DOI: 10.1002/pul2.12253

LETTER TO THE EDITOR

Pulmonary Circulation Open Access | PVRI | WILEY

Risk assessment in pulmonary arterial hypertension: A step towards clinical implementation based on the 2022 ESC/ERS pulmonary hypertension guidelines

Dear Editor,

We read with great interest the studies by Wilson et al.[1] "Current clinical utilization of risk assessment tools in pulmonary arterial hypertension: a descriptive survey of facilitation strategies, patterns, and barriers to use in the United States," and "Clinical application of risk assessment in PAH: Expert center APRN recommendations,"[2] as well as the recent publication by Sahay et al.[3] "Utilization of risk assessment tools in management of PAH: A PAH provider survey"; all published in previous issues of *Pulmonary Circulation*. We acknowledge the authors for their contributions on assessing the clinical utilization of risk assessment in pulmonary arterial hypertension (PAH),[1,3] identifying potential major barriers impacting clinical underutilization and presenting recommendations to overcome these barriers.[2,3]

From a brief historical perspective, the 2004 European Society of Cardiology (ESC) PAH guidelines and the succeeding 2009 ESC/European Respiratory Society (ERS) pulmonary hypertension (PH) guidelines, advocated multiparametric assessments in patients with PAH, to acquire better prognostication.[4,5] With the growing body of evidence, multiparametric risk assessment has retained the highest class of recommendation, and the level of evidence increased from C to B in the 2022 ESC/ERS PH guidelines.[4,6,7] Following the publication of the 2015 ESC/ERS PH guidelines, a number of calculations models based on the guidelines' risk stratification strategy were validated by independent registries, including the Swedish PAH registry (SPAHR), the French PH registry, and the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA) (Figure 1).[7,8] Other models established from the US Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL), have been validated, where the most recent being REVEAL 2.0 and its abridged version REVEAL 2.0 Lite, based on weighted predictors derived from the REVEAL-equation.[9] Recently, a simplified three-parametric, four-strata model, COMPERA 2.0, employing only functional class, 6 min walking distance, and natriuretic peptides has been proposed, which was externally validated by a large cohort using the French PH registry[7] (Figure 1).[8]

The increasing number of risk assessment models that are subject to continuous validation and refinement may appear deluging, impacting clinical utilization. A study by Wilson et al.[1] found that nonphysicians compared with physicians had two major issues accounting for the underutilization of risk assessment tools, including lack of education and training (20% vs. 4%), and lack of clarity on the best tool to use (30% vs. 18%).[1] A study by Sahay et al.[3] found that risk assessment was used among 63% of clinicians and the most commonly identified barriers of underutilization were time constraints and lack of integration into electronic medical records. Additionally, a study by Simons et al.[10] found a 55% discordance between clinical gestalt and calculated risk score, as well as that 80% of patients clinically judged as low-risk were assigned to higher risk categories based on their calculated risk.

Another study by Wilson et al.,[2] aiming to put forth recommendations to overcome barriers for incorporation of risk assessment into clinical practice, found that time constraints and to a lesser extent insufficient awareness and training, prevented regular use of risk assessment tools. The recommendation to overcome the "time constraint barrier" was to introduce "technology-based solutions" such as computer- or phone-based risk calculating applications, and integrating risk assessment tools into electronic medical records.[1,2]

The current 2022 ESC/ERS PH guidelines recommend the use of a three-strata model at baseline and a simplified four-strata model during follow-up assessments to guide treatment in PAH. The transition from three-strata to four-strata is based on that 67%–76% of patients with PAH were classified within the

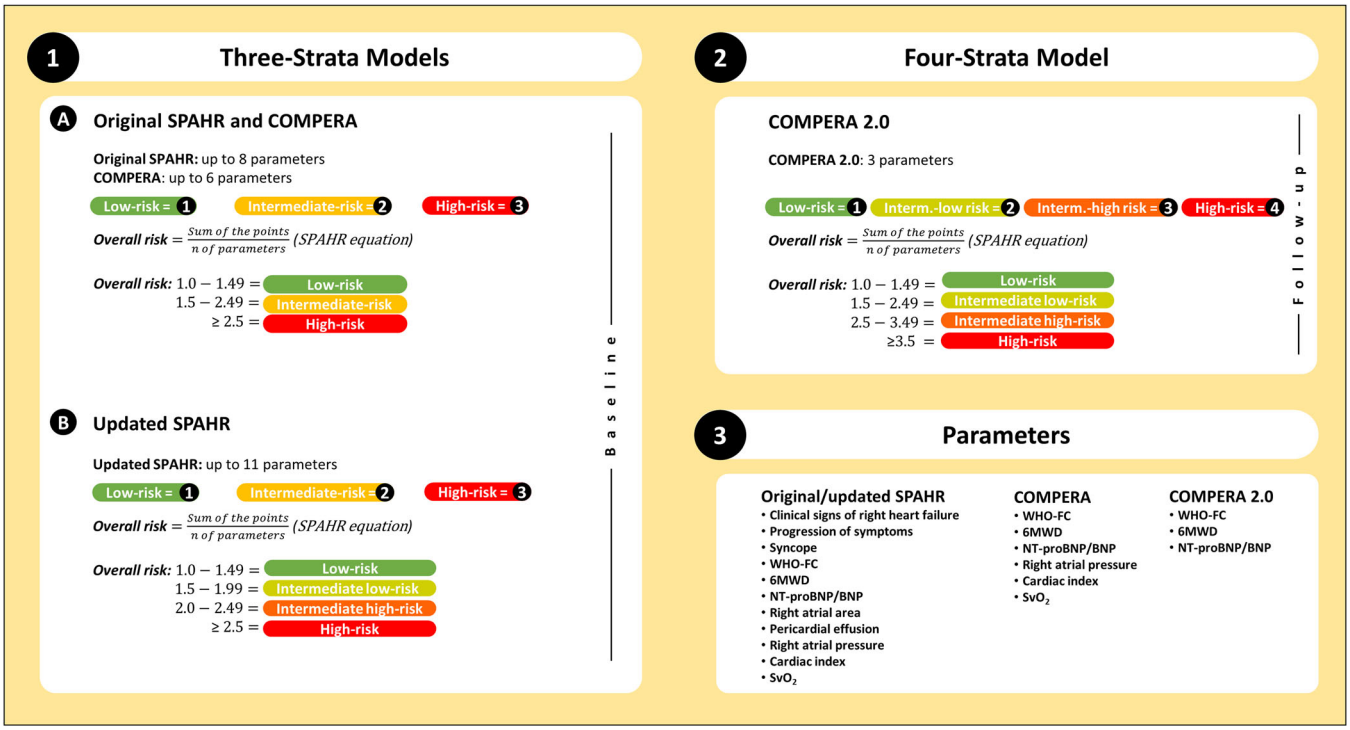

FIGURE 1 Calculation of risk scores using the European Society of Cardiology/European Respiratory Society (ESC/ERS)-based risk stratification three-strata and four-strata models. First published in *European Heart Journal Open*, 2023. Illustration by Abdulla Ahmed.

intermediate risk group at diagnosis, and 60%–64% during follow-up assessments.[7,8] Additionally, the guidelines emphasize the importance to include additional parameters into the four-strata model when clinically needed during follow-up assessments, for a more comprehensive overview.[7] This is, however, not offered by the simplified three-parametric COMPERA 2.0 four-strata model, and a strategy on how a comprehensive multiparametric approach should be performed was not specified in the 2022 ESC/ERS PH guidelines. In our recent study, "Evaluation of the European Society of Cardiology/European Respiratory Society derived three- and four-strata risk stratification models in PAH: introducing an internet-based risk stratification calculator," we aimed to evaluate the different ESC/ERS based three-strata models and the four-strata COMPERA 2.0 model.[8] Also, in light of the recommendations proposed by Wilson et al.,[1,2] to overcome the barriers of clinical underutilization of risk assessment, we introduced a comprehensive internet-based risk score calculator (https://www.svefph.se/risk-stratification).[8]

Our results evaluate and validate the updated SPAHR calculation model with divided intermediate risk, that unlike the SPAHR/COMPERA model can calculate "four-strata" through new rounding off limits of the calculated average scores (Figure 2). At baseline, both the original SPAHR/COMPERA and the updated SPAHR models, using up to six parameters, provided the highest prognostic accuracy (time-dependent C-statistics, uAUC) = 0.73 for both models) in predicting 1-, 3-, and 5-year mortality. At follow-up assessments, the updated SPAHR model with divided intermediate risk (7–11 parameters) provided the highest accuracy for 1-, 3-, and 5-year mortality (uAUC = 0.90), followed by the original SPAHR/COMPERA model (7–11 parameters, uAUC = 0.88) and the COMPERA 2.0 model (uAUC = 0.85). Although promising, larger multicenter studies are encouraged to validate the utility of the updated SPAHR model.[8]

In the comprehensive internet-based risk stratification calculator, we have initially included the ESC/ERS risk assessment models including the original SPAHR/COMPERA, updated SPAHR, French PH registry invasive and noninvasive models, as well as COMPERA 2.0. Our ambition is in the future to add REVEAL 2.0 and/or REVEAL 2.0 Lite, and update the website as new evidence emerges.

In conclusion, there are several contemporary risk stratification models differing in terms of the type and number of included parameters, calculation method, and weighting. Risk assessment should be used more regularly as 59-63% utilization among clinicians is far from sufficient.[1–3,10] However, risk assessment should not replace clinical gestalt, as the former only fulfils an

Determinants of prognosis		Risk Group Corresponding to 1-year Mortality			
		Low risk (<5%)	Intermediate risk (5 - 20%) Intermediate-low	Intermediate-high	High risk (> 20%)
Clinical Observations	Clinical signs of right heart failure	Absent	Absent		Present
	Progression of symptoms	No	Slow		Rapid
	Syncope	No	Occasionally		Repeated syncope
Modifiable Parameters	WHO functional class	I or II	III		IV
	Six-minute walking distance	> 440 m	165 - 440 m		< 165 m
	Cardiopulmonary excercise testing	Peak VO_2 > 15 ml/min/kg (> 65 % predicted) VE/VO_2 slope < 36	Peak VO_2 11 - 15 ml/min/kg (35 - 65 % predicted) VE/VO_2 slope 36 - 44		Peak VO_2 < 11 ml/min/kg (< 35 % predicted) VE/VO_2 slope > 44
	Biochemical markers	NT-proBNP < 300 ng/l BNP < 50 ng/l	NT-proBNP 300 - 1100 ng/l BNP 50 - 800 ng/l		NT-proBNP > 1100 ng/l BNP > 800 ng/l
	Echocardiography	RA area < 18cm^2 TAPSE/sPAP > 0.32 mm/mmHg No pericardial effusion	RA area 18 - 26 cm^2 TAPSE/sPAP 0.19 - 0.32 mm/mmHg Minimal pericardial effusion		RA area > 26 cm^2 TAPSE/sPAP < 0.19 mm/mmHg ≥Moderate pericaridal effusion
	Cardiac magnetic resonance imaging	RVEF > 54 % SVI > 40 mL/m^2 RVESVI < 42mL/m^2	RVEF 37-54 % SVI 26 - 40 mL/m^2 RVESVI 42 - 54 mL/m^2		RVEF < 37 % SVI < 26 mL/m^2 RVESVI > 54 mL/m^2
	Haemodynamics	RAP < 8 mmHg CI ≥ 2.5 L/min/m^2 SVI > 38 mL/m^2 SvO_2 > 65 %	RAP 8 - 14 mmHg CI 2.0 - 2.4 L/min/m^2 SVI 31 - 38 mL/m^2 SvO_2 60 - 65 %		RAP > 14 mmHg CI < 2.0 L/min/m^2 SVI < 31 mL/m^2 SvO_2 < 60 %
Original SPAHR/COMPERA equation score		1 - 1.49	1.5 - 2.49		2.5 - 3.0
Updated SPAHR equation score with divided intermedaite risk		1 - 1.49	1.5 - 1.99	2.0 - 2.49	2.5 - 3.0

FIGURE 2 Comprehensive risk assessment in pulmonary arterial hypertension (three-strata) using the original Swedish Pulmonary Arterial Hypertension Registry/Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (SPAHR/COMPERA) model and the updated SPAHR model with divided intermediate risk. First published in *European Heart Journal Open*, 2023. Illustration by Abdulla Ahmed.

objective complement to clinical assessment. Given these findings, it is all the more important to implement the 2022 ESC/ERS PH guidelines through integrating risk assessment, irrespective of preferred validated calculation model, into clinical practice to guide treatment in PAH.[7]

AUTHOR CONTRIBUTIONS

Abdulla Ahmed, Salaheldin Ahmed, and Göran Rådegran stood for the concept. Abdulla Ahmed drafted the letter. Salaheldin Ahmed and Göran Rådegran revised the manuscript critically and approved the final version for publication.

ACKNOWLEDGMENTS

We thank Daniel Kempe for programming the web-based calculator.

CONFLICT OF INTEREST STATEMENT

Abdulla Ahmed and Salaheldin Ahmed report no conflicts of interest. Göran Rådegran reports unrestricted research grants from ALF, GoRadCare AB, and Nordic Infucare, as well as a noninterventional investigator-initiated study research grant from Janssen-Cilag AB, during the conduct of this work. Abdulla Ahmed and Salaheldin report personal lecture fees from Janssen-Cilag AB and Nordic Infucare outside the submitted work. Göran Rådegran reports personal lecture fees from Actelion Pharmaceuticals Sweden AB, Bayer Health Care, GlaxoSmithKline, Janssen-Cilag AB, Merck Sharp & Dohme AB, Nordic Infucare, and Orion Pharma outside the submitted work. Göran Rådegran is and has been the primary, or co-, investigator in clinical PAH trials for Acceleron, Actelion Pharmaceuticals Sweden AB, Bayer, Janssen-Cilag AB, Merck Sharp & Dohme AB, Pfizer, and United Therapeutics, and in clinical heart transplantation immunosuppression trials for Novartis.

ETHICS STATEMENT

The present letter is based on a recent study, which conforms with the Declaration of Helsinki and Istanbul and was approved by the regional ethical board in Lund, Sweden (Dnr: 2010/114, 2011/777).[8]

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