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RESEARCH ARTICLE

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The MRC Dyspnoea Scale and mortality risk prediction in pulmonary arterial hypertension: A retrospective longitudinal cohort study

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Abstract

Risk stratification models in pulmonary arterial hypertension (PAH) rely on World Health Organisation Functional Class (WHO FC). A high proportion of patients are classified as WHO FC III, a heterogenous group which limits the stratification abilities of risk models. The Medical Research Council (MRC) Dyspnoea Scale may allow a more precise assessment of functional status and improve current risk models. We investigated the ability of the MRC Dyspnoea Scale to assess survival in PAH and compared performance to WHO FC and the COMPERA 2.0 models. Patients with Idiopathic, Hereditary or Drug-induced PAH who were diagnosed between 2010 and 2021 were included. The MRC Dyspnoea Scale was retrospectively applied as derived from a combination of patient notes, 6MWD tests results and WHO functional status using a purpose-designed algorithm. Survival was assessed using Kaplan–Meier analyses, log rank testing and Cox proportional hazard ratios. Model performance was compared with Harrell's C Statistic. Data from 216 patients were retrospectively analyzed. At baseline, of 120 patients classified as WHO FC III, 8% were MRC Dyspnoea Scale 2, 12% Scale 3, 71% Scale 4 and 10% Scale 5. The MRC Dyspnoea Scale performed well compared to the WHO FC and COMPERA models at follow up (respectively, C-statistic 0.74 vs. 0.69 vs. 0.75). It was possible to use the MRC Dyspnoea Scale to subdivide patients in WHO FC III into groups which had distinct survival estimates. We conclude that at follow-up, the MRC Dyspnoea Scale may be a valid tool for the assessment of risk stratification in pulmonary arterial hypertension.

KEYWORDS

pulmonary hypertension, risk stratification, SMRC Dyspnoea Scale

Martin Johnson and Harrison Stubbs are joint last authors.

INTRODUCTION

Pulmonary hypertension (PH), when untreated, leads to progressive right ventricular failure and death and therefore accurately assessing prognosis is vital.[1] The 2022 European Respiratory Society (ERS)/European Society of Cardiology (ESC) guidelines advocate the use of the COMEPRA 2.0 risk model at first follow up following the initiation of disease targeted therapy, to assess the therapeutic response and consider treatment escalation.[2] COMPERA 2.0 incorporates three noninvasive variables, namely N-terminal prohormone of brain natriuretic peptide (NT-proBNP), World Health Organisation functional class (WHO FC) and six-minute walk distance (6MWD) to allocate patients to low, intermediate-low, intermediate-high, or high risk strata.[3,4] WHO FC is derived from the New York Heart Association (NYHA) class for use in left sided heart failure. It has been shown to predict mortality at diagnosis and follow-up in pulmonary arterial hypertension and a deterioration in FC is an indicator of disease progression.[5–7] However, the majority of PH patients are classified as WHO FC III (defined as a "marked limitation of physical activity"), at both baseline and follow-up and therefore represent a heterogeneous group limiting the stratification abilities of the risk models into which it is incorporated.[2,8]

The 1959 Medical Research Council (MRC) Dyspnoea Scale measures the perceived disability arising from breathlessness, categorizing this into one of five scales.[9,10] Respiratory physicians, who in many centers are responsible for the care of PH patients, are better acquainted with this scale. While validated for assessing disability and predicting survival in interstitial lung disease and chronic obstructive pulmonary disease,[11–14] the MRC Dyspnoea Scale has not been studied in a PH population and the association with survival is unknown. The fact that the MRC Dyspnoea Scale has a greater number of categories (five) compared with WHO FC (four) may enable it to separate patients in WHO FC III into separate classes and thereby improve prognostication. Consequently, this study aimed to assess the performance of the MRC Dyspnoea Scale model at predicting survival and how it performed when compared to the WHO FC and COMPERA 2.0 models for the assessment of mortality risk. Furthermore, this study aimed to see whether replacing WHO FC with the MRC Dyspnoea Scale in the COMPERA 2.0 model improved the ability of this model at predicting survival.

METHODS

Approval was obtained from the West of Scotland Research Ethics Service (Ref 22/WS/0149). The Scottish Pulmonary Vascular Unit (SPVU) is the pulmonary hypertension referral center for Scotland. A retrospective analysis of records was taken for all patients who were diagnosed with pulmonary arterial hypertension at SPVU between January 1, 2010 and December 31, 2021. Patients were included into the baseline cohort at the point of diagnosis if they met the following criterial; (i) ≥18 years (ii) treatment-naïve, (iii) diagnosed via multidisciplinary team with Idiopathic, Hereditary or Drug Induced Pulmonary Arterial Hypertension (IPAH/HPAH/DPAH), (iv) baseline haemodynamics demonstrated an mPAP ≥25 mmHg, PAWP ≤ 15 and PVR ≥ 3.0 and (v) all three of NT-proBNP, 6MWD and WHO functional class were available at baseline as part of routine care. Patients were excluded from the first follow-up cohort if they had not had follow-up within 2 years of diagnosis or were missing more than one of the above noninvasive measures at follow-up. The MRC Dyspnoea Scale was retrospectively applied at baseline and first follow-up using a combination of patient clinical notes, records from 6MWD tests and WHO functional status and was systemically allocated using an algorithm devised for this purpose (Figure 1). In cases of doubt, the investigators used their discretion in assigning the MRC Dyspnoea Scale. The Enright equations were used to calculate the proposed lower limits of normal for 6MWD.[15] The performance of three models was assessed which included the COMPERA 2.0 4 strata model (which was performed as described by Hoeper et al.[3]), WHO FC and the MRC Dyspnoea Scale. Risk stratification was performed at baseline (i.e., at diagnosis, before pulmonary arterial vasodilator therapy) and at first follow-up following treatment commencement. The primary outcome for each model was all cause mortality with survival time calculated from both the date of diagnosis and first follow-up until death, truncated at 5 years, as calculated for each model.

Refined model: "MRC Dyspnoea Risk Score"

An alternative 4 strata model was developed within the COMPERA 2.0 model, whereby WHO functional class was replaced with the MRC Dyspnoea Scale—described henceforth as the "MRC Dyspnoea Risk Score." The MRC Dyspnoea Scale was divided in a similar to method to how WHO FC is divided, in that

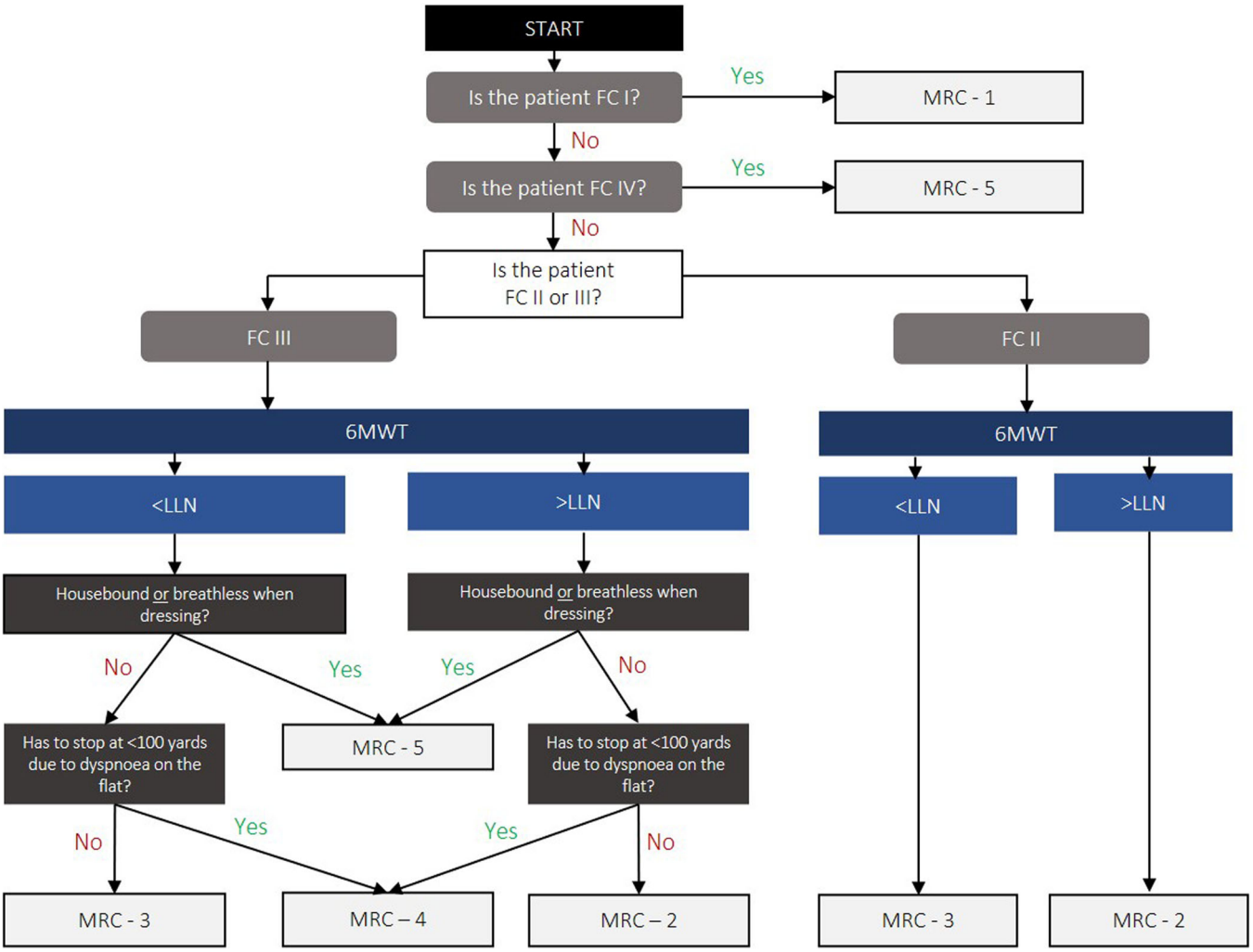

FIGURE 1 Algorithm for retrospectively applying the MRC Dyspnoea Scale.

scales one and two were attributed 1 point, scale three and four attributed 3 points and scale five 4 points. This was added to the established variable cuts offs of the COMPERA 2.0 for 6MWD and NT-proBNP with an overall designation of risk calculated from the integer of the mean for the MRC Dyspnoea Risk Score (i.e., 1 = low risk, 2 = intermediate-low risk, 3 = intermediate-high risk, 4 = high risk).

Statistical analysis

Significance was set at the $p < 0.05$ level. Continuous data were presented as mean ± standard deviation or median (interquartile range). Categorical data are presented as number (n), (percentage, %). GraphPad Prism (v9.3.0) was used for analysis. Survival analysis was performed with Kaplan–Meier analysis and log rank test. Patients who underwent lung transplantation and patients who were lost to follow-up were censored at the date of the last contact. Cox proportional hazard ratios (HR) were calculated in reference to the high risk category (due to no deaths in the lowest risk strata for each model) and are presented as hazard ratios (with 95% confidence intervals). Model scores were analyzed as ordinal categorical data. Harrell's C Statistic was used to compare Cox models for mortality. The Akaike information criterion (AIC) was used to further evaluate the goodness-of-fit for each model.

RESULTS

A total of 216 patients were diagnosed with IPAH/HPAH/DPAH in the study period. Figure 2 demonstrates the flow of patients into the cohort at baseline and follow up. Characteristics at baseline are demonstrated in Table 1. The overall 1-, 3- and 5-year

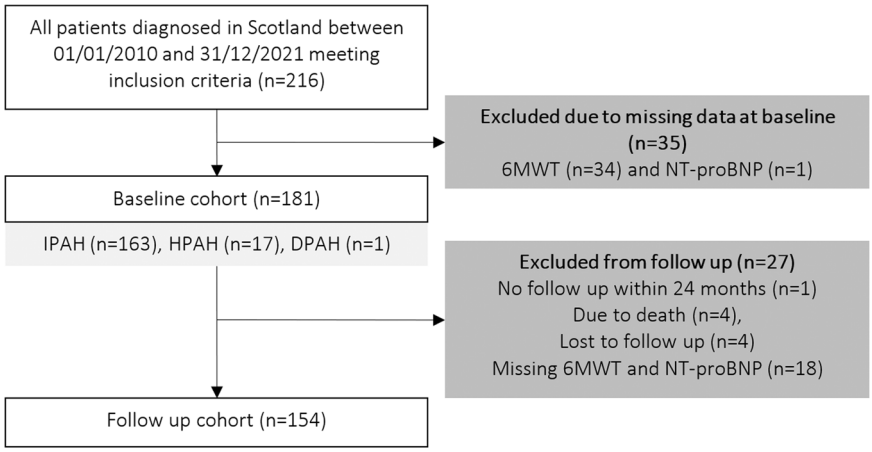

FIGURE 2 CONSORT diagram showing inclusion into the baseline (diagnosis) and first follow-up cohort.

TABLE 1 Patient demographics at diagnosis (baseline) as stratified by MRC Dyspnoea Scale.

		MRC Dyspnoea Scale				
	All	**1**	**2**	**3**	**4**	**5**
Number	181	1	34	27	86	33
Age (years)	60 ± 17	16	48 ± 18	58 ± 18	64 ± 15	61 ± 14
Male, *n* (%)	75 (41)	1 (100)	8 (24)	16 (59)	35 (41)	15 (45)
PAH aetiology, *n* (%)						
IPAH	163 (90)	0	31 (91)	27 (100)	76 (88)	29 (88)
HPAH	17 (9)	1	2 (6)	0	10 (12)	4 (12)
DPAH	1 (1)	0	1 (3)	0	0	0
Comorbidities, *n* (%)						
Obesity	79 (44)	0	11 (32)	10 (37)	47 (55)	11 (33)
Coronary Heart disease	51 (28)	0	2 (6)	3 (11)	28 (33)	18 (55)
Diabetes mellitus	53 (290	0	4 (12)	7 (26)	34 (40)	8 (24)
Systemic hypertension	59 (33)	0	7 (21)	10 (37)	32 (37)	10 (30)
Atrial fibrillation	20 (11)	0	0	4 (15)	12 (14)	4 (12)
WHO functional class, *n* (%)						
I/II	40 (22)	1	25 (74)	13 (48)	1	0
III	120 (66)	0	9 (26)	14 (52)	85 (99)	12 (36)
IV	21 (12)	0	0	0	0	21 (64)
COMPERA 2.0 strata, *n* (%)						
Low risk	14 (8)	1	11 (32)	2 (7)	0	0
Intermediate-low risk	42 (23)	0	19 (56)	7 (26)	13 (15)	3 (9)
Intermediate-high risk	84 (46)	0	4 (12)	18 (67)	53 (62)	9 (27)
High risk	41 (23)	0	0	0	20 (23)	21 (64)
Baseline data and right heart catheterization haemodynamics						
6MWD, m	250 (150–374)	525	422 (361–498)	285 (203–395)	201 (129–291)	145 (75–337)
NT-proBNP, pg/mL	1835 (552–3914)	13	465 (115–1527)	1901 (753–3846)	1632 (548–3598)	2735 (964–5257)

TABLE 1 (Continued)

		MRC Dyspnoea Scale				
	All	**1**	**2**	**3**	**4**	**5**
RAP, mmHg	8.5 ± 5.4	5	5.7 ± 5.4	8.6 ± 4.2	9.3 ± 5.2	8.8 ± 5.2
mPAP, mmHg	48.6 ± 12	47	49.5 ± 13	52.2 ± 16	49.5 ± 12	50 ± 11
PAWP, mmHg	7.7 ± 3.6	10	6.6 ± 3.6	7.9 ± 3.2	7.6 ± 3.6	7.4 ± 3
CI, L/min/m^2	2.0 ± 0.5	2.9	2.1 ± 0.5	1.9 ± 0.4	1.9 ± 0.5	1.8 ± 0.4
PVR, WU	12.1 ± 5.8	8.6	12.1 ± 6.1	13.7 ± 7.1	12.6 ± 5.8	13.4 ± 5.5
SvO2, %	59.5 ± 10	77	66 ± 7	58 ± 9	59 ± 10	58 ± 9
Initial treatment strategy, *n* (%)						
Monotherapy	98 (54)	1	23 (68)	19 (70)	43 (50)	12 (26)
Dual oral therapy	70 (39)	0	10 (29)	7 (26)	39 (45)	14 (42)
Oral + V therapy	5 (3)	0	0	0	2 (2)	3 (9)
Oral + Neb Iloprost	2 (1)	0	0	0	1 (1)	1 (3)
Triple oral therapy	1 (1)	0	0	0	0	1 (3)
Dual oral + IV therapy	5 (3)	0	1 (3)	1 (4)	1 (1)	2 (6)

Note: Data are presented as mean ± standard deviation, number (percentage) or median (interquartile range).

Abbreviations: 6MWD, six minute walk distance; CI, cardiac index; IV, intravenous; I/H/D-PAH, Idiopathic/hereditary/drug induced–pulmonary arterial hypertension; mPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SvO2, mixed venous oxygen saturation.

survival for the cohort was 94%, 76%, and 66% respectively, with an overall 28.7% mortality at the end of the follow-up. The median follow-up duration was 2.7 (1.4–5.6) years.

Baseline

The proportion of patients within each stratum per model at baseline are demonstrated in Table 1. The majority of patients were MRC Dyspnoea Scale 4 (47.5%). Of 120 patients classified as WHO FC III, 7.5% were MRC Dyspnoea Scale 2, 11.6% Scale 3, 70.8% Scale 4, and 10% Scale 5. Survival at baseline for 1-, 3-, and 5-year is demonstrated within Supporting Information: Table S1. Kaplan–Meier curves are compared in Figure 3a–c. A comparison of overall model performance is demonstrated in Table 2. All three models were unable to delineate risk accurately at baseline. For the MRC Dyspnoea Scale and WHO FC model, survival curves and confidence intervals overlapped. The COMPERA 2.0 model failed to delineate risk between the low risk and intermediate-low risk groups (HR 0.08 vs. 0.07).

First follow-up

The median time between diagnosis and first follow-up was 109 (IQR 95–137) days. Follow-up information was available in 154 (85%) cases (Figure 2). Fifty-four percent of patients were on monotherapy (75% phosphodiesterase 5 inhibitor, 18% endothelin receptor antagonist) and 39% were on dual oral therapy with 5.5% on parenteral Epoprostenol. In the COMPERA 2.0 model, 75 (41%) of patients changed risk strata compared to 90 (50%) for the MRC Dyspnoea Scale model and 59 (33%) for the WHO functional class model (Supporting Information: Figure 1F). Kaplan–Meier curves are compared in Figure 3d–f. Survival at 1-,3-, and 5-year is shown in Supporting Information: Table S1. Hazard ratios and model performance are shown in Table 2.

At follow-up, 87 (56%) patients were classified as WHO functional class III, of which 12 (14%) were MRC Dyspnoea Scale 2, 29 (33%) Scale 3, 40 (46%) Scale 4, and 6 (7%) Scale 5. A survival curve demonstrating the survival estimates for WHO FC III as broken down by MRC Dyspnoea Scale at follow-up is shown in Figure 4, which demonstrates that WHO FC III patients may be further stratified by MRC Dyspnoea Scale to obtain a more detailed assessment of exercise capacity.

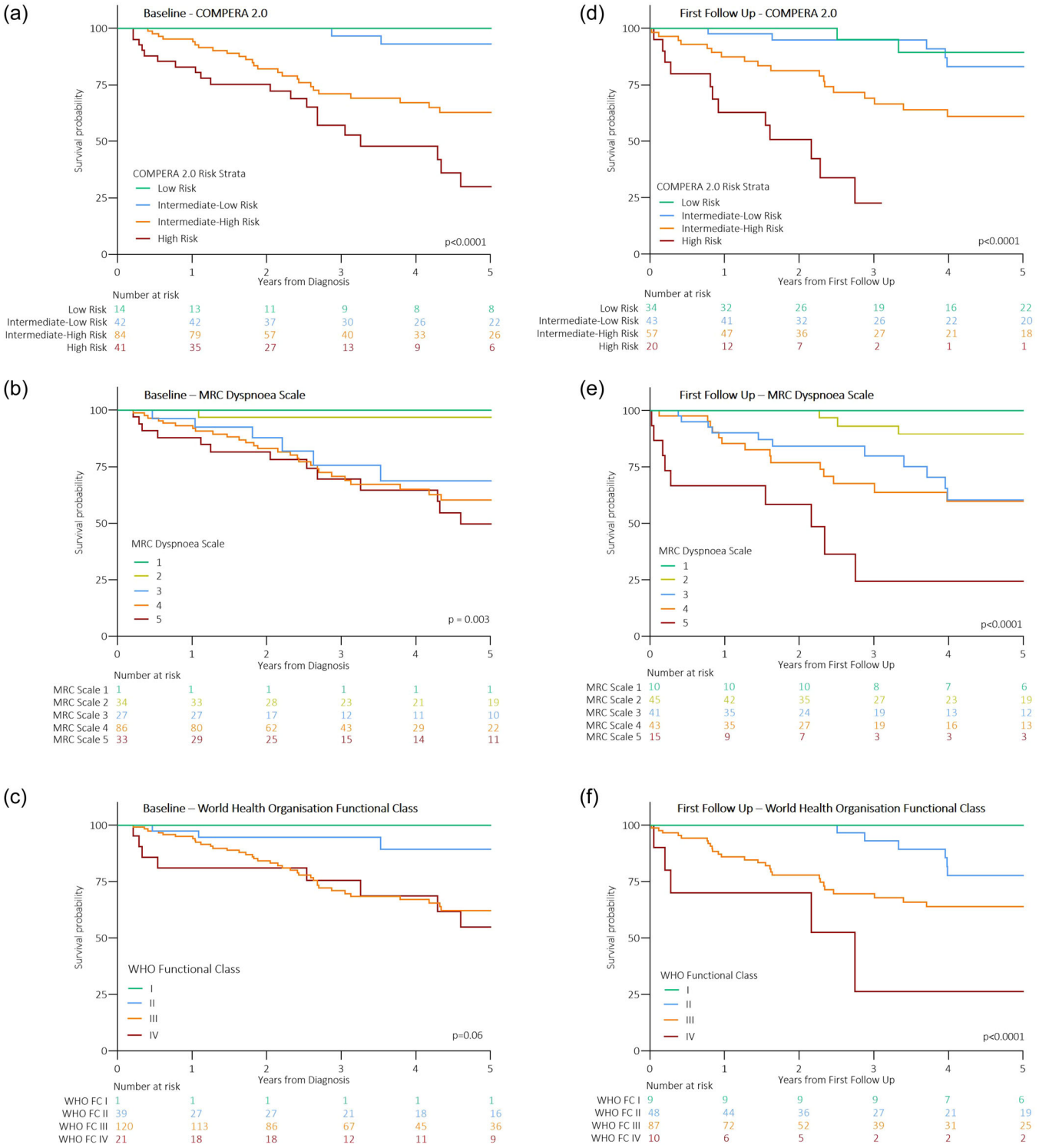

FIGURE 3 Kaplan–Meier curve demonstrating the respective survival estimates of the COMPERA 2.0 model, the MRC Dyspnoea Scale model and the WHO functional class model at baseline (a–c) and first follow-up (d–f). WHO, World Health Organisation.

MRC Dyspnoea Risk Score

As the WHO FC, MRC Dyspnoea Scale and COMPERA 2.0 models performed more poorly at baseline, the novel 4 strata MRC Dyspnoea Risk Score was only analyzed at first follow-up. The survival curve is demonstrated in Figure 5. Thirty-three (21.4%) patients were low risk, 37 (24%) patients intermediate-low risk, 61 (39.6%) patients intermediate-high risk, and 23 (14.9%) patients high risk. Survival at 1-, 3-, and 5-year in the low risk category was

TABLE 2 Cox proportional hazard ratios and 95% confidence intervals (CI), as calculated in reference to the highest risk strata and the Harrell's C and AIC for each model.

	Cox hazard ratios									
Model	**Low risk**	**95% CI**	**Intermediate-low**	**95% CI**	**Intermediate-high**	**95% CI**	**High**		**C statistic**	**AIC**
(a) COMPERA 2.0										
Baseline	0.08	0–0.4	0.07	0.02–0.21	0.45	0.25–0.81	-		0.71	457.7
First follow-up	0.04	0–0.13	0.11	0.04–0.27	0.20	0.10–0.49	-		0.75	359.6
	1	**95% CI**	**2**	**95% CI**	**3**	**95% CI**	**4**	**95% CI**	**5**	
(b) MRC Dyspnoea Scale										
Baseline	0	-	0.05	0–0.26	0.59	0.23–1.44	0.84	0.45–1.63	-	0.63	470.8
First follow-up	0	-	0.06	0.02–0.17	0.25	0.11–0.60	0.27	0.12–0.64	-	0.74	351.6
	I	**95% CI**	**II**	**95% CI**	**III**	**95% CI**	**IV**			
(c) WHO functional class										
Baseline	0	-	0.26	0.07–0.84	0.92	0.45–2.13	-		0.59	482.0
First follow-up	0	-	0.10	0.04–0.28	0.28	0.13–0.65	-		0.69	363.7
	Low risk	**95% CI**	**Intermediate-low**	**95% CI**	**Intermediate-high**	**95% CI**	**High**			
(d) MRC dyspnoea risk score										
First follow-up	0.04	0–0.14	0.09	0.03–0.24	0.23	0.11–0.47	-		0.76	349.0

Abbreviations: AIC, Akaike information criterion; MRC, Medical Research Council.

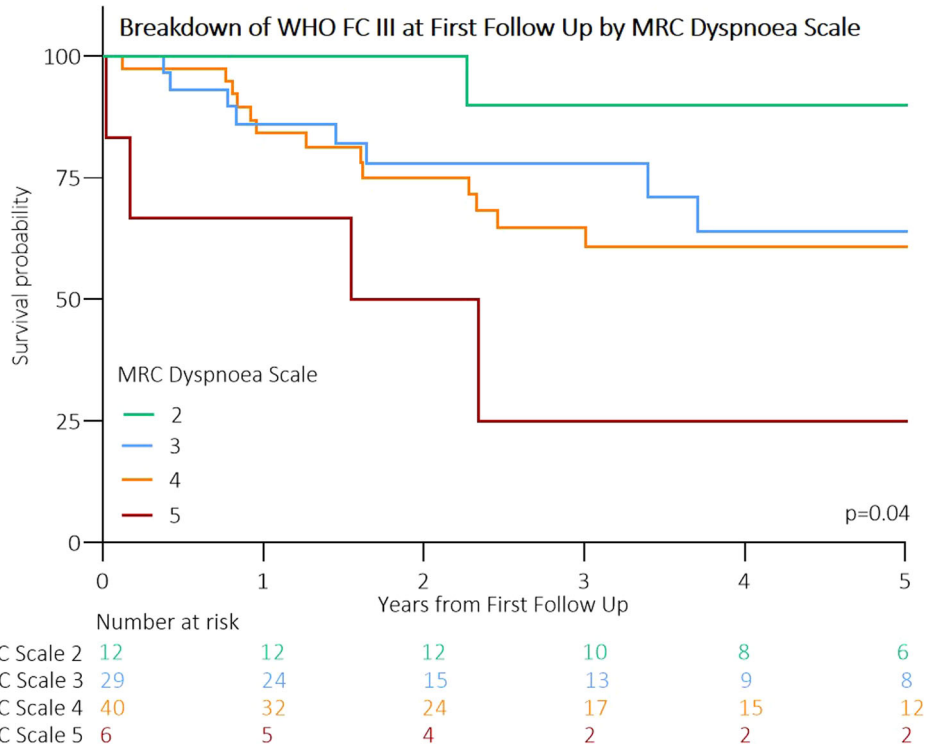

FIGURE 4 Kaplan–Meier curve demonstrating the survival estimates of patients classified as World Health Organisation Functional Class III at follow-up, as stratified by MRC Dyspnoea Scale.

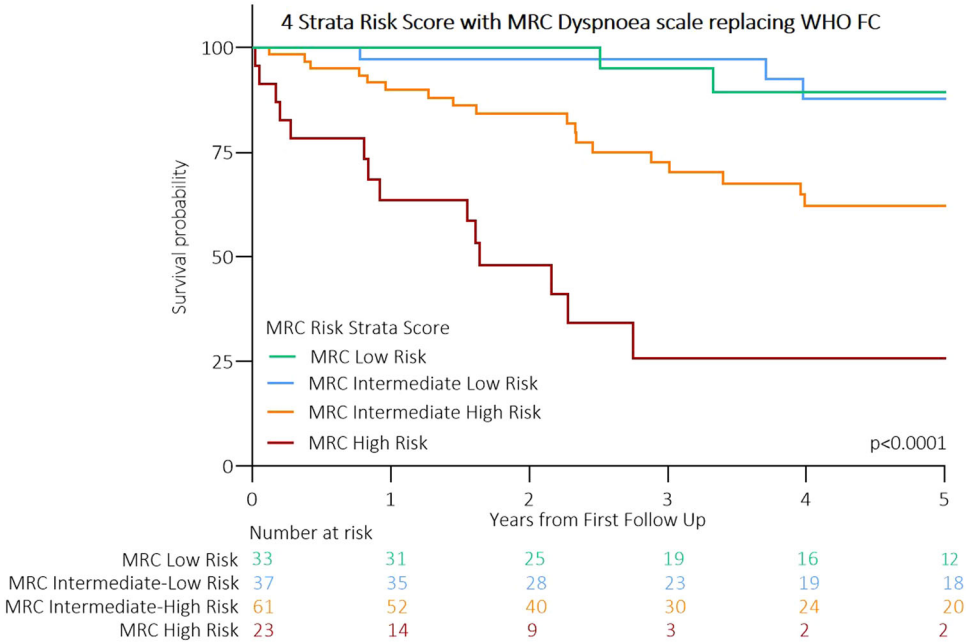

FIGURE 5 Kaplan–Meier curve demonstrating the survival estimates of patients at follow-up when stratified by the MRC Dyspnoea Risk Score (where the MRC Dyspnoea Scale replaces WHO FC in the 4 strata COMPERA 2.0 model). WHO FC, World Health Organisation Functional Class.

100%, 94.8%, 89.4%, intermediate-low risk 97%, 97%, 87%, intermediate-high risk 89.7%, 72.7%, 61.9%, and high risk 63.3%, 25.4%, 25.4%. Hazard ratios and the overall model performance are demonstrated in Table 2.

DISCUSSION

This study investigated the MRC Dyspnoea Scale as a risk assessment tool within pulmonary arterial hypertension and has demonstrated it is able to predict survival in PAH. WHO FC III patients may be subdivided using the MRC Dyspnoea Scale, which has the potential to further stratify this risk group based on exercise capacity. Replacing WHO FC with the MRC Dyspnoea Scale (the MRC Dyspnoea Risk Score) within the COMPERA 2.0 model led to a similar performance at estimating mortality risk at first follow-up. Overall, this study demonstrates the potential for the MRC Dyspnoea Scale to be used as an alternative risk assessment tool in PAH at the point of first follow-up.

All models performed poorer at baseline compared to first follow-up, with inferior C-statistics alongside reduced delineation of mortality on survival curves. However, compared with WHO FC both baseline and follow-up, the MRC Dyspnoea Scale allowed greater resolution in assessing perceived disability due to dyspnoea since patients within WHO FC III were able to be further subdivided into MRC Dyspnoea Scales. Furthermore, a greater number of patients moved risk category between baseline and follow up using the MRC Dyspnoea Scale model compared to the other models. At first follow-up, the MRC Dyspnoea Scale model outperformed the WHO functional class model (C statistic 0.74 vs. 0.69) with comparable performance to the current COMPERA model (C statistic 0.75). Compared to the validation cohort in the COMPERA 2.0 study, this study demonstrates similar discrimination for the COMPERA 2.0 model at baseline (C-statistic 0.71 vs. 0.64) and follow-up (0.75 vs. 0.73).[4] This may indicate a role for the MRC Dyspnoea Scale as an alternative and perhaps more granular measure to WHO FC.

Exchanging the WHO FC for the MRC Dyspnoea Scale at follow-up within the 4 strata system gave a novel model (MRC Dyspnoea Risk Score) that had an equivalent performance and fit to the COMPERA model (C statistic 0.76). Patients were reasonably distributed between risk strata, although the survival curves crossed between the low and intermediate-low risk population.

The first follow-up has been shown to be a vital point for assessing ongoing treatment response and mortality; patients who fail to achieve a lower risk status within 3–6 months of starting on disease targeted treatment are unlikely to do so in the future and have poorer outcomes.[16] The MRC Dyspnoea Scale model performed well in assessing these changes, with a large number of patients moving between risk groups with a superior C-statistic, therefore suggesting it is a more sensitive tool in detecting clinical change.

This study has limitations. It is a retrospective study from a single center, in a relatively small cohort. Retrospective analysis gives rise to issues with missing values and lack of standardized timings for patient visits. A reasonable proportion of patients (~15%) were unable to be included in the first follow-up cohort. The algorithm used to assign MRC Dyspnoea Scale was designed to closely mirror the criteria of the MRC scale and therefore create a robust functional assignment as possible, yet regardless this remains a retrospective process and will be prone to error. Furthermore, this process relies on clinicians accurately describing WHO FC and therefore the improved performance of the MRC Dyspnoea Scale when compared to WHO FC may be partially due to a refined allocation of functional status. Further work would be required to validate the MRC Dyspnoea Risk score, such as further analysis in an alternative PH center or a prospective analysis.

In summary, this study demonstrates the potential for the MRC Dyspnoea Scale to replace WHO functional class as an alternative risk assessment strategy at first follow-up for pulmonary arterial hypertension. In this small, retrospective study, the MRC Dyspnoea Scale outperformed the WHO functional class model. Furthermore, when incorporated within a 4 strata risk assessment model, the MRC Dyspnoea Scale had equivalent performance to the COMPERA 2.0 model. Further analysis and validation are required to confirm these findings.

AUTHOR CONTRIBUTIONS

Folawemimo Arogundade: Investigation; writing—review and editing. **Bhautesh Jani**: Supervision; writing—review and editing. **Colin Church**: Supervision; writing—review and editing. **Melanie Brewis**: Supervision; writing—review and editing. **Martin Johnson**: Conceptualization; supervision; writing—review and editing; project administration; approval of the final draft for submission; guarantor. **Harrison Stubbs**: Methodology; formal analysis; supervision; project administration; investigation; data curation; writing—original draft; visualization. Martin Johnson is the guarantor for the study.

ACKNOWLEDGMENTS

The MRC Dyspnoea Scale was used with the permission of the Medical Research Council. No external funding was required for this study.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Approval was obtained from the West of Scotland Research Ethics Service (Ref 22/WS/0149). This was a retrospective study, involving data which had already been collected as part of routine clinical care, and therefore patients were not included directly in the design of the study. However, the research objectives were formed with patients directly in mind.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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