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RESEARCH ARTICLE

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Assessing quality of life in pulmonary arterial hypertension: An independent prognostic marker

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Abstract

Pulmonary arterial hypertension (PAH, or PH Group 1), a disease of aberrant pulmonary vascular remodeling, causing progressive right heart failure (RHF) due to elevation of pulmonary vascular resistance (PVR). Patient mortality risk stratification guides choice and intensity of pharmacological intervention and is assessed by haemodynamics (especially PVR) as well as noninvasive tools including WHO functional class (FC), 6-min walk distance (6MWD), and NT-proBNP levels. Quality of life (QOL) assessment is acknowledged as a central aspect of patient-centered care, but our study sought to extend QOL's role as an additional noninvasive risk marker that could further refine risk stratification and hence therapeutic choices within a "treatment to target" paradigm (aiming to achieve low-risk status). This study found that QOL assessment using the PAH-SYMPACT© physical activity tool provided enhanced, independent mortality risk information, with one unit rise in this score associated with a 41% increase in likelihood risk (odds ratio 1.41, 95% confidence interval: 1.01–1.98 ($p < 0.05$)) of falling within intermediate versus low-group category. We therefore found further support for additional prognostic value being conferred by measurement of QOL as part of routine PAH evaluation, reinforcing its critical role.

KEYWORDS
functional ability/impairment/quality of life/physical activity, health outcomes assessment/cost effectiveness, mortality, prognosis, pulmonary arterial hypertension

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a condition of elevated pulmonary arterial resistance, causing pathological pulmonary vascular remodeling and, with advancing disease, the development of symptoms including breathlessness, palpitations, chest pain, and syncope. The condition is confirmed with abnormal hemodynamic parameters: most importantly, a pulmonary vascular resistance (PVR) exceeding 2 Wood units (WU) and a mean pulmonary artery pressure (mPAP) > 20 mmHg,[1,2] without elevation of pulmonary artery wedge pressure (PAWP ≤ 15 mmHg). PAH is associated with variable prognosis, reflective of its heterogeneity, based upon

etiology, functional impairment, and hemodynamic abnormalities. The development of pharmacological interventions for PAH management has enhanced outcomes substantially, but there is still much room for improvement, especially in "high-risk" patient subgroups. PAH management strategies focus on lowering mortality risk, extending the patient's life span through improved hemodynamics, improving health-related quality of life (QOL), and decreasing the burden of illness.[3] Prognostic subsets can be defined using so-called risk stratification markers,[4] with best practice being to offer ongoing PAH management with sequential escalation of treatments aiming to achieve the lowest risk category and hence to confer superior outcomes.

There is growing evidence that the measurement of patient-reported outcome measures (PROs) and QOL is not merely central to comprehensive health practice, but that QOL scores may also add further prognostic information (independent of traditional risk stratification markers) regarding expected outcomes in each individual.

The aim of this study was to explore the assessment of PROs using both disease-specific (PAH-SYMPACT©) and nonspecific (EQ-5D-5L™) tools in a cross-section of Group 1 pulmonary hypertension (PAH) subjects attending the Hunter-New England (HNE) PAH clinic (Newcastle, Australia) and, through modeling, to assess whether any signals arose consistent with independent prognostic information being provided by these QOL tools.

TABLE 1 Demographic data on all patients.

n	33
Females: *n* (%)	28 (85)
Age: mean (SD) [range]	69.5 (11.5) [39–84]
WHO-FC I (%), WHO-FC II (%), WHO-FC III (%)	14 (42), 16 (49), 3 (9)
NT-proBNP: mean (SD) [range]	1546.6 (2333.9) [20–9626]
6-Min walk distance: mean (SD) [range]	325.4 (89.5) [140–498]
PAH-SYMPACT© tools: mean (SD) [range]	
Cardiopulmonary symptoms	6.1 (3.8) [1–15]
Cardiovascular symptoms	2.5 (3.0) 0–14
Symptom score	4.3 (3.1) [1–12.5]
Physical impact	10.5 (6.5) [2–28]
Cognitive/emotional impact	3.8 (2.7) [1–11]
Impact score	7.2 (3.6) [1.5–15]
EQ-5D-5L tools: median [range]	
Mobility	2.0 [1–5]
Self-care	1.0 [1–5]
Usual activities	2.0 [1–5]
Pain/distress	2.0 [1–5]
Anxiety/depression	2.0 [1–4]
EQ-5D-5L Health VAS: mean (SD) [range]	65.5 (22.0) [10–100]
Health Utility Score: mean (SD) [range]	0.76 (0.24) [0.163–1]

METHODS

This cross-sectional study analyzed a set of consecutive adult patients with a confirmed diagnosis of WHO Group 1 PAH (ages 39–84, mean age 69.5; WHO-FC I–III) sequentially attending the Hunter multidisciplinary PAH clinic between July 2020 and June 2021 ($n = 17$) combined with a randomly-extracted risk-matched group of PAH database patients ($n = 16$). Tables 1 and 2 summarize the key features of the study population overall (Table 1), and by calculated risk stratum (Table 2). Using electronic medical records, online instruments, and paper-based questionnaire data collected at a single time point, the results of three standard noninvasive prognostic clinical measures (WHO-FC, 6MWD, and NT-proBNP) and two QOL tools (PAH-SYMPACT© and EQ-5D-5L) were collected.

The hospital institutional review board approved the protocol, which was conducted in accordance with the Declaration of Helsinki principles[5] and the Good Clinical Practice guidelines of the International Council for Harmonization.[6]

Risk stratification was performed in accordance with the ESC/ERS consensus recommendations[4] proposing harmonization of existing three- and four-strata risk models, and advising that baseline and treatment monitoring use the three- and four-strata methods, respectively. Our cohort included a roughly equal mix of existing and newly diagnosed patients, and the three-stratum method was chosen. The NT-proBNP cut-off levels were accordingly updated from the 2015 version based on data from the REVEAL registry, acknowledging that the European validation studies had used original cut-offs.[7–13] In brief, each risk variable (6MWD, WHO-FC, and NT-proBNP) was graded from 1–3 where 1 = "Low risk," 2 = "Intermediate risk," and 3 = "High risk," with the mean grade calculated for each variable, and from this the overall patient risk category was allocated, with 1-year

TABLE 2 Demographic data on PAH patients by risk category.

	Low risk	Intermediate risk	High risk
n	6	23	4
Females (%)	5 (83.3)	19 (82.6)	4 (100)
Age: mean (SD) [range]	56.3 (8.9) [47–72]	71.0 (10.0) [39–83]	80.3 (2.9) [78–84]
WHO-FC I (%)	5	9	0
WHO-FC II (%)	1	14	1
WHO-FC III (%)	0	0	3
NT-ProBNP: mean(SD)[range]	231.7 (268.9) [20–699]	1519.4 (2111.3) [30–7135]	3675.8 (3972.9) [1503–9626]
6-Min walk distance: mean (SD) [range]	435.8 (55.0) [375–498]	317.3 (60.8) [192-430]	206.0 (75.4) [140–280]
PAH-SYMPACT© tools: mean (SD) [range]			
Cardiopulmonary symptoms	7.2 (4.4) [1–12]	5.5 (3.5) [1–15]	8.3 (4.3) [2–11]
Cardiovascular symptoms	3.3 (3.2) [1–9]	2.0 (2.0) [0 - 8]	4.3 (6.7) [0-14]
Symptom score	5.3 (3.7) [1–10.5]	3.7 (2.5) [1-11.5]	6.3 (4.8) [1-12.5]
Physical impact	8.8 (5.2) [2–16]	9.6 (5.9) [2–19]	18.5 (7.5)[12–28]
Cognitive/emotional impact	3.7 (3.3) [1–10]	4.1 (2.8) [1–11]	2.3 (1.0) [1–3]
Impact score	6.3 (3.6) [1.5-10]	6.8 (3.4) [1.5-12]	10.4 (3.8) [7–15]
EQ-5D-5L tools *median [range]*			
Mobility	1.5 [1–4]	2.0 [1–4]	3.0 [2–5]
Self-care	1.0 [1–2]	1.0 [1–3]	2.0 [1–5]
Usual activities	2.0 [1–4]	2.0 [1–5]	4.0 [3–5]
Pain/distress	2.5 [1–4]	2.0 [1–5]	3.5 [1–4]
Anxiety/depression	2.0 [1–4]	2.0 [1–4]	3.0 [1–4]
EQ-5D-5L Health VAS mean (SD) [range]	69.2 (26.3) [25–90]	69.0 (18.6) [30–100]	40.0 (21.6) [10–60]
Health Utility Score mean (SD) [range]	0.73 (0.34) [0.164–1]	0.80 (0.21) [0.163–1]	0.61 (0.29) [0.192–0.834]

Abbreviations: PAH, pulmonary arterial hypertension; SD, standard deviation.

mortality estimates of <5% for those at "low risk" (score < 1.5), 5%–20% for those at "intermediate risk" (mean score 1.5–2.49), and level 3 representing the highest risk group (mean score >2.5; >20% 1-year mortality). Low risk corresponded to WHO-FC I or II, 6MWD > 440 m, and NT-proBNP < 300 ng/L; the highest risk level included WHO-FC IV, 6MWD < 165 m, and NT-proBNP of >1100 ng/L, and patients with intermediate values for these markers were accorded intermediate risk.

To measure QOL, we employed the disease-specific PAH-SYMPACT©[8] tool to assess both symptoms and disease impacts. PAH-SYMPACT© uses 23 items (each descriptively graded from 1 to 5 ranging from no (1) to severe (5) impairment) to capture the degree of PAH-associated health impairment within two symptom domains (cardiovascular and cardiopulmonary) and two impact domains (physical and cognitive/emotional) monitored over a 7-day period, capturing overall illness experience in this labile condition. This was complemented by the nondisease-specific but widely employed EQ-5D-5L tool for QOL assessment,[14,15] from which Australia-specific health utility scores (HUS) were derived.[16] The EQ-5D-5L is a brief, multi-attribute generic measure exploring five health domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each with five levels of severity (descriptive scale ranging from 0 (no problems) through to 4 (extreme symptoms)). This tool also includes a visual analog score (VAS) (0 – 100 = worst to best imaginable health) of self-reported health perception (EQ-VAS), recorded at a single time point. EQ-5D-5L health states were converted to a single HUS using an Australia-derived preference scoring algorithm.[14,17]

Statistical analysis

We assessed the relationship with estimated 1-year mortality risk for each of the QOL tools and standard noninvasive prognostic markers (WHO-FC, 6MWD, and NT-proBNP), using mortality rates derived from existing data sets.

Correlations between variables were assessed using the Pearson product-moment correlation coefficient (r), with significant correlations reported for $|r| > 0.70$. The level of statistical significance for correlations was set at $p < 0.01$.

Ordinal logistic regression modeling (cumulative logit (log odds) parameterization under the proportional odds assumption) was employed to explore the interaction between the dependent variable (risk category - low, intermediate, and high, corresponding to 1 year mortality rates of <5%, 5%–20%, and >20%) and independent variables (WHO FC, 6-MWD, NT-pro-BNP, PAH-SYMPACT© scores, and EQ-5D-5L scores). Purposeful covariate selection[18] was used to define significant terms for the model with an initial exclusion value set at $p < 0.25$ and inclusion at $p > 0.15$. A final model was fitted after removal of noncontributory and collinear variables. Continuous data were analyzed as mean (SD) or as median (interquartile range (IQR)), and categorical data as number (percentage). Regression risk estimates were reported as odds ratios (95% confidence intervals, 95% CI). All statistical analyses were performed using Stata (version 15; College Station, TX, USA).

RESULTS

Measures of PAH risk and HR-QOL were assessed in 42 patients, from whom 33 patients with complete data sets were included. Listed below are the key characteristics of the overall study population (Table 1) and subsets by risk level (Table 2).

Thirty-three patients were included in the study, with an average age 69.5 (range 39–84) and approximately 85% (28/33) being female. None of the patients experienced WHO-FC IV impairment: WHO-FC I, WHO-FC-II, and WHO-FC III included 14 (42%), 16 (49%), and three patients (9%), respectively. HUS scores ranged from 0.163 to 1, where values close to 0 equate to QOL "close to death" and 1 represents unimpaired health perception.[15]

Reassuringly, there was generally good agreement between the two tools when measuring the same or similar factors. The PAH-SYMPACT© score for cardiopulmonary symptom burden correlated with EQ-5D-5L domain measuring ability to undertake usual activities ($r = 0.71$, $p < 0.01$) and also associated with greater health utility score (HUS) impairment ($r = -0.75$, $p < 0.01$). Not surprisingly, HUS impairment correlated with a number of scores of symptom and impact burden, including PAH-SYMPACT© symptom ($r = -0.85$, $p < 0.01$) and impact domains ($r = -0.73$, $p < 0.01$). PAH-SYMPACT© physical impact domain correlated highly with all physical components of the EQ-5D-5L questionnaire - mobility ($r = 0.82$, $p < 0.01$), self-care ($r = 0.75$, $p < 0.01$), and usual activities ($r = 0.77$, $p < 0.01$). PAH-SYMPACT© symptom domain score correlated with EQ-5D-5L mobility score ($r = 0.71$, $p < 0.01$). EQ VAS (well-being at a single time point) was inversely associated with PAH-SYMPACT© overall disease impact ($r = -0.70$, $p < 0.01$).

As expected, when comparing patients in lowest vs highest risk groups, significant differences were observed for 6MWD (Figure 1) and SYMPACT physical impact score (Figure 2), with a mean 6MWD of 435.8 m in the low-risk group compared with 206.0 m in those with the highest risk.

The parsimonious ordinal logistic regression model determined likelihoods for falling into low, intermediate, and high risk/mortality groups through the use of one standard noninvasive predictor (6MWD), and two QOL scores—for PAH-SYMPACT©, the physical impact score, and for EQ-5D-5L, the derived Australia-specific HUS (Table 3). For this model, the PAH-SYMPACT© physical impact score (odds ratio [OR] 1.41, 95% CI: 1.01–1.98) and the 6MWD (OR 0.96, 95%CI: 0.94–0.99) each provided significant independent contributions towards accurately defining the three risk categories in our model, with the HUS contribution approaching significance ($p = 0.07$). When compared with the likelihood of being at low risk, each unit rise in the PAH-SYMPACT© physical impact score was associated with a 1.41 times (41% increased) likelihood of being at intermediate-high mortality risk ($p = 0.05$); a similar estimated risk elevation between these two patient subsets was observed with a 40 m decrease in 6MWD (OR 0.96, $p < 0.005$).

DISCUSSION

Our study adds to the literature indicating the potential to further refine existing risk-assessment tools by including patient-reported outcome measures (PROs). Previous studies report the independent prognostic value of PROs in PAH patients: for example, Lewis et al.[19] describe the independent power of the emPHasis-10 tool in predicting mortality, with cut-offs defining mortality risk groups (score ≥ 34 defined a patient group with 23% 1 year mortality). This is further supported by the

FIGURE 1 Six-minute walk distance by risk category (low vs. high).

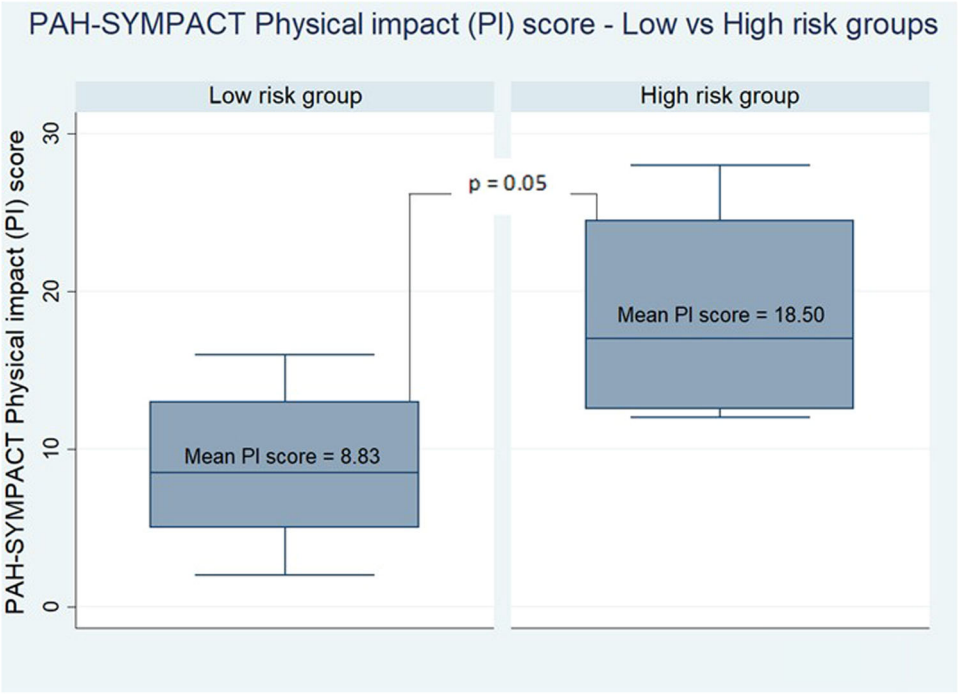

FIGURE 2 PAH-SYMPACT physical impact (PI) score by risk category (low vs. high).

findings of DuBrock et al.[20] demonstrating independent prognostic value for mortality risk from the PAH-SYMPACT© cognitive/emotional impact domain. Our study also identified similar mortality predictive value for both disease-specific (PAH-SYMPACT©) and generic (EQ-5D-5L) QOL tools.

The strong association between QOL scores and mortality is most likely partially mediated by the mutual

TABLE 3 Ordinal logistic regression model [3-level risk category] ($n = 33$).

	Odds ratio	Standard error	z	$p > \|z\|$	95% Confidence interval	
6 min walk (m)	0.961273	0.0128125	−2.96	0.003	0.9364861	0.9867159
SYMPACT physical impact score	1.406716	0.2447755	1.96	0.05	1.000214	1.978425
Health utility score*	42.84	90.25	1.78	0.07**	0.69	260.76

Model parameters: LR($\chi^2(3)$) = 30.31; $p > \chi^2 < 0.005$.

*Log transformed values.

**Included in the regression model due to plausibility and value approaching $p = 0.05$.

associations between symptoms, QOL and PAH severity. However, our multivariate model suggests that PROs such as PAH-SYMPACT© and EQ-5D-5L carry information independent of WHO-FC or 6MWD. Compared with 6MWD testing, which is quite a subjective "physician-filtered" instrument (with limited reproducibility), PRO tools directly communicate patients' experience of their illness, while also covering a much broader range of activities and impacts than simply measuring breathlessness on exertion.

A noteworthy finding from this study was the strong association between disease impact (at physical and psychological levels) and reduced survival. This is a little-studied area, as PAH-SYMPACT© is one of the few available tools including specific reference to the impact and burden of living with PAH, beyond measurement of symptoms.[21]

According to the WHO definition, QOL refers to "how well a patient feels, filtered through their values and expectations."[22] Patients often regard QOL gains as being at least as important as improved life expectancy, so PROs will be increasingly included as part of composite disease indices alongside established predictors such as 6MWD. The inclusion of such PROs ensures a holistic approach to the patient's disease experience, attending to their goals, expectations, and concerns, and allowing their health priorities to be a central management consideration. There was no patient feedback suggesting any difficulties with completing questionnaire components, and the performance of this QOL measurement fit readily within our routine clinical review process. Without these parameters, questions such as—how many side-effects is a person willing to experience for a given degree of gain in lifespan?—will be neither asked nor answered, despite being arguably one of the central issues for this (or any) chronic health condition. There is an increasing commitment to patient involvement in the PAH field[23,24] in realms ranging from research priorities through to trial design[25] and innovation targets,[26] as reflected in the consensus recommendations for PAH treatment developed at the 6th World Symposium on Pulmonary Hypertension.[27]

Despite the importance of QOL, its formal measurement is not included in the risk assessment methodology proposed by the latest ESC/ERS pulmonary hypertension guidelines,[4] no doubt partly due to limitations of current tools, including a lack of complete standardization across varied populations and the challenges of capturing the full spectrum of symptoms and impact of the condition.[3] Other aspects of QOL assessment needing refinement include idiosyncratic variations in question framing and emphases, an incompletely defined relationship to hemodynamics, QOL responsiveness to therapy (and minimal important clinical differences (MIDs)), population-specific translation and validation, tool complexity, and cost (e.g., fee for CAMPHOR use). It therefore seems likely that future composite markers of risk and treatment efficacy will demand the inclusion of more than one PRO instrument.[23,28]

Excluding QOL from consideration in PAH patient management runs the risk of delivering suboptimal care. Biases favoring quantitative data over qualitative outcomes are unproductive and, as seen in this study, "traditional" and PRO-based risk factors can work together in a complementary way to inform and optimize appropriate patient management. Of the multitude of tools available for PRO assessment,[29–32] the only tool we could identify which met criteria for regulatory use (FDA-approved) as well as capturing disease impact was PAH-SYMPACT©,[18,33] and this instrument is being used in current trials of innovative directed PAH therapies such as sotatercept (antiproliferative activin signaling inhibitor).[34]

Demonstrable additional value is imparted by such QOL assessments in allowing "treatment to target," prognostic refinement, and submission for registry

analyses, and they can be readily included within routine clinical assessment with minimal time cost. The increasing incorporation of PRO data into cost-effectiveness analysis (CEA) decisions made by regulatory bodies drove our decision to employ the EQ-5D-5L Tool, which benefits from an Australia-specific index for health utility score (HUS) assessment.[14] "Health utility,"[35–37] a concept incorporating quality of life, expected survival, and patient preferences, can be reduced to the HUS summary statistic and "quality-adjusted life years"[38,39] (1 QALY = 1 year of life × "1 Utility" [utility of 1 = perfect health, 0 = life quality "close to death"]), allowing for CEA.[40]

Study limitations

This was a limited study performed in a single tertiary center. The relatively small number of events did not allow extensive multivariate modeling, and confidence intervals surrounding each estimate were wide.

For further study

Based upon the preliminary findings of this pilot study, our group proposes that the following areas are worthy of further study: (i) larger QOL studies in PAH using the four-stratum risk model introduced after this study was designed[41]; (ii) further assessing the relative values of disease-specific (PAH-SYMPACT©) vs generic (EQ-5D-5L) PRO analyses (and/or their combination); (iii) the use of composite endpoints (QOL plus "standard" tools) for assessment of treatment benefits; and (iv) estimating PAH treatment cost-effectiveness (CEA) within this paradigm.

CONCLUSIONS

In summary, the use of PROs can refine existing risk-assessment tools by enhancing their predictive value and allowing risk stratification to occur even more accurately. Despite the challenges involved in using and interpreting these instruments, there should be more widespread and uniform use of PROs as part of standard PAH assessment and management.

AUTHOR CONTRIBUTIONS

Julie Shepherd and Glenn Edward Malcolm Reeves conceived the study and developed the study protocol, Julie Shepherd gained ethics approval and coordinated patient recruitment and Glenn Edward Malcolm Reeves performed data analysis and wrote the first and final drafts of the manuscript. Julie Shepherd, Nicholas John Collins, Scott Twaddell, and Rajinder Harjit Singh reviewed and approved the final version of the manuscript. All authors contributed equally to this article.

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CONFLICT OF INTEREST STATEMENT

GR has received funding from Actelion, AstraZeneca, GSK, and Janssen. The authors declare no conflicts of interest.

ETHICS STATEMENT

This study was approved by The Hunter New England Human Research Ethics Committee.

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