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Health-related quality of life and socio-economic correlates in patients with pulmonary arterial hypertension

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Abstract

Pulmonary Arterial Hypertension (PAH) imposes a substantial burden on individuals with the disease. The symptoms of PAH are unspecific and of varying severities; breathlessness, fatigue, edema of the lower limbs, dizziness and syncope. The importance of measuring the associated impact on health-related quality of life (HRQoL) is increasingly recognized and new instruments are available. This article reviews the validation and use of recently published questionnaires to evaluate HRQoL in PAH, the economic burden of PAH and new evidence in non-pharmacological supportive treatments.

Introduction

Pulmonary hypertension (PH) is defined by an elevation of the pulmonary arterial pressure and pulmonary vascular resistance, which will eventually lead to heart failure and death. Pulmonary arterial hypertension (PAH) (World Health Organization, WHO, Group I of the pulmonary hypertension classification), is a subset of PH and is a rare, severe and progressive form of PH [1]. PAH may be idiopathic, heritable, toxin-or drug induced or associated with other systemic conditions [2]. The most common symptoms of PAH are non-specific and related to progressive right ventricle dysfunction for instance complaints of dyspnea, fatigue, weakness, angina, dizziness, syncope. Less frequent but troublesome symptoms are a dry cough or exercise-induced nausea and vomiting. Reported frequencies differ depending on the severity of the disease. Symptoms of right heart failure e.g. ankle edema and abdominal distention, may also be present in more advanced stages of the disease [2]. While a right heart catheterization is required for diagnosis of PAH, the evaluation of symptoms and HRQoL is increasingly acknowledged in current guidelines, which recommend to regularly assess patients clinically. This evaluation can provide valuable information for determining disease severity, improvement, deterioration or stability [2,3-5]. In addition, the HRQol is proven to correlate with survival in PAH [6]. We present an overview of the disease burden of PAH in terms of quality of life, daily activities, physical activity, sleep, comorbid anxiety and depression, as well as risk of disease prognosis.

Impact on quality of life

For patients with PAH, the disease can be devastating and exert an adverse impact in all aspect of life [7]. Due to the obstructed flow in the pulmonary artery and the resulting impaired uptake of oxygen into the blood, a lack of energy and fatigue is commonly reported during the course of their disease [8-10]. This can undermine daily functioning and lead to negative effects on quality of life.

Although, the physical consequences of PAH are widely acknowledged, the relative importance of psychological (e.g., depression, anxiety) and situational (e.g., sleep deprivation) factors is usually unclear. Interest in characterizing the health-related quality of life of PAH-related factors has intensified in recent years. Newly validated PAH-specific patient reported outcome (PRO) instruments might help ensure a standardized assessment of HRQoL in research settings and clinical practice. Recently, two proposed PAH-specific questionnaires were validated and showed good psychometric properties.

The pharmaceutical industry has engaged with US investigators to develop the Pulmonary Arterial Hypertension-Symptoms and Impact Questionnaire (PAH-SYMPACT) according to the 2009 US Food and Drug Administration PRO guidance [11]. The questionnaire measures important, patient-relevant aspects of PAH symptoms and impacts that are not captured by other clinical endpoints. With 11 symptom items and 11 impact items, this brief questionnaire is easy to apply. It was validated in the SYMPHONY trial and approved for administering in clinical practice and clinical studies [11,12]. SYMPHONY is a phase III study including 278 patients treated with macitentan 10 mg once daily, who completed four times the PAH-SYMPACT [11,12]. Its main limitation was a selection bias, with a lack of untreated patients, patients belonging to WHO functional class (FC) IV and patients with heritable PAH or with PAH associated with congenital heart disease or HIV infection [12]. Correlations with other commonly used questionnaires like the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) questionnaire and the 36-item Medical Outcomes Study Short Form Survey (MOS SF-36) were moderate to high ([r]=0.34-0.80). The questionnaire differentiated well between patients with varying disease severity levels and was sensitive to improvements in clinician- and patient-reported disease severity.

In parallel, the Pulmonary Hypertension Association UK developed the emPHasis-10 quality-of-life questionnaire in collaboration with nationally designated specialist PH centers in the UK and Ireland, in

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order to provide an a PAH-specific HRQoL instrument that can be used in routine clinical practice [13]. The questionnaire consists of 10 items and is currently translated into multiple languages with cultural and linguistic validation [14]. The emPHasis-10 assesses breathlessness, energy, feelings of dependency, and perceived control that PH has over life, among other relevant constructs. EmPHasis-10 items are rated on a zero to five Likert scale, with potential sum scores ranging from zero to fifty and higher scores indicating more disruption of life due to PH symptoms [13].

The emphasis-10 was recently used in a longitudinal cohort study that assessed symptom-based variables in PH and its effect on HRQoL in real-life clinical practice. 185 patients with PH (74% PAH) were included and followed for a 18-month period [15].

A strong relation between HRQoL as measured by emPHasis-10 and breathlessness, fatigue, depression, anxiety and sleep was found over time. Dyspnoea, fatigue, anxiety, depression, WHO FC and poor sleep quality were all found to be predictors of reduced HRQoL. These results were in line with a resembling study that assessed the HRQol with the Pulmonary Arterial Hypertension Symptom Interference Scale (PAHSIS) and the MOS SF-36 and the authors found similar interfering symptoms [5,16].

Recently, an initial investigation was performed, beyond the traditional domains of HRQoL, to assess the impact of PAH and PAH therapies on sexual health and intimacy. The authors demonstrated that women with PAH appear to have reduced sexual HRQol captured with the Female Sexual Dysfunction Scale-Revised (FSDS-R scale). The FSDS-R scale was well correlated to the emPHasis-10 and the Short Form 36 (SF-36 questionnaire). Participants treated with intravenous or subcutaneous prostanoids had worse FSDS-R scores than those on oral therapies while emPHasis-10 scores were similar across treatment types. This data demonstrated that PAH has an impact on both the patients but also their partners, who often play a central role in caregiving [17]. The debilitating effects of PAH on family relationships was already mentioned in the past by patients in a survey conducted by the European Pulmonary Hypertension Association and the Food and Drug Administration (FDA). Especially the inability to perform routine household activities and family activities was mentioned [8,9]. In this regard, a large scale survey was conducted with 174 Chinese participants (114 PAH patients and 60 caregivers) to assess the impact of PAH on patients and their caregivers [18]. Caregivers reported being exhausted by the disease's demands, which led to a subtle change in the patient-caregiver relationship and to stress. A reduction in intimacy and decreased sexual relations was reported by 84% of the caregivers since their partner became ill, that declined further as PAH progressed [18]. Moreover, most patients also experience feelings of isolation, which may be potentiated by a lack of public understanding about the disease, resulting in less compassion towards PAH patients from the community and close relatives [18]. In this regard, most patients and caregivers express a desire to talk about the impacts of PAH on their lives with their family and friends, followed by patient organizations, PAH specialists, other PAH patients. This was also demonstrated in surveys conducted in the UK and US [8,19,20].

In this regard, a first clinically patient reported experience measurement (PREM) scale was developed and validated in 2018 for patients who visit a PAH outpatient clinic. This eight-item questionnaire can be a reliable instrument for evaluating patient experience of health care and provide structural information to address their needs [21].

Economic burden of PAH

Although the impact of PAH on patients HRQoL is well-described, PAH is also accompanied by a significant economic burden. A recent study showed that the total cost of respiratory disease in the 28 countries of the EU amounts to more than 380 billion euro annually. The economic burden of pulmonary vascular diseases could not be estimated and would also add to the economic burden, both for healthcare and work limitation [22]. Several trials have shown that treatment earlier in the course of disease and a combination of multiple PAH drugs is beneficial [23-25]. Combination therapy is shown to improve the outcome and as a result its use is recommended in current guidelines [2]. Of course, the use of a combination of drugs will also lead to an additive pharmacy cost. On the other hand, the benefits of a combination therapy include a decrease in hospitalisations [26,27]. This can result in a cost-reduction bearing in mind that, more than half of the PAH patients require at least one hospitalisation during a one year follow-up and that the length of stay is greater for patients with PAH than for those with other principal diagnoses [27]. A study including 504 subjects with PAH demonstrated that the estimated average total health care costs are substantively high relative to costs reported for other chronic diseases. It also confirmed that medical costs appeared to decrease following PAH medication use, but with a concomitant increase in pharmacy costs [28]. Due to the very expensive PAH treatment, in some countries a large financial burden is carried by the patient's family. A large survey conducted in a Chinese PAH population and their caregivers, demonstrated that treatment expenses represent a major financial burden and a source of stress to families, particularly those with lower-than-average income [18]. Also a survey conducted in Europe, revealed that in the majority of the patients their work or employment was affected by PAH and both patients and caregivers reported a major impact on family finances [8]. In Europe, national health insurance or social security systems offer support, which alleviates the stress and let patients benefit from long-term therapy. Currently, most clinical trials lack an economic endpoint. It is therefore recommended to incorporate specific economic endpoints to facilitate more accurate financial modelling [26]. Results from a recent study indicate that PAH disease severity, measured by functional class (FC), is associated with increase healthcare costs. These findings suggest that if higher risk patients, according to the current recommendations, are treated more aggressively, their risks could be lowered, leading to improvements in their function and QoL, and potentially lowering median healthcare costs. Therefore, the authors state that disease severity documentation could be an important tool as part of a PAH patient's management plan [29].

Non-pharmaceutical therapeutic options

Despite optimized combination-medical therapy most patients remain symptomatic, have reduced exercise capacity, quality of life and reduced survival rates, with an annual mortality rate of approximately 5 -15 % or even higher [2]. Supportive therapies may be beneficial in addition to targeted medical treatment. European guidelines provide recommendations for supportive care and general measures, however its use varies largely between countries and can be challenging in routine clinical care. Recently, some new evidence of beneficial supportive therapies of interest became available.

Exercise rehabilitation for PH

Evidence shows that in patients with severe chronic heart and lung diseases, a rehabilitation program results in an improved exercise tolerance, quality of life and survival [30]. Rehabilitation was for long

time not recommended in patients with PH because of the fear to aggravate the symptoms and the potential of negatively influencing the heart function [31]. In 2006, a first randomized controlled trial was published, showing an improvement of exercise capacity and quality of life as result of a (partly inpatient) rehabilitation program. Recently published reviews show that based on the available small number of studies, supervised pulmonary rehabilitation is safe when performed in expert centers. The weighted results show an increase of mean walking distance measured during a six-minute walk test, largely exceeding the minimal important difference of 30 meters. In addition, a weighted between group difference in HRQol questionnaire scores was concluded [32-34]. A study even shows an improvement of pulmonary hemodynamics, in addition to the exercise tolerance improvement [35]. On the other hand, the most optimal duration, methodology and follow-up of the patients is still unknown. A study published in 2017 showed that that oscillatory whole-body vibration (WBV) can be a feasible and easily accessible method of continuous and potentially home-based physical exercise for patients with PAH [36].

We can conclude that given the small number of available studies and the small sample sizes, more studies have to be performed, in order to provide hard evidence to support the benefit of exercise in PAH.

Sleep disturbances

Recently, increasing occurrence of sleep disturbance are reported caused by insomnia or restless legs syndrome and associated with worse PAH symptoms, psychological states, and HRQOL [15,37-39] Moreover, a study published in 2015 even found that poor quality of sleep was associated with impaired exercise capacity besides the reduction of the HRQoL [39]. However, this was contradicted in a previous study, where no significant difference was observed in 6MWD of patients with a good and poor sleep quality [37]. Interventions that decrease sleep disturbances may improve symptoms and HRQOL. In this regard, a pilot study was performed in order to assess the feasibility and efficacy of daily slow-paced respiration therapy to treat dyspnea, fatigue and sleep disturbance in women with PAH. Although only ten patients were included, improved sleep along with an improvement of the HRQoL, dyspnea and fatigue was suggested [40]. On the other hand, a study that attempted to identify predictors of reduced HRQoL in PAH patients, the relationship between poor sleep and HRQoL was not significant. Although, sleep quality in the sample was poor overall. Many of the factors affecting HRQoL, such as physical and psychological symptoms, may have also affected quality of sleep in these patients [15]. Further investigation is warranted in order to better understand the nature of sleep disturbances.

Conclusion

Although the life expectancy of PAH has increased the past decades, the disease can still not be cured and patients are faced with a considerable burden and impact on their HRQol. Whether facing pain in severe PAH or ongoing headache, jaw pain and diarrhea caused by PAH treatment, patients endure a long road of discomfort. While, the assessment of HRQoL has some barriers, clinicians currently better accept to collect meaningful data on patients subjective experiences. It is becoming clear that HRQoL information may, in some settings, lead to improvements in the clinical state of the individual patient. HRQoL can be effectively improved with the combination of pharmacological and non-pharmacological therapies.

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