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LETTER TO THE EDITOR

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Risk assessment in pulmonary arterial hypertension patients with multiple comorbidities and/or advanced age—Where do we stand and what's next?

Dear Editor,

The 2022 ESC/ERS pulmonary hypertension (PH) guidelines evaluated the evidence and clinical role of risk stratification, by answering *key narrative question 4 -"Should a risk-stratification strategy be used to guide treatment in patients with pulmonary arterial hypertension (PAH)?"* The guidelines concluded that therapeutic decision-making in PAH should be based on two prognostic determinators, that is, PAH severity assessed by risk stratification, and comorbidity burden. Despite the fact that those with comorbidities and/or elderly constitute the majority of patients with PAH, there are no clear recommendations for how the comorbidity burden can be integrated into prognostic risk assessment. Thus, most patients are excluded from risk assessment, as a means to guide treatment, due to scarcity of evidence.[1] These patients are also often excluded from PAH trials, and apart from retrospective data, there is limited evidence on treatment strategies in this patient group.[1,2] Considering further re-evaluations of treatment strategies in the upcoming World Symposium on PH (WSPH) in 2024, it is important to shed light on emerging PAH phenotypes, defined by the type and number of comorbidities as well as age, in relation to life expectancy and treatment goals—all of which are paramount to optimize prognostic risk assessment.

PAH was previously believed to predominantly affect younger individuals and mostly females.[1] Contemporary registries in Europe and the United States, however, suggest that PAH is more frequently diagnosed in older patients, often with a nonnegligible comorbidity burden.[1,2] The concurrence of idiopathic PAH (IPAH) and at least one comorbidity—multimorbidity—in the Swedish PAH registry (SPAHR) and the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA) is estimated to be approximately 80%, compared to approximately 25% in the general adult population.[2–4] In recent years, different PAH phenotypes have been described. While acknowledging that cohorts differ in the number of comorbidities reported, there appear to be three phenotypes; (i) the classical phenotype, defined by young, mostly females, with no comorbidities, predominantly nonsmokers with high D_{LCO}; and two additional phenotypes with comorbidities, often elderly—that is, (ii) the cardiac phenotype characterized by a predominance of risk factors for left heart disease, and (iii) the pulmonary phenotype characterized by significant smoking history, slight predominance of males, low D_{LCO}, and mild emphysema and/or lung fibrosis.[1–3,5,6] In general, patients with the cardiac- or pulmonary phenotype exhibit worse prognosis, improve less to PAH-specific therapy, and improve less in relation to prognostic risk parameters.[2,3,5,6]

Moreover, the pathophysiology in the cardiac- and pulmonary phenotypes is likely driven by different dominating mechanisms, making the distinction from PAH with comorbidities or PH due to comorbidities challenging.[1,3,5] In PAH, both the type and number of comorbidities influence prognosis.[2,7] SPAHR data demonstrated that in patients with IPAH, renal dysfunction, and ischemic heart disease were independent predictors of survival among seven comorbidities.[2] In a COMPERA analysis based on patients with IPAH, the number of comorbidities, up to 4, was independently associated with mortality.[7] Only coronary heart disease and diabetes were, however, associated with mortality.[7] Although certain comorbidities appear of particular importance, a study from the United States on the elderly found that the impact of the type of comorbidity on life expectancy diminished with increasing age and number of comorbidities.[8] Thus, the lower the number of comorbidities, the more relevant the type may be regarding prognostic assessment.

Both the ESC/ERS three-strata and four-strata risk assessment instruments have been investigated in elderly with multiple comorbidities.[2,7] The four-strata instrument appeared more sensitive to changes in risk categories than the three-stata instrument, probably related to that most patients were classified in the intermediate-risk group and that in comorbid patients, most improvements occurred within the intermediate-risk group.[7] However, a limitation

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Determinants of prognosis		Risk Group Corresponding to 1-year Mortality				
		Low risk (<5%)*	Intermediate-low	Intermediate risk (5 - 20%)*	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 %
The type and number of comorbidities		The impact of the type of comorbidity on life expectancy diminishes with increasing number of comorbidities[10] Atrial fibrillation, dementia, diabetes mellitus, heart failure, ischemic heart disease, ischemic stroke, lung fibrosis, malignancy, obesity (30 kg/m^2), obstructive pulmonary disease, peripheral artery disease, renal dysfunction (eGFR <60 mL/min/1.73 m^2), sleep apnoea, systemic hypertension, and thyroid disease				
Demographics		Age, gender, and PAH aetiology				
Frailty		Higher frailty → worse prognosis (comorbidities and frailty are independent predictors of mortality)[9]				
Treatment goals (in relation to life expectency)		Low comorbidity burden		High comorbidity burden		
Original SPAHR/COMPERA score		1 - 1.49		1.5 - 2.49		2.5 - 3.0
Updated SPAHR score with divided intermedaite risk		1 - 1.49	1.5 - 1.99		2.0 - 2.49	2.5 - 3.0

FIGURE 1 Suggestion of a modified risk assessment and prognostic evaluation approach in PAH patients with respect to comorbidity burden, demographics, and frailty. Apart from comorbidity burden, demographic characteristics, and frailty, treatment goals should be based on life expectancy. The ESC/ERS guidelines recommend the use of a three-strata instrument (original SPAHR/COMPERA) at baseline assessments. At follow-up assessments, the guidelines recommend the use of the three-parametric four-strata instrument (COMPERA 2.0), while acknowledging that more parameters should be included if needed, without addressing how this should be performed. The Updated SPAHR instrument can, however, employ additional parameters by using the three-strata table to calculate a four-strata score, as shown in the last row. The updated SPAHR instrument with divided intermediate risk category therefore offers as a complement to COMPERA 2.0. In patients with frailty, multiple comorbidities, and/or elderly, the 1-year mortality rates are likely higher than in those without comorbidities (denoted by *) due to lower life expectancy. Frailty is a state of increased vulnerability to stressors due to depleted physiologic reserves and is considered as a distinct entity from comorbidities. Further validation of these instruments are warranted.[9] First published in European Heart Journal Open, 2023.[10] Illustrated and modified by Abdulla Ahmed.

of both the three- and four-strata instruments is the low percentage of patients with comorbidities reaching or maintaining a low-risk category. Data from SPAHR using the three-strata instrument demonstrated that in patients with IPAH, approximately 20% of those ≥65 years and approximately 5% of those ≥75 years reached or maintained a low-risk category.[2] Data from COMPERA using the four-strata instrument found that in patients with IPAH and 1–2, respectively, 3–4 comorbidities, nearly 12%, respectively, 3% reached or maintained a low-risk category. However, in both groups (1–2 and 3–4 comorbidities) nearly 20% at baseline and 30% during follow-up exhibited an intermediate-low risk profile.[7]

Finally, the 2022 ESC/ERS PH guidelines recommend a goal-oriented approach defined by reaching or maintaining a low-risk category corresponding to a 1-year mortality rate <5%, yet acknowledging that in PAH patients with comorbidities, a low-risk category is not always achievable.[1]

Based on COMPERA data, patients with IPAH and 1–4 comorbidities (median age 73–74 years), that were classified in the intermediate-low-risk group had approximately 65%–85% 5-year survival.[7] Based on SPAHR data, patients with IPAH aged between 65 and 74 years had a 5-year survival rate of 58% (all risk categories included).[2] In comparison, a study from the United States ($n = 479{,}646$; aged ≥66 years) found that the 5-year survival rates of 66–75-year-olds with at least 3 comorbidities were 54%, respectively 76%, depending on the presence or absence of frailty.[9] Moreover, among those aged ≥ 67 years, each chronic comorbidity decreased the life expectancy on average by 1.8 years.[8] A 70-year-old (typical age for PAH-diagnosis), with at least three comorbidities have a life expectancy between 6 and 12.5 years depending on the presence or absence of frailty. Altogether, this raises the question of whether low-intermediate-risk, exhibiting a slightly higher 1-year mortality rate, is a more reasonable treatment goal for those with multiple comorbidities and/or elderly,[9] (Figure 1).[10]

In conclusion, the ability of risk stratification to provide accurate information on treatment response and prognosis is encouraged to be further evaluated in those with multiple comorbidities and/or elderly.[1] First, risk assessment should be sensitive enough to detect incremental, clinically relevant improvements/deteriorations, and provide guidance for reasonable treatment goals in relation to population-based versus phenotype-based life expectancy. Second, the role of frailty should be further explored. Third, joint efforts should be made in collecting and reporting a wider range of chronic comorbidities to achieve a more precise phenotyping.

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.

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CONFLICTS OF INTEREST STATEMENT

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ETHICS STATEMENT

The present letter is based on data from published literature, and hence no specific ethical approval was required.

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