplementary material available from www.erj.ersjournals.com

These contemporary prognostic algorithms utilise baseline variables to calculate a predicted probability of survival at a certain time point during follow-up. Validation data on these equations published so far support their predictive value. The REVEAL equation and its simplified risk score (a 22-point scoring system) have been shown to have good discriminatory ability in a prospective PAH cohort of newly diagnosed patients [7]. When the PHC registry and French registry equations were applied to a prospective cohort of PAH patients followed up in four randomised controlled clinical trials and their extension studies, there was good agreement between predicted and observed survival [8]. As these equations were developed from patient populations in the USA and France with differing demographics, healthcare systems and treatment approaches to the UK, they may not perform as well in UK PAH populations as a locally derived scoring scheme. The aims of this study were to develop a UK risk score to predict prognosis in PAH patients from a well-defined cohort in Scotland, and to validate its prognostic performance against other published prognostic equations in an independent UK PAH cohort.

METHODS

Study design

A retrospective cohort of incident and treatment naïve patients diagnosed with WHO Group I PAH in the Scottish Pulmonary Vascular Unit (Glasgow, UK) between November 2000 and September 2009 were used to derive the Scottish composite score (SCS). Exclusion criteria were PAH associated with congenital heart disease (CHD-PAH), long-term calcium channel blocker (CCB) responders, pulmonary capillary wedge pressure (P_{pcw}) >15 mmHg and significant lung disease (defined by forced expiratory volume in 1 s or forced vital capacity or total lung capacity <60% predicted based on the European Coal and Steel Community reference values) [9]. The diagnosis of PAH was based on right heart catheterisation (RHC) in accordance with contemporary guidelines [1, 10]. Patients were subsequently treated with conventional therapy (long-term warfarin, diuretics or supplemental oxygen) and PAH-specific monotherapy (prostacyclin analogues, phosphodiesterase-5 inhibitors or endothelin receptor antagonists). Sequential combination therapy was initiated as clinically indicated. Baseline data on demographics, RHC, lung function, WHO functional class (FC), 6MWD, N-terminal-pro-brain natriuretic peptide (NT-pro-BNP) and Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) score [11] recorded within 3 months of diagnostic RHC and prior to starting PAH-specific therapy were collected. The variables found to be independent mortality predictors in multivariate Cox analysis were included in the SCS. Weighted points were assigned to the threshold values of each variable identified by exploratory analysis. The SCS was obtained by summation of the points scored for each variable and finalised prior to validation in a cohort of incident and treatment naive idiopathic and heritable PAH patients treated in the Pulmonary Vascular Disease Unit at Papworth Hospital (Cambridge, UK) between January 2001 and December 2009. Patients with significant lung disease (defined by lung function), raised P_{pcw} and long-term CCB responders were excluded. Baseline data were collected to apply the SCS, French registry and PHC registry equations. The ability of the SCS to predict survival over time and stratify patients into prognostic groups in the whole cohort and in WHO FC III patients was tested. The French registry and PHC registry equations were used to compute survival estimates at 1 and 2 yrs post-diagnosis. Their predictive accuracy was compared with that of the SCS using the Brier score (BS). Patient consent was considered unnecessary by the local research ethics committee in the respective institutions.

Statistical analysis

Statistical analysis was performed using Statview version 5.0.1 (SAS Institute, Cary, NC, USA) and Graphpad Prism version 5.00 (Graphpad Software, La Jolla, CA, USA). Continuous variables were checked for normality using a D'Agostino and Pearson omnibus normality test. Normally distributed variables were described using the mean and standard deviation, and compared using an unpaired t-test. Non-normally distributed variables were described using the median and interquartile range and compared using Mann–Whitney U test. Categorical variables were described using number (percentage) and compared by the Chi-squared test.

Univariate Cox proportional hazards analysis was used to identify baseline mortality predictors in the derivation cohort. Survival time was calculated from the date of RHC to the date of data cut-off (May 1, 2010). Patients who received lung transplantation or were lost to follow-up were censored on the date of procedure or last clinical contact. Significant continuous variables were transformed into categorised variables using threshold values identified in exploratory Cox analysis (see online supplementary data) and were assessed with their corresponding indicator variable coding for missing data ("missing" and "not missing") in a multivariate Cox model using a backward selection procedure. The use of indicator variables was to allow inclusion of patients with missing data in multivariate analyses. None of the indicator variables for missing data was predictive of survival. Sex was not significant in univariate Cox analysis but was entered in the multivariate model as its prognostic significance has been confirmed in previous studies. Aetiology was divided into two subgroups: connective tissue disease associated pulmonary arterial hypertension due to systemic sclerosis (CTD-PAH-SSc) and WHO Group I PAH others *versus* idiopathic, heritable, anorexigen-associated and CTD-PAH non-SSc (reference subgroup). Anorexigen-associated PAH was included in the reference subgroup as these patients are regarded as having similar outcomes to those with idiopathic and heritable PAH. "WHO Group I PAH others" included patients with portopulmonary hypertension, HIV and pulmonary veno-occlusive disease. Variables with p<0.1 were retained in the final multivariate Cox model. Weighted points were assigned to each variable subgroup according to their adjusted hazard ratio (HR) in the final model, for example, 0 point was assigned to the reference subgroup with an adjusted HR of 1. For the other subgroups, 1 point was assigned if the adjusted HR was 2, 2 points if the adjusted HR was 3 and 3 points if the adjusted HR was 4.

Kaplan–Meier analysis was used to estimate survival rates and comparison between groups was made by the log-rank test for trend. Cox analysis was used to evaluate the ability of the SCS to predict survival in the validation cohort. The BS [12, 13] was used to assess the accuracy of the SCS, French registry and PHC registry equations in predicting 1- and 2-yr survival in the validation cohort allowing for censoring. It measures the mean squared deviation of predicted probability from the actual

outcome. A BS of 0 indicates perfect prediction. A BS of 0.25 indicates that the prediction is equivalent to the outcome occurring by chance alone. Higher prediction accuracy is indicated by a lower BS. To compare the performance of the SCS with other equations, a point estimate of difference in BS between SCS and each equation and its 95% confidence interval was obtained from 200,000 bootstrap re-samples. A difference in BS of >0.02 was considered clinically relevant. A p-value <0.05 was defined as statistically significant.

RESULTS

Derivation of the SCS

Characteristics of the derivation cohort and the aetiology reference subgroup are summarised in table 1. 10% of patients

received prostacyclin analogues (7% intravenous epoprostenol, 2% inhaled iloprost, 1% subcutaneous treprostinil), 47% phosphodiesterase-5 inhibitors (45% sildenafil 45% and 2% tadalafil) and 44% endothelin receptor antagonists (29% bosentan, 7% sitaxentan and 8% ambrisentan). After a median follow-up period of 25 months (range 0.1–113 months), 81 patients died from all causes, two patients received lung transplantation, one patient was lost to follow-up and two patients transferred care to another centre. The survival estimates for the whole cohort were 79% at 1 yr, 68% at 2 yrs and 57% at 3 yrs. Out of the 17 baseline variables considered in the univariate Cox model, age, aetiology, carbon monoxide diffusing capacity % pred, P_{ra}, CO, WHO FC, 6MWD, NT-pro-BNP and CAMPHOR score were significant mortality predictors (table 2). When these variables

TABLE 1	Baseline characteristics of the derivation cohort (all patients *versus* patients in the aetiology reference subgroup)		
	All patients	**Aetiology reference subgroup**	**p-value**
Subjects n	182	125	
Age yrs	62 (48–73)	61 (45–71)	0.592
Females	125 (69)	81 (65)	0.477
Aetiology			
Idiopathic PAH	97 (53)	97 (78)	
Heritable PAH	2 (1)	2 (2)	
CTD-PAH			
SSc associated	33 (18)		
non-SSc associated	26 (14)	26 (21)	
WHO Group I PAH others			
PoPH	15 (8)		
HIV	1 (0.5)		
PVOD	8 (4)		
Lung function % pred			
FEV1	87 (75–98)[#]	86±17[##]	0.605
FVC	99 (86–112)[#]	98±19[##]	0.628
$D_{L,CO}$	42 (28–60)[¶]	44 (28–63)[¶¶]	0.645
Pulmonary haemodynamics			
P_{ra} mmHg	7 (4–11)	6 (4–10)	0.421
Mean P_{pa} mmHg	47 (39–55)	48 (40–58)	0.459
CO L·min⁻¹	3.6 (2.9–4.7)	3.6 (2.9–4.7)	0.929
PVR Wood units	10.8 (7.4–15.5)	11.2 (7.6–15.7)	0.596
S_{v,O_2} %	64 (57–70)	65 (58–70)	0.789
WHO FC			
I and II	25 (14)	19 (15)	0.899
III	131 (72)	87 (70)	
IV	26 (14)	19 (15)	
6MWD m	260±109[+]	273±110[++]	0.342
NT-pro-BNP pg·mL⁻¹	1026 (298–2637)[§]	972 (316–2258)[§§]	0.856
CAMPHOR	38 (27–57)[ƒ]	40±18[ƒƒ]	0.933
Year of diagnosis			
Prior to 2005	51 (28)	36 (29)	0.882
2005 onwards	131 (72)	89 (71)	

Data are expressed as median (interquartile range), n (%) or mean±SD, unless otherwise stated. PAH: pulmonary arterial hypertension; CTD-PAH: connective tissue disease associated PAH; SSc: systemic sclerosis; WHO: World Health Organization; PoPH: portopulmonary hypertension; PVOD: pulmonary veno-occlusive disease; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; $D_{L,CO}$: diffusing capacity of the lung for carbon monoxide; P_{ra}: right atrial pressure; P_{pa}: pulmonary artery pressure; CO: cardiac output; PVR: pulmonary vascular resistance; S_{v,O_2}: mixed venous saturation; FC: functional class; 6MWD: 6-min walk distance; NT-pro-BNP: N-terminal-pro-brain natriuretic peptide; CAMPHOR: Cambridge Pulmonary Hypertension Outcome Review. [#]: n=171; [¶]: n=158; [+]: n=177; [§]: n=96; [ƒ]: n=76; [##]: n=117; [¶¶]: n=108; [++]: n=122; [§§]: n=63; [ƒƒ]: n=51.

TABLE 2	Univariate Cox proportional hazards analysis in the derivation cohort

	HR (95% CI)	p-value
Age at diagnosis per decade increase yrs	1.32 (1.12–1.57)	0.010
Sex		
Female	0.76 (0.47–1.23)	0.260
Male (reference)		
Aetiology subgroups		0.001
WHO Group I PAH others[#]	3.21 (1.79–5.76)	<0.001
CTD-PAH-SSc	1.74 (0.98–3.09)	0.057
CTD-PAH non-SSc	1.29 (0.67–2.50)	0.445
Idiopathic or heritable PAH (reference)		
Lung function % pred		
FEV_1 per 10% increase	0.07 (0.00–3.02)	0.165
FVC per 10% increase	0.32 (0.02–5.32)	0.892
$D_{L,CO}$ per 10% increase	0.80 (0.70–0.91)	<0.001
Pulmonary haemodynamics		
P_{ra} per 5 mmHg	1.30 (1.08–1.57)	<0.001
Mean P_{pa} per 5 mmHg	1.03 (0.96–1.10)	0.480
S_{v,O_2} per 5%	0.95 (0.83–1.09)	0.464
PVR per 5 Wood units	1.13 (0.95–1.33)	0.170
CO per $L \cdot min^{-1}$	0.83 (0.68–1.01)	0.058
WHO FC		0.010
I and II	0.30 (0.12–0.72)	0.007
III	0.49 (0.28–0.85)	0.010
IV (reference)		
6MWD per 100 m increase	0.61 (0.50–0.67)	<0.001
NT-pro-BNP per 200 $pg \cdot mL^{-1}$ increase	1.02 (1.00–1.04)	0.036
CAMPHOR per 5 points increase	1.16 (1.04–1.29)	0.008
Year of diagnosis		
2005 onwards	1.15 (0.71–1.86)	0.572
2000–2005 (reference)		

WHO: World Health Organization; PAH: pulmonary arterial hypertension; CTD-PAH: connective tissue disease associated PAH; SSc: systemic sclerosis; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; $D_{L,CO}$: diffusing capacity of the lung for carbon monoxide; P_{ra}: right atrial pressure; P_{pa}: pulmonary artery pressure; S_{v,O_2}: mixed venous saturation; PVR: pulmonary vascular resistance; CO: cardiac output; FC: functional class; 6MWD: 6-min walk distance; NT-pro-BNP: N-terminal-pro-brain natriuretic peptide; CAMPHOR: Cambridge Pulmonary Hypertension Outcome Review. [#]: includes portopulmonary hypertension, HIV and pulmonary veno-occlusive disease.

TABLE 3	Multivariate mortality predictors and derivation of the Scottish composite score

Variables	Categories	Adjusted HR (95% CI)	Points
Age yrs	⩾70	2.20 (1.35–3.61)	1
	<70 (reference)		0
Sex	Male	2.01 (1.15–3.51)	1
	Female (reference)		0
Aetiology	CTD-PAH-SSc or Group I PAH others[#]	2.33 (1.42–3.82)	1
	Idiopathic, heritable, anorexigen-associated PAH or CTD-PAH non-SSc		0
6MWD m	<50	5.04 (2.33–10.89)	3
	50–149	3.45 (1.48–8.05)	2
	150–299	2.48 (1.28–4.79)	1
	⩾300 (reference)		0
P_{ra} mmHg	⩾10	1.50 (0.90–2.49)	1
	<10 (reference)		0
CO $L \cdot min^{-1}$	<3	2.18 (1.32–3.61)	1
	⩾3 (reference)		0

6MWD: 6-min walk distance; P_{ra}: right atrial pressure; CO: cardiac output; CTD-PAH: connective tissue disease associated pulmonary arterial hypertension (PAH); SSc: systemic sclerosis; [#]: includes portopulmonary hypertension, HIV and pulmonary veno-occlusive disease.

were categorised into two to four subgroups and assessed in a multivariate Cox model, age at diagnosis, sex, aetiology, P_{ra}, CO and 6MWD were retained as independent mortality predictors and were used to construct the SCS (0 to 8) (table 3).

Validation of the SCS
Out of 119 patients in the validation cohort, 99 patients had complete data to calculate the SCS (table 4). 38 patients died and four received lung transplantation during follow-up (median 29 months, range 0.3–102 months). The 1-, 2- and 3-yr survival estimates for patients in whom SCS was available were 87, 74 and 68%, respectively which were not significantly different from those in whom SCS was not available (log-rank p=0.196). The risk of death increased with the SCS (HR 1.7 per

point increase, 95% CI 1.4–2.1, p<0.001). When patients were stratified into three SCS risk groups ("high risk": 4–8 (n=23); "intermediate risk": 2–3 (n=44); and "low risk": 0–1 (n=32)), there was a significant difference in survival between groups (p<0.001 by log-rank test for trend) (fig. 1). The SCS further stratified WHO FC III patients (HR 1.8 per point increase, 95% CI 1.4–2.4, p<0.001) (n=66, 30 deaths). When these patients were stratified into three SCS risk groups ("high risk" = 4–8, "intermediate risk" = 2–3, "low risk" = 0–1), there was a significant difference in survival between groups (p<0.001 by log-rank test for trend) (fig. 2).

Comparison of prognostic equations
When the SCS, French registry and PHC registry equations were applied to the validation cohort to predict 1- and 2-yr survival, the SCS had a lower BS than both equations but only the comparison with the French registry equation reached statistical significance (table 5).

DISCUSSION
The present study is the first to describe the derivation and validation of a risk score to predict prognosis in incident patients with PAH based on UK data. The data analysis showed that the SCS, an 8-point simple scoring system based on age, sex, aetiology, P_{ra}, CO and 6MWD at diagnosis, can be used to categorise patients into prognostic groups and provide further risk stratification in WHO FC III patients. When tested in an independent UK PAH cohort, the predictive accuracy of the SCS was comparable to that of the PHC registry equation and may be greater than the French registry equation. The

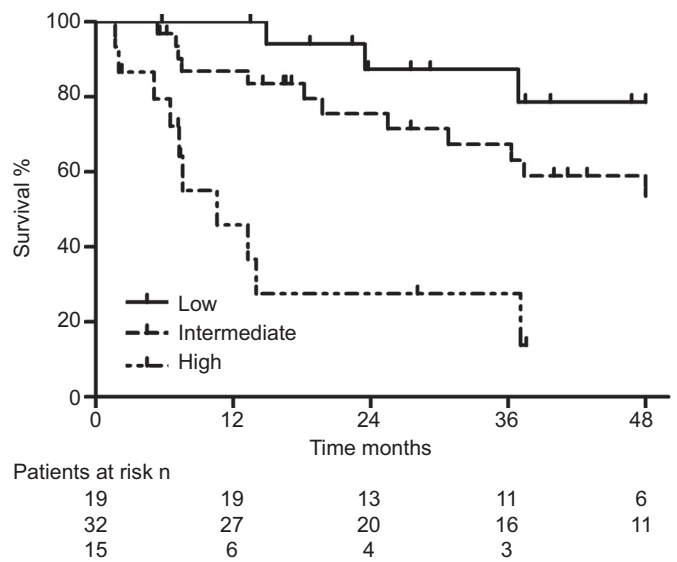| TABLE 4	Characteristics of the validation cohort		
	Derivation cohort	Validation cohort	p-value
Subjects n	182	99	
Age yrs	62 (48–73)	53 (42–69)	0.010
Females	125 (69)	72 (73)	0.479
Aetiology			
Idiopathic PAH	97 (53)	96 (97)	
Heritable PAH	2 (1)	3 (3)	
CTD-PAH			
SSc associated	33 (18)		
non-SSc associated	26 (14)		
WHO Group I PAH others			
PoPH	15 (8)		
HIV	1 (0.5)		
PVOD	8 (4)		
Lung function % pred			
FEV_1	87 (75–98)[#]	84±15	0.038
FVC	99 (86–112)[#]	97±17	0.094
$D_{L,CO}$	42 (28–60)[¶]	59±22[##]	<0.001
Pulmonary haemodynamics			
P_{ra} mmHg	7 (4–11)	9±6	0.013
Mean P_{pa} mmHg	47 (39–55)	50 (42–59)	0.016
CO L·min[1]	3.6 (2.9–4.7)	3.2 (2.6–3.8)	0.002
PVR Wood units	10.8 (7.4–15.5)	13.3±5.4	0.011
S_{v,O_2} %	64 (57–70)	63±8	0.889
WHO FC			
I and II	25 (14)	18 (18)	0.572
III	131 (72)	66 (67)	
IV	26 (14)	15 (15)	
6MWD m	260±109[+]	267±121	0.669
NT-pro-BNP pg·mL^{-1}	1026 (298–2637)[§]	2029 (330–4407)[¶¶]	0.134
CAMPHOR	38 (27–57)[f]	38 (26–57)[++]	0.804
Year of diagnosis			
Prior to 2005	51 (28)	45 (45)	0.003
2005 onwards	131 (72)	54 (55)	

Data are expressed as median (interquartile range), n (%) or mean±SD, unless otherwise stated. PAH: pulmonary arterial hypertension; CTD-PAH: connective tissue disease associated PAH; SSc: systemic sclerosis; WHO: World Health Organization; PoPH: portopulmonary hypertension; PVOD: pulmonary veno-occlusive disease; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; $D_{L,CO}$: diffusing capacity of the lung for carbon monoxide; P_{ra}: right atrial pressure; P_{pa}: pulmonary artery pressure; CO: cardiac output; PVR: pulmonary vascular resistance; S_v, O_2: mixed venous saturation; FC: functional class; 6MWD: 6 min walk distance; NTproBNP: N-terminal pro-brain natriuretic peptide; CAMPHOR: Cambridge Pulmonary Hypertension Outcome Review; [#]: n=171; [¶]: n=158; [+]: n= 177; [§]: n=96; [f]: n=76; [##]: n=81; [¶¶]: n=45; [++]: n=49.

prognostic significance of sex and aetiology demonstrated by previous studies is also confirmed. These findings add to the growing body of literature on prognostication in PAH and provide further insights into the use of contemporary prognostic equations derived from other registry studies.

The predictive value of the French registry, PHC registry and REVEAL equations has been demonstrated in respective validation studies. However their applicability in other patient populations would be influenced by factors such as study
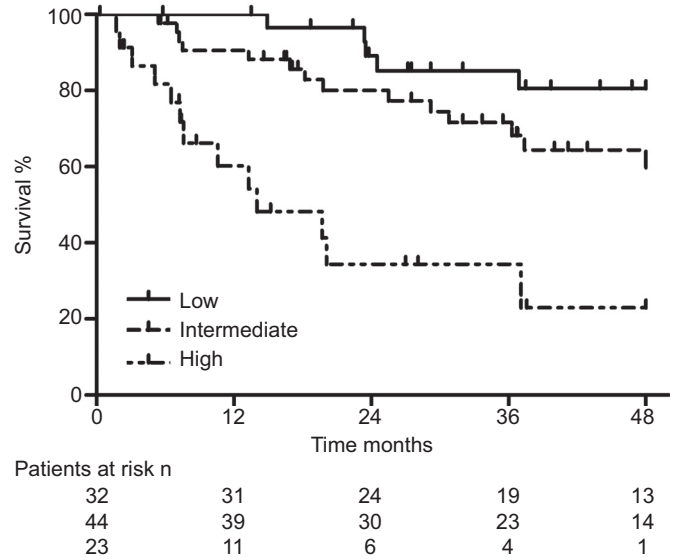
FIGURE 1. Kaplan–Meier survival estimates of the validation cohort stratified by three Scottish composite score risk groups.

FIGURE 2. Kaplan–Meier survival estimates of World Health Organization functional class III patients in the validation cohort stratified by three Scottish composite score risk groups.

population characteristics, treatment pathways and statistical methodology (table 6). The SCS was designed as a simple point-based risk score to stratify patients into prognostic groups whereas the other equations were developed to compute predicted survival probabilities at certain time points post-diagnosis. Both SCS derivation and validation cohorts were treated in single tertiary centres and this would ensure complete data capture and uniformity of care. In contrast, the French registry and REVEAL included national cohorts from selected centres. This may lead to selection bias, variations in clinical practice and patient outcome. The SCS was derived from a strictly incident and treatment naive patient cohort, whereas French registry, PHC registry and REVEAL equations were derived from mixed

TABLE 5 Comparison of predictive accuracy between the Scottish composite score (SCS) and other published prognostic equations

	BS (95% CI)	p-value
Predicting 1-yr survival		
French registry equation	0.146 (0.120–0.175)	
PHC registry equation	0.111 (0.060–0.168)	
SCS	0.092 (0.058–0.130)	
Difference: SCS - French registry equation	-0.055 (-0.083– -0.024)	0.001
Difference: SCS - PHC registry equation	-0.019 (-0.059–0.017)	0.328
Predicting 2-yr survival		
French registry equation	0.255 (0.210–0.302)	
PHC registry equation	0.189 (0.133–0.250)	
SCS	0.131 (0.091–0.175)	
Difference: SCS - French registry equation	-0.124 (-0.176– -0.070)	<0.001
Difference: SCS - PHC registry equation	-0.058 (-0.122– -0.002)	0.060

BS: Brier score; PHC: Pulmonary Hypertension Connection. A Brier Score of 0 indicates perfect prediction and 0.25 indicates a prediction equivalent to random chance.

incident and prevalent cohorts. The inclusion of prevalent patients would introduce survivor bias as these patients have survived long enough to be recruited in the study and would have a better prognosis than those who die early from severe disease or lack of response to PAH therapy. This was clearly demonstrated by comparing survival between incident and prevalent cohorts in the French registry study [5]. In order to remove this survivor bias, authors of the French registry equation estimated survival from time of diagnosis as opposed to time of enrolment and only considered patients to be at risk from their time of study entry. This adjustment for the time delay between diagnosis and study entry in prevalent patients was not adopted in the development of the PHC registry or REVEAL equations. The study period of the PHC registry spanned both pre- and post-modern treatment eras. Changes in patient prognosis over this period due to treatment advances are probable and this may have affected the survival analysis. These factors, in addition to variations in healthcare systems and treatment approaches, would impact on the performance of these prognostic algorithms in different clinical settings.

It is well recognised that patient outcome differs according to PAH aetiology. Patients with CHD-PAH were excluded from this study as they have a distinct haemodynamic profile and natural history from other PAH patients [14]. Pulmonary arterial hypertension associated with systemic sclerosis is known to confer a worse prognosis than idiopathic PAH despite a similar degree of haemodynamic derangement for reasons that are not fully understood [15, 16]. When PAH associated with different types of connective tissue disease including mixed connective tissue disease, overlap syndromes and rheumatoid arthritis were grouped together and compared with CTD-PAH-SSc in the derivation cohort, CTD-PAH-SSc

TABLE 6 Prognostic algorithms in pulmonary arterial hypertension (PAH)

	Study population	Recruitment period	Variables	End-point	Validation
French registry equation [4, 5]	Idiopathic, familial and anorexigen-associated PAH n=190, 29% incident and 71% prevalent cases	2002–2003, follow-up time 3 yrs for all patients	6MWD, sex, CO	Survival up to 3 yrs post-diagnosis	Prospective validation in PAH cohorts from clinical trials
Pulmonary Hypertension Connection registry equation [3]	Idiopathic, familial and anorexigen-associated PAH n=282, incident and prevalent cases	1991–2007, median (interquartile range) follow-up time 3.9 (1.7–7.8) yrs, maximum follow-up time 16.6 yrs	P_{ra}, mean P_{pa}, CI	Survival at number of yrs post-diagnosis	Prospective validation in PAH cohorts from clinical trials
REVEAL registry equation and risk score [6, 7]	WHO Group I PAH n=2716, 14% incident and 86% prevalent cases	2006 onwards, mean follow-up time 1.4 yrs, range 0–2 yrs	Age, aetiology, sex, renal insufficiency, SBP, HR, WHO FC, 6MWD, BNP or NT-pro-BNP, P_{ra}, PVR, ipresence of pericardial effusion, % pred $D_{L,CO}$	1-yr survival	Prospective validation in newly diagnosed PAH patients from REVEAL
Scottish composite Score	WHO Group I PAH (except for CHD-PAH) n=182, all incident cases	2000–2009, median follow-up time 2.1yrs, range 3 days to 9.4 yrs	Age, aetiology, sex, 6MWD, P_{ra} and CO	Survival at number of yrs post-diagnosis	Retrospective validation in an independent UK idiopathic and heritable PAH cohort

REVEAL: Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management; 6MWD: 6-min walk distance; CO: cardiac output; P_{ra}: right atrial pressure; P_{pa}: pulmonary artery pressure; CI: cardiac index; WHO: World Health Organization; SBP: systolic blood pressure; HR: heart rate; FC: functional class; BNP: brain natriuretic peptide; NT-pro-BNP: N-terminal-pro BNP; PVR: pulmonary vascular resistance; $D_{L,CO}$: diffusing capacity of the lung for carbon monoxide; CHD-PAH: congenital heart disease associated PAH.

conferred a worse prognosis. This would be consistent with the findings from a UK-wide epidemiology study [17]. Patients with idiopathic, heritable, anorexigen-associated PAH are regarded as having similar outcomes as they share clinical and pathophysiological features [18]. Hence, the grouping of aetiologies in the SCS would be consistent with findings from previous studies. There is also increasing evidence to support a sex difference in patient outcome and this is confirmed by the present study. More females are affected by PAH than males but they have a better prognosis [4, 19]. Recent analysis of patients enrolled in REVEAL showed that men had a higher mean P_{pa} and mean P_{ra} at diagnosis and those aged $\geqslant 60$ yrs had lower survival rates compared with females aged $\geqslant 60$ yrs [20]. Sex hormones are thought to play a role but the precise mechanisms remain to be elucidated. The individual prognostic value of other component variables in the SCS has also been demonstrated in other studies (age [3, 19], 6MWD [4, 6, 21–25], P_{ra} [6, 23–27], CO [4]).

Algorithms advising on the initial choice of drugs and the use of combination therapy advocated by current guidelines on PAH management are primarily based on WHO FC as its prognostic value has been firmly established [1, 28, 29]. However, WHO FC may not be a sufficiently reliable measure of functional status as wide variation in clinicians' assessment has been reported [30]. The differences between WHO FC I or II and IV are clear-cut, but WHO FC III encompasses patients with a wide range of functional capacity. The results of this study showed that the SCS could provide further risk stratification in WHO FC III patients and hence supplement WHO FC in clinical assessment. Variables measured during follow-up may be more predictive of long-term outcome than those measured at baseline evaluation as they would capture the impact of treatment response and disease progression on survival. A recent study has confirmed the prognostic impact of changes in outcome variables during the course of disease and demonstrated the importance of incorporating them into risk assessment [31], but there are currently no published prediction tools specifically developed to address this issue. We propose that the SCS could be used to assess the initial risk of mortality in the one to two year time horizons with a view to develop a risk score incorporating changes in mortality predictors over time for repeated use during follow-up.

This study has several limitations. Missing data were unavoidable due to the retrospective nature of the study. As measurements of NT-pro-BNP and CAMPHOR score were not introduced into clinical practice until 2004, there were fewer data compared with other baseline variables which may have introduced bias against them in multivariate survival analyses despite statistical adjustment. The derivation cohort consisted of patients with heterogeneous aetiologies of PAH with relatively small numbers in some subgroups. However, this simply reflects the relative incidence of different PAH aetiologies in a real-life clinical cohort. The data on vasoreactivity status at diagnosis were incomplete, so the effect of a positive vasodilatory response on survival could not be assessed. Only one patient demonstrated sustained response from CCB and was excluded from the study. This is based on the finding that long-term CCB responders have a better prognosis than non-CCB responders [32]. As the number is small, the bias associated with this exclusion would be insignificant. There were no patients with rarer causes of WHO Group I PAH

such as schistosomiasis or chronic haemolytic anaemia in the derivation or validation cohort, and only patients with idiopathic and heritable PAH were included in the validation cohort. Hence, the performance of the SCS in other PAH subgroups is still to be validated. 17% of patients in the validation cohort did not have all the required variables to calculate the SCS. It was not possible to determine how the SCS would perform in these patients compared with other equations, but there was no difference in survival between patients with and without the SCS. Heart rate (HR) and systolic blood pressure (SBP) were measured in each patient at diagnosis but not recorded in the validation database and hence unavailable for this analysis. The REVEAL equation could not be included in the comparison as the systematic omission of HR and SBP data would lead to bias in its performance. This is a limitation of database analysis that does not reflect the potential value of an assessment tool in clinical practice.

In conclusion, the SCS is a simple multidimensional risk score combining the impact of demographics, pulmonary haemodynamics and functional status on survival in incident PAH patients. When validated in an independent UK idiopathic and heritable PAH cohort, it correlated with mortality and provided further risk stratification in WHO FC III patients. It may perform better in UK populations than prognostic equations derived from other registry studies but further validation in wider PAH populations is required before firm conclusions on its clinical utility can be made.

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