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Quality of life of patients with pulmonary arterial hypertension: a meta-analysis

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Abstract. – OBJECTIVE: Pulmonary arterial hypertension (PAH) is a rare condition, with an incidence of 15-50 cases per million annually. Available studies demonstrate that despite the longer survival of PAH patients, their quality of life (QoL) deteriorates as the condition progresses. Consequently, the goals of PAH therapy have expanded from increasing survival to improving health-related quality of life. The objective of this systematic review and meta-analysis was to summarize the available evidence about the level of QoL in patients with PAH.

MATERIALS AND METHODS: A systematic search was performed using the Cochrane guidelines for conducting meta-analysis following the PRISMA statement. The meta-analysis includes findings from 11 studies evaluating the QoL of PAH patients at baseline and at follow-up (12 weeks) using the Short Form (36) Health Survey (SF-36), the Minnesota Living with Heart Failure Questionnaire (MLHFQ) and the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR).

RESULTS: The mean physical component score (SF-36) for the group was 37.2 points (95% CI: 33.24-41.16) and the heterogeneity coefficient was I^2=97.71% ($p < 0.001$). The mean mental component score (SF-36) was 46.38 (95% CI: 44.21-48.56) and the heterogeneity coefficient was I^2=87.92% ($p < 0.001$). The result indicates improved QoL 12 weeks after the intervention, though three papers did not fully confirm this. The greatest improvement in QoL was found in patients treated with bosentan and iloprost and the smallest improvement in QoL was found in patients treated with epoprostenol sodium. The heterogeneity coefficient was I^2=91.36%, $p < 0.001$ for CAMPHOR and I^2=97.65%, $p < 0.001$ for MLHFQ.

CONCLUSIONS: PAH patients tend to have a poor QoL, mainly in the physical functioning domain, less so in the psychological functioning domain. QoL may be improved by therapeutic interventions, mainly pharmaceutical ones. Patients with PAH also tend to suffer from depression, anxiety, stress, or sleep disorders. All these factors are significantly correlated with poorer QoL.

Key Words:
Pulmonary hypertension, Meta-analysis, Health-related quality of life, Systematic review, Outcome.

Abbreviations

6MWD: 6-minute walk distance; QoL: quality of life; CTEPH: chronic thromboembolic pulmonary hypertension; PAWP: pulmonary artery wedge pressure; PAH: pulmonary arterial hypertension; PH: pulmonary hypertension; NYHA: New York Heart Association; HRQoL: health-related quality of life; MLHFQ: the Minnesota Living with Heart Failure Questionnaire; WHO: the World Health Organization; CAMPHOR: the Cambridge Pulmonary Hypertension Outcome Review; PAH-SYMPACT: the Pulmonary Arterial Hypertension-Symptoms and Impact; PCS: physical component score; MCS: mental component score; SF-36: the Short Form (36) Health Survey; PVR: pulmonary vascular resistance; ESC: the European Society of Cardiology; SSc: systemic sclerosis; SWB: subjective well-being; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; WBV: whole-body vibration.

Introduction

Pulmonary arterial hypertension (PAH) belongs to group 1 according to WHO classification and it is a rare condition, with an incidence of 15-50 cases per million annually. Data from the

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REVEAL registry reported a 3-year survival rate of 74% for idiopathic PAH[1,2]. The condition may be idiopathic, hereditary, or associated with other conditions, i.e., ingestion of certain drugs or toxins, connective tissue disease, or HIV infection. PAH is characterized by epithelial cell dysfunction, pulmonary artery smooth muscle cell (PASMC) proliferation, pulmonary vascular stenosis, and thrombosis. All these factors lead to a sustained increase in pulmonary vascular resistance (PVR) and cause progressive dysfunction of the right ventricle, resulting in death[1-3]. PAH is diagnosed in the case of precapillary PH with PVR >3 Wood units in the absence of other causes of precapillary PH such as lung diseases and CTEPH[3-5]. PAH symptoms, including dyspnea, fatigue, chest pain, and fainting[6-9] are non-specific, thus the patients may be misdiagnosed with obstructive airway disease prior to establishing a diagnosis of PAH[10]. At the initial stages of PAH development, the condition is usually asymptomatic at rest, however, patients with advanced disease (NYHA class IV) do manifest PAH symptoms at rest[7]. These symptoms lead to difficulties in performing one's daily professional and social activities, and considerably impair the patient's quality of life in all its aspects, as evidenced by a number of studies[11].

Over the last 30 years, the life expectancy of PAH patients has increased[12]. It results from advances in research on the condition, the development of new treatments and the establishment of programs to finance PAH treatment. Available studies demonstrate that despite the longer survival of PAH patients, their health-related quality of life (HRQoL) deteriorates as the condition progresses. The disease interferes with the patient's functioning both on the physical plane (pain, dyspnea, insomnia, apnea, fatigue, etc.) and on the psychological one (anxiety, depression, social isolation, etc.)[13]. Functional exercise capacity and hemodynamic measures have been the primary treatment outcomes for PAH[1,4]. However, many patients do not experience any significant improvement in physical functioning and daily activities associated with hemodynamic parameters at rest. Therefore, it is suggested that HRQoL may better reflect the effectiveness of therapeutic interventions[11]. HRQoL reflects the impact that both the condition and its treatment have on the patient's daily functioning. Consequently, the goals of PAH therapy have expanded from increasing survival to improving health-related quality of life[13].

Among PAH patients, HRQoL is most commonly evaluated using generic questionnaires (SF-36, WHOQoL-BREF). However, these instruments may be insufficiently sensitive and fail to account for PH-specific symptoms associated with perceived HRQoL[14,15]. Among specific HRQoL questionnaires, authors commonly use the Minnesota Living with HF Questionnaire, though one must keep in mind that it is mainly dedicated to patients with left-sided heart failure[16]. Specific questionnaires sensitive to all changes in health associated with PH include the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR), the Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT) questionnaire[17,18] and the emPHasis-10 questionnaire[19]. However, both studies using specific HRQoL questionnaires and literature on HRQoL and its determinants in general are relatively scarce. In the available publications, the authors describe the impact of various medical interventions on HRQoL at different times following PAH diagnosis[10,11,19-30]. The reported findings vary, and the number of interventions is not large. The objective of this systematic review and meta-analysis was to summarize the available evidence about the level of HRQoL in patients with PAH. The meta-analysis includes findings from studies evaluating the HRQoL of PAH patients at baseline and at follow-up. Additionally, interventions potentially affecting HRQoL were analyzed, and an attempt was made to identify the positive and negative determinants of HRQoL.

Materials and Methods

Search Strategies

A systematic search of the PubMed; MEDLINE; Academic Search Ultimate; CINAHL Complete; Health Source: Nursing/Academic Edition databases was performed using the Cochrane guidelines for conducting meta-analysis following the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) statement.

All published studies that addressed the issue of HRQoL in patients with PAH and used the term pulmonary hypertension [Title/Abstract] OR pulmonary arterial hypertension [Title/Abstract] OR pulmonary artery hypertension [Title/Abstract])) AND (quality of life [Title/Abstract] OR wellbeing [Title/Abstract]

OR well-being [Title/Abstract] OR health-related quality of life [Title/Abstract])) pulmonary hypertension [Title/Abstract] OR pulmonary arterial hypertension [Title/Abstract] OR pulmonary artery hypertension [Title/Abstract])) AND (quality of life [Title/Abstract] OR well-being [Title/Abstract] OR well-being [Title/Abstract] OR health-related quality of life [Title/Abstract])) in subheadings were identified (3107). The search limits were defined as "English" (language), "January 1, 2009" and "December 31, 2020" (publication date), "humans" (species), and full text (777). The review was limited to studies that were conducted using the SF-36, PAH-SYMPACT, WHO-QoL, MLHFQ, CAMPHOR validated questionnaires and emPHasis-10 (107) (Figure 1).

Exclusion criteria were as follows: review articles, meta-analyses, study protocols, no numerical data, duplicates, studies on children. Then, two reviewers (KS, NŚL) independently selected relevant studies for inclusion by examining the remaining titles, abstracts, or full papers (n=11). Disagreements were resolved by consensus reached through discussion.

Study Selection and Assessment of Risk of Bias

The retrieved articles were independently reviewed and were considered eligible if two reviewers (KS, NŚL) independently decided that they met the inclusion criteria described previously. Disagreements were resolved by consensus or by consulting a third reviewer (BJP) and discussion. The agreement between the two primary reviewers was measured using Cohen's kappa coefficient (κ).

At the first stage, all records were identified from searches of electronic databases. At the next stage, two researchers (NŚL and KS) independently screened the titles and abstracts to identify potentially eligible studies and remove duplicates. At the third stage, potentially eligible studies were selected for full-text review. Disagreements were resolved by discussion to reach a consensus. Ultimately, 11 full-text papers were included in the subsequent statistical analyses (Figure 1, Table I).

Description of Included Studies

The 11 studies included in the meta-analysis were performed in 15 countries in 5 continents. The meta-analysis included research papers pub-

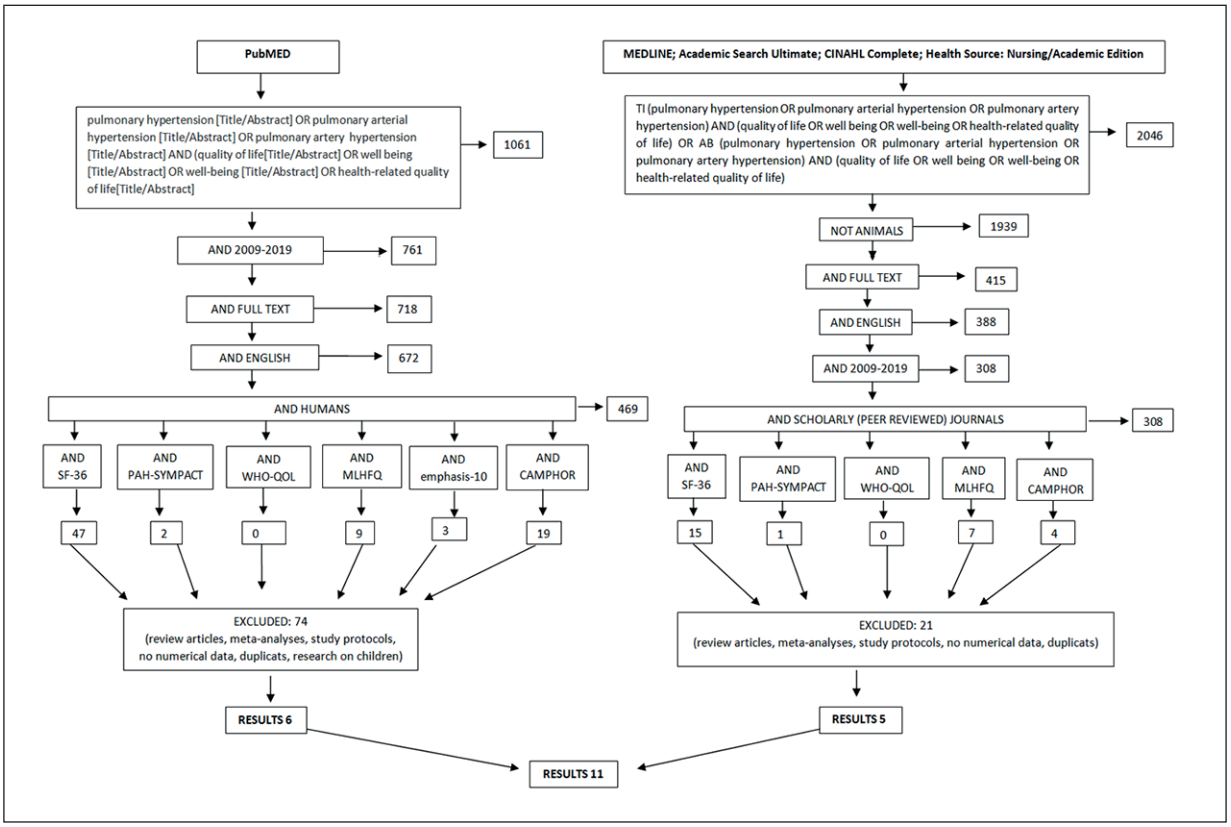

Figure 1. Study flow diagram.

Table I. Summary of studies on the QoL of PAH patients.

No.	Author and year	Study group	Questionnaire used	Intervention	Results		Follow-up	Comparison between groups	Type of patients
					Domains	Baseline			
1.	Amedro et al [21]	208 PAH-CHD patients (pulmonary arterial hypertension with chronic heart disease); (63 male), aged 42.6 ± 15.8 years, WHO functional class I-22, II-100, III-78, IV-8 Treatment: no treatment: (n = 49), monotherapy (n = 85), double combination therapy (n = 66), triple combination therapy (n=8)	CAMPHOR SF-36	NO	QoL PCS MCS	6.7 ± 5.6 40.8 ± 9.6 44.6 ± 10.8	NO	– – –	Prevalent
2.	Ganderton et al [11]	61 PAH patients (13 male), aged 56.9 ± 14.5 years, WHO functional class I-3, II-18, III-36, IV-4 Treatment: n/o	CAMPHOR	NO	Symptom activity QoL	12.6 ± 6.0 10.9 ± 6.2 11.0 ± 6.3	NO	–	n/o
3.	Halimi et al [20]	55 PAH patients (20 male), aged 57.8 ± 15.3; NYHA functional class I-8, I-25, III-19, IV-3 Treatment: no treatment (n = 1), monotherapy (n = 21), bitherapy (n = 23), tritherapy (ERA, IPDE-5, PGI2) (n = 9), calcium channel blockers (n = 1)	SF-36	NO	Physical functioning physical role performance bodily pain general health perceptions vitality social functioning emotional role performance mental health PCS MCS	46.3 ± 26.2 40.4 ± 38.6 58.4 ± 26.1 39.8 ± 18.6 45.6 ± 17.8 60.9 ± 25.8 48.4 ± 42.4 56 ± 18.6 37.1 ± 8.03 42.4 ± 10.9	NO	–	Prevalent and incident

Continued

Table I *(Continued)*. Summary of studies on the QoL of PAH patients.

No.	Author and year	Study group	Questionnaire used	Intervention	Results			Follow-up	Comparison between groups	Type of patients
					Domains	Baseline				
4.	Morrisroe et al [23]	132 PAH patients (20 male), aged 62 ± 11; NYHA functional class I-3, II-23, III-79, IV-12, unknown-15 Treatment: pulmonary vasodilator therapy: monotherapy (n= 91), combination therapy (n= 41), warfarin therapy (n=37) hydroxychloroquine therapy (n=12), antiplatelet agent (n=48), mycophenolate mofetil therapy (n= 7), hormone replacement therapy (n=16), proton pump inhibitor (n=105), home oxygen (n = 28)	SF-36	Consecutive SSc (systemic sclerosis) patients with newly diagnosed (incident) World Health Organization (WHO) Group 1 PAH compared with no-PAH patients		No PAH	PAH	NO	PAH patients had worse QoL compared to no-PAH patients	Incident
					Physical functioning	57.5 ± 28.9 49.2 ± 43.4	35.7 ± 23.8 27.2 ± 39.1			
					Physical role performance					
					bodily pain	67.3 ± 40.4	55.9 ± 44.9			
					general health perceptions	70.5 ± 26.9	64.2 ± 27.7			
					vitality	68.9 ± 20.2	66.1 ± 21.1			
					social functioning	47.1 ± 24.1 60.7 ± 27.9	38.6 ± 22.2 55.3 ± 28.8			
					emotional role performance					
					mental health	46.2 ± 22.7	36.6 ± 20.5			
					PCS	38.9 ± 11.6	31.7 ± 8.7			
					MCS	46.3 ± 10.4	46.3 ± 10.7			
5.	Mehta et al [24]	Total 473 PAH patients (63 male) aged 45.5 ±1 5.9; CG: 239 (48 male) aged 46.4 ± 16.8; NYHA functional class I-0, II-126, III-109, IV-4 Treatment: No (n = 149), PDE-5 inhibitors (n = 145), oral or inhaled prostanoids (n = 7), no anticoagulant therapy (n = 115) IG: 234 (48 males) aged 45.5 ± 14.9; NYHA functional class I-1, II-117, III-111, IV-5 Treatment: No (n = 150), PDE-5 inhibitors (n = 146), oral or inhaled prostanoids (n = 13), no anticoagulant therapy (n = 119)	SF-36	Macitentan 10 mg per day		CG	IG	No data available statistical	No significant changes have been observed between CG and IG After 6 months of follow-up, QoL in the intervention group improved compared with the control group	N/o
					Physical functioning	32.7 ± 9.8	33.1 ± 9.8			
					physical role performance	34.8 ± 10.8	34.4 ± 10.8			
					bodily pain	45.6 ± 11.9	44 ± 11.6			
					general health perceptions	34.8 ± 9	35.4± 8.5			
					vitality	43.9 ± 10.3	44.3 ± 9.7			
					social functioning	38.5 ± 11.3 36.3 ± 13.3	39.3 ± 11.7 35.8 ± 13.8			
					emotional role performance					
					mental health	41.8 ± 11.3	43.4 ± 10.2			
					PCS	36.5 ± 8.5	35.9 ± 8.7			
					MCS	42.1 ± 11.3	43.1 ± 11			

Continued

Table I *(Continued)*. Summary of studies on the QoL of PAH patients.

No.	Author and year	Study group	Questionnaire used	Intervention	Results		Follow-up	Comparison between groups	Type of patients
					Domains	Baseline			
6.	Gerhardt et al [25]	11 PAH patients (5 males), aged 50 ± 14.3 years, WHO functional class I-0, II-7, III-4, IV-0, aged 46 ± 3.7 Treatment: Phosphodiesterase type 5 inhibitor monotherapy (n=6), Endothelin receptor Antagonist and Phosphodiesterase type 5 inhibitor (n=2), Endothelin receptor Antagonist and soluble guanylate cyclase stimulator- (n=1), Endothelin receptor Antagonist and Phosphodiesterase type 5 inhibitor and Prostanoid (n=1) Endothelin receptor Antagonist and Phosphodiesterase type 5 inhibitor and Tyrosine kinase inhibitor (n=1)	SF-36	Full body vibrations	PCS MCS	48.8 ± 3.3 52.3 ± 5.4	61.8 ± 3.6 (follow-up 4 weeks) 69. 3 ± 3.5 (follow-up 4 weeks)	After 4 weeks of follow-up, QoL was better compared to baseline	

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Table I *(Continued)*. Summary of studies on the QoL of PAH patients.

No.	Author and year	Study group	Questionnaire used	Intervention	Results		Follow-up	Comparison between groups	Type of patients
					Domains	Baseline			
7.	Vanhoof et al [26]	101 PAH patients (27 male), aged 55.4±16.4 years, WHO functional class I-19, II-43, III-32, IV-7 Treatment: Prostacyclin analogs: • Intravenous (n = 8) • Subcutaneous (n = 8) • Inhalation (n = 1) • None (n = 84) Endothelin receptor antagonists (n = 70), Phosphodiesterase 5 inhibitors (n = 57), Combination Oral therapies (n = 26): • 1 oral and 1 prostacyclin analog (n=1) • 2 oral and 1 prostacyclin analog 16 (15.8) • None (n = 58) Study medication: • Oral medication (n = 18) • Intravenous prostacyclin analog (n = 4) • None (n = 79)	SF-36 Minnesota Living with Heart Failure Questionnaire	NO	PCS MCS QoL	33.53 ± 10.43 49.81 ± 12.66 36.47 ± 23.46	NO	–	Prevalent
8.	Chen et al [10]	128 PAH patients (33 male), aged 60 ± 14 years, WHO functional class I-8, II-45, III- 66, IV-9 Treatment: Intravenous or subcutaneous prostacyclin infusion (n=49), Inhaled prostacyclin (n= 4), Oral endothelin receptor antagonist (n = 82), Oral phosphodiesterase-5 inhibitor (n = 41)	SF-36 Minnesota Living with Heart Failure Questionnaire	NO CAMPHOR	PCS MCS QoL Symptom Activity QoL	32.6 ± 10 47.2 ± 11.6 49.5 ± 25.4 9.1 ± 6.4 8.3 ± 5.1 7.7 ± 6.3	NO	– – –	Incident

Continued

Table I *(Continued)*. Summary of studies on the QoL of PAH patients.

No.	Author and year	Study group	Questionnaire used	Intervention	Results		Follow-up	Comparison between groups	Type of patients
					Domains	Baseline			
9.	Kurzyna	12 PAH patients (8 male), aged 42±13 years, WHO functional class I-0, II-5, III-7, IV-0 Treatment: Subcutaneous treprostinil infusion (n=12)	SF-36	Implantation of Lenus Pro® pump	Bodily pain physical role functioning Vitality	31 ± 12 31 ± 7 37 ± 8	50 ± 1 4 41 ± 12 50 ± 14	After 12 weeks of follow-up, QoL was better compared to baseline	Incident
10.	Provencher et al [29]	16 PAH patients (4 male), aged 50 ± 13.4 years, WHO functional class I-0, I-10, III-6, IV-0 Treatment: n/o	SF-36	Patients treated (4 weeks) with the new thermostable formulation of Flolan	Physical component score Mental component score	38.0 (9.7) IQR 54.4 (6.3) IQR	37.9 (8.6) IQR 55.5 (8.1) IQR	After 12 weeks of follow-up, QoL was better compared to baseline	
11.	Han et al [22]	21 PAH patients (7 male), aged: group 1 – 30.1 ± 7.4; Group 2 – 39.4 ± 5.2; Group 3 – 41.8 ± 5.3 years, WHO functional class I-0, II-6, III-15, IV-0 Treatment: n/o	MLHFQ	Group 1 – combination therapy (bosentan+ iloprost) Group 2 –bosentan Group 3 –iloprost	QoL	56.8 ± 7.5 67.7 ± 3.6 65.6 ± 3.7 67.7±3.6 60.8±15.6 65.6±3.7 63.8±6.7	19.8 ± 7.5 60.8 ± 15.6 63.8 ± 6.7	After 12 weeks of follow-up, QoL was lower compared to baseline	Incident

N/o – no information available, NYHA – New York Heart Association, WHO – World Health Organization, CG – control group, IG – intervention group, N – number of patients, ERA – endothelin receptor antagonist, PCA – prostanoid, PDE5i – phosphodiesterase type 5 inhibitor; sGC-S – soluble guanylate cyclase stimulator, TKI – tyrosine kinase inhibitor, PGI2 – prostacyclin.

lished in English, in the years 2009-2020, in one of the listed databases. Another inclusion criterion was the use of one of the following instruments for QoL evaluation: a) generic: the Short Form (36) Health Survey (SF-36), the Minnesota Living with Heart Failure Questionnaire (MLHFQ), WHOQoL-BREF; b) specific: the Pulmonary Arterial Hypertension -Symptoms and Impact (PAH-SYMPACT) questionnaire, the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) questionnaire, emPHasis-10 questionnaire. Studies on children with PAH, other meta-analyses, review articles, study protocols, duplicates, and studies with incomplete data were excluded from the meta-analysis.

In the studies analyzed, patient inclusion criteria were as follows: patients treated with subcutaneous treprostinil infusion (1 study), age >18 years (10 studies), PAH confirmed by right heart catheterization (11 studies); 3 months of PAH therapy (1 study), fluency in English (5 studies), mean pulmonary artery pressure of 25 mmHg (1 study), pulmonary capillary wedge pressure of 15 mmHg (1 study), no pregnancy (3 studies), non-lactating women (2 studies), inability to walk (1 study), on a stable dose of Flolan for at least 3 months for the treatment of PAH prior to screening (1 study), on stable doses of other PAH treatments for at least 30 days prior to screening (1 study), prevalent or incident cases (newly diagnosed, stable for ≥3 months) (9 studies); specific NYHA functional class I to IV (11 studies); not operable (1 study); not receiving psychological care in the Competency Centre (1 study), confirmed diagnosis of PAH according to the World Health Organization (WHO) Diagnostic Classification (Group 1) (11 studies), SSc patients (1 study).

Patient exclusion criteria were as follows: unable to complete a 6-minute walk test (1 study), diagnosed with an unstable psychiatric disorder (5 studies), actively smoking (1 study), acute pulmonary thromboembolism (3 studies), left-sided heart diseases (1 study), pulmonary disease with FEV1/FVC 50% (1 study), predicted or total lung capacity 60% (1 study), renal insufficiency (1 study), chronic liver disease (1 study), portal hypertension (1 study), resting arterial oxygen saturation <90% (1 study), congestive heart failure arising from severe left ventricular dysfunction (1 study), a hospitalization or emergency room visit for a PAH-related condition in the past 3 months (1 study), individuals not expected to be clinically stable for the duration of the study (1 study), taking Flolan for a condition or in a manner outside the approved indication (1 study), low cardiac output [cardiac index <2 L/min/m2] (1 study); pre-mortem state (1 study); cognitive impairments (3 studies), clinically significant cardiovascular or pulmonary comorbidities (1 study), WHO Group 2–5 pulmonary hypertension (11 studies) or Group 1 PAH but with co-existing ILD with FVC (1 study), participation in training (1 study), training program within 3 months prior to screening (1 study), physical inability to perform WBV (1 study), osteoporosis (1 study), acute thrombosis (1 study), hip or knee implants (1 study), recent fractures or injuries (1 study), pulmonary hypertension due to left heart disease (1 study), lung disease (1 study), hypoxemia (1 study), chronic thromboembolic pulmonary hypertension (CTEPH) (1 study) pulmonary hypertension with unclear and/or multifactorial mechanisms (1 study).

Data Extraction

An initial database was developed, pilot-tested and refined to ensure consistency with outcomes reported in the literature. Data were independently extracted from eligible articles by two reviewers. Data extraction discrepancies between the reviewers were resolved by consensus. The types of data recorded in the standardized data extraction forms included general manuscript information, study design, risk of bias using the Newcastle-Ottawa scale, patient characteristics, study characteristics, and intermediate- to long-term (≥6 months) main outcomes.

Definitions and Outcomes

The main outcomes of interest for this review included the New York Heart Association (NYHA) functional class and QoL.

Materials

The meta-analysis focused on QoL in the 1218 PAH patients studied. Male patients comprised 26.44% of the study groups. Physical fitness was evaluated using the WHO functional classification (I – 5.3%, II –43.1%, III – 46.3%, IV – 4.23%, unknown – 1.2%). The NYHA/WHO classification was also included, as, in practice, it is used interchangeably for PAH patient evaluation[30]. Fifty-four patients received oxygen therapy, of whom 28 received it at home.

Questionnaires Used to Assess HRQoL

- The Short Form (36) Health Survey (SF-36) is a 36-item questionnaire used to assess a patient's health. The original version of the SF-36 was developed in the Medical Outcome Study (MOS). It comprises eight domains: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health. Responses in each domain are converted into scores on a scale from 0 to 100, with all items assigned the same weight. The higher the score, the better the patient's HRQoL[14].
- The Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) comprises 65 items: 25 involve symptoms, 15 – daily activities, and 25 – QoL. On the symptom and QoL subscales, patients answer "yes/true" (1 point) or "no/not true" (0 points), for a total score of 0-25. On the daily activities subscale, patients select one of three response variants (0-2 points) for a total score of 0–30. The total score for the questionnaire ranges between 0 and 80 points. Higher scores indicate poorer QoL and more restrictions in daily functioning[17].
- The Minnesota Living with Heart Failure questionnaire (MLHFQ) includes 21 items which comprise the physical dimension (8 items), emotional dimension (5 items), and additional items (8). Each item is scored from 0 to 5, and the total score ranges from 0 to 105. Lower scores indicate better HRQoL[16]. Researchers estimated that a score of <24 on the MLHFQ represents a good HRQoL, a score between 24 and 45 represents a moderate HRQoL, and a score >45 represents a poor HRQoL.

Statistical Analysis

Meta-analysis was conducted in a fixed or random model according to the homogeneity test. For the random model, the DerSimonian-Laird estimate was used. Analyses were performed with a 0.05 significance threshold. The R software, version 3.6.2 was used[31].

Results

In the studies analyzed, HRQoL was assessed using three standardized questionnaires: the SF-36[10,20-26,28,29], the MLHFQ[10,22,26], and CAMPHOR[10,11,21]. No studies using the PAH-SYMPACT and EMPHASIS-10 questionnaires were eligible. HRQoL meta-analysis was performed separately for each questionnaire used.

HRQoL Based on the CAMPHOR Questionnaire

The meta-analysis included three studies using the CAMPHOR questionnaire. The maximum score in its HRQoL domain is 25 points. The higher the score, the poorer the HRQoL. Combined, the studies included 397 patients, 109 of whom were male (27.46%), with a mean age of 53.17±14.77 years. Most patients were in NYHA functional classes II and III: 41.1% (n=163) and 43.3% (n=180), respectively. NYHA classes IV (n=21, 5.3%) and I (n=33, 8.3%) were the least numerous.

The mean HRQoL score in the meta-analysis was 8.37 (95% CI: 6.2–10.53). The test for heterogeneity demonstrated considerable heterogeneity of the studies analyzed ($p < 0.001$). The above results were obtained using the random-effects model. The heterogeneity coefficient was I^2=91.36%.

HRQoL Based on MLHFQ

The meta-analysis included 3 studies using the MLHFQ. The total MLHFQ score ranges between 0 and 105 points, with lower scores indicating better HRQoL. Combined, the studies included 250 patients, 67 of whom were male (26.8%), with a mean age of 48.5±12.6 years. More than half of the patients were in NYHA functional class III (n=113, 45.2%). NYHA classes II and I were represented by 37.6% (n=94) and 10.8% (n=27) patients, respectively. Only 6.4% (n=16) were in NYHA class IV.

The mean HRQoL score in the meta-analysis was 55.19 (95% CI: 51.23-59.16) (Figure 2). The test for heterogeneity demonstrated considerable heterogeneity of the studies analyzed ($p < 0.001$). The above results were obtained using the random-effects model. The heterogeneity coefficient was I^2=97.65%.

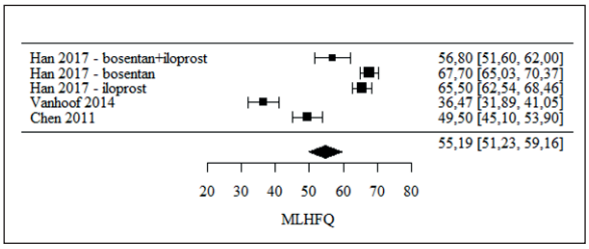

Figure 2. Forest plot for the patients' HRQoL at follow-up..

HRQoL Based on SF-36

The meta-analysis included 7 studies using the SF-36. The total score for the questionnaire is between 0 and 100 points. The higher the score, the better the QoL. Combined, the studies included 1108 patients, 279 of whom were male (25.2%), with a mean age of 52.72±3.26 years. Most patients were in NYHA functional class II (n=501, 43.2%) or III (n=536, 46.2%). Only 5.2% (n=60) and 4.1% of patients were in classes I and IV, respectively. For 1.3% (n=15), NYHA class was not reported in one study.

PCS: In the meta-analysis, the mean physical component score for the group was 37.2 points (95% CI: 33.24-41.16), indicating that patients were considerably limited in their activities (Figure 3). The test for heterogeneity demonstrated considerable heterogeneity of the studies analyzed ($p < 0.001$). The above results were obtained using the random-effects model. The heterogeneity coefficient was I^2=97.71%.

MCS: The mean mental component score in the group analyzed was 46.38 (95% CI: 44.21-48.56). Thus, despite a score higher than that found in the PCS analysis above, the result remains poor (Figure 4). The test for heterogeneity demonstrated considerable heterogeneity of the studies analyzed ($p < 0.001$). The above results were obtained using the random-effects model. The heterogeneity coefficient was I^2=87.92%.

Follow-up – QoL Meta-Analysis in the Intervention Groups – at Baseline and at 12-Week Follow-up

The follow-up was carried out for 3 studies on the basis of the differences between the baseline and follow-up results at week 12. Baseline HRQoL results obtained with MLHFQ by Han et al[22] for group 3 were as follows: Group 1 (combination therapy bosentan and iloprost): 56.8±7.5; Group 2: (monotherapy – bosentan) 67.7±3.6; Group 3: (iloprost monotherapy) 65.5±3.7. In turn, the results of the HRQoL baseline in the study by Kurzyna et al[28] using the SF-36 questionnaire for selected domains were as follows: Bodily pain: 31±12; Physical role functioning: 31±7, Vitality: 37±8. The third work for which HRQoL was determined using the SF-36 questionnaire was that of Provencher et al[29] where the baseline HRQoL results were as follows: PCS: 38.0±9.7; MCS: 54.4±6.3.

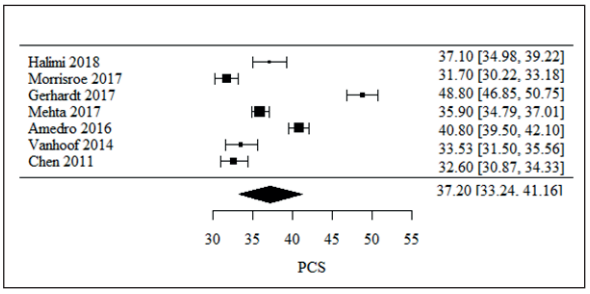

Figure 3. Mean HRQoL in the meta-analysis – physical component score from the SF-36 questionnaire.

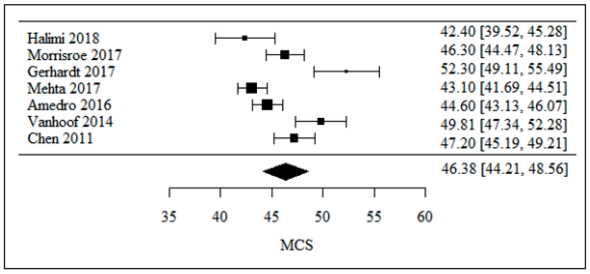

Figure 4. Mean HRQoL in the meta-analysis – mental component score from the SF-36 questionnaire.

Overall, the result indicates improved HRQoL 12 weeks after the intervention, though three papers did not fully confirm this[22,28,29]. The 95% confidence interval for the total effect in the random-effects model does not contain 0. Heterogeneity test results indicate that results are heterogeneous (Q=35.7277, DF=4, $p < 0.0001$, I^2=88.8%). The low p value indicates that intervention effects are highly heterogeneous (estimated effect variance greater than random). The lower and upper limits of the CI are above 0, which warrants the conclusion that HRQoL was better after 12 weeks (Figure 5). The greatest improvement in HRQoL was found in group 1 (patients treated with bosentan and iloprost) in the study by Han et al[22]. The smallest improvement in HRQoL was found in patients treated with epoprostenol sodium in the study by Provencher et al[29].

Factors Affecting HRQoL

Most of the included studies analyzed predictors affecting the quality of life in addition to assessing it. Most of the relevant predictors are consistent with those described in the WHO definition of health-related quality of life and are in line with studies by other authors. The identification of these predictors may be important in

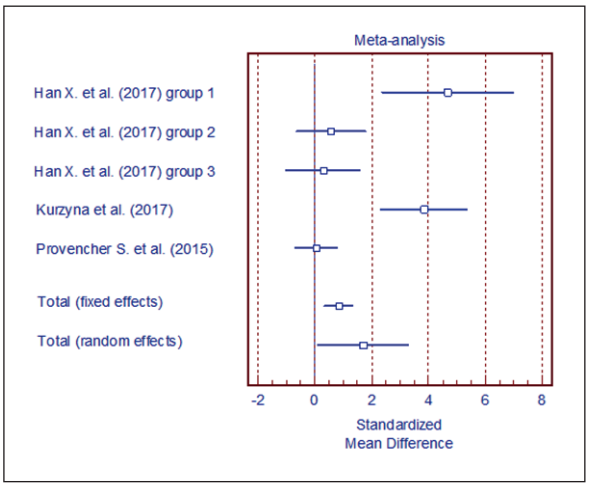

Figure 5. Forest plot for the patients' HRQoL at follow-up.

clinical practice in selecting patients particularly vulnerable to poor quality of life. Knowledge of positive predictors will help to enhance the quality of life. From the studies qualified for meta-analysis, we selected those factors which, according to individual authors, correlated with the quality of life. Table II shows socio-demographic, clinical and psychological factors contributing to better HRQoL in patients with PAH. The studies analyzed most commonly reported a positive impact of the WHO/NYHA functional classification – classes I and II.

The most commonly reported factors that adversely affect the HRQoL in PAH patients include anxiety and depression, and insomnia (Table III). Among the clinical factors with a negative impact of HRQoL, the most frequently reported factors, i.e., NYHA functional class III and IV, and a poor 6-minute walk test result, were significant.

Discussion

Symptoms of PAH may significantly limit a patient's HRQoL. The primary objective of PAH treatment is to extend the patients' survival and eliminate or reduce symptoms that interfere with their daily functioning. HRQoL assessment is increasingly proposed as a measure of clinical management outcomes. The purpose of our study was to analyze the HRQoL of patients with PAH based on original papers published in the years 2009–2020. A total of 11 studies including 1218 patients were included in the final analysis. The number of studies in this meta-analysis is an indication of the scarcity of research on the subject in this specific patient population. HRQoL is a relatively recent concept in medicine, associated with the development of a revised definition of health by the WHO. Our meta-analysis performed with the use of quality of life questionnaires demonstrated that HRQoL in patients has significantly deteriorated.

Meta-analysis findings are similar to those published in studies on HRQoL[26], using both generic and specific instruments. When using generic questionnaires or ones specific to conditions other than PAH, it should be considered that both types of instruments are suitable for evaluating HRQoL in PAH but may be significantly limited by their lack of responsiveness to deterioration in health status over time. According to the authors, cardiac-specific instruments demonstrated stronger performance characteristics than respiratory-specific ones[10].

The HRQoL of PAH patients is poor, even worse than that of patients with cancer or left-sided heart failure[20]. In our meta-analysis, we also included results after PAH treatment with a follow-up period ranging between 3 weeks and

Table II. Factors positively affecting HRQoL.

Group of factors	Factor	Authors
Clinical	WHO/NYHA functional classification (class I, II)	Ganderton et al [11] Chen et al [10]
	Treatment with macinetan 10 mg once daily	Mehta et al [24]
	A high 6MWD score	Halimi et al [20]
	Lower BDI (Borg dyspnoea index) score	Chen et al [10]
	Whole-body vibration (WBV)	Gerhardt et al [25]
	Combination therapy	Morrisroe et al [23]
	Anticoagulation	Morrisroe et al [23]
	Subcutaneous infusion of treprostinil with the use of an implantated Lenus Pro pump	Kurzyna et al [28]
Socio-demographic	Gender (female)	Amedro et al [21]

Table III. Factors negatively affecting QoL.

Group of factors	Factor	Authors
Clinical	WHO/NYHA functional classification (class III and IV)	Ganderton et al [11] Amedro et al [21] Vanhoof et al [26] Chen et al [10]
	Worse 6MWD score	Halimi et al [20] Vanhoof et al [26] Chen et al [10]
	Higher BDI (Borg dyspnea index) score	Chen et al [10]
	Decreased oxygen saturation	Halimi et al [20]
	Digital ulcers, warfarin therapy	Morrisroe et al [23]
Psychological	Depression	Amedro et al [21] Halimi et al [20] Vanhoof et al [26]
	Anxiety	Amedro et al [21] Halimi et al [20] Vanhoof et al [26]
	Stress	Vanhoof et al [26] Amedro et al [21]
Socio-demographic	Gender (male)	Amedro et al [21]

6 months. It seems that few published papers demonstrate HRQoL improvement after the interventions studied.

Many interventions have been proven to impact functional capacity and HRQoL of PAH patients including supervised exercise programs[25,32,33]. PAH specialists agree that some form of exercise is not harmful for PAH patients and may actually be helpful. In a 2017 study by Gerhardt et al[25], patients participated in 16 one-hour sessions over 4 weeks. After that time, the authors found an improvement in HRQoL that correlated with better 6MWD and increased muscle strength, compared to baseline.

Another important determinant of HRQoL in PAH is the type of treatment used. Mehta et al[24] (2017) studied a group of patients treated with macitentan. This PAH-specific drug has been demonstrated to improve physical function (better NYHA functional classification) and 6MWD test results. What is more, macitentan has demonstrated benefits in patients with PAH not only in terms of morbidity but also mortality[2].

Combination therapy has been demonstrated to further improve HRQoL, exercise capacity and prognosis in PAH patients and according to the 2015 PH guidelines, is the standard treatment for PAH[5].

Patients treated with a combination of bosentan (125 mg twice daily) and iloprost (10 μg 4-6 times daily) had a better HRQoL than those on bosentan monotherapy (125 mg twice daily) and those on iloprost monotherapy (10 μg 4–6 times daily)[24]. The better HRQoL of patients who had undergone 3 months of combination therapy was also correlated with better hemodynamic parameters.

PAH affects different HRQoL aspects to various extents. Results obtained using the SF-36 questionnaire show that the HRQoL scores are lower in terms of physical health and functioning than in terms of mental health. Though the condition is associated with high levels of stress and depression (present in approx. 25-50% of patients)[20,26], disease progression and outcomes are among the most commonly reported problems in PAH patients. Physical ailments such as dyspnea, limitations in activity, and pain can significantly affect HRQoL. Disease symptoms, even if they are moderate, can interfere with a patient's professional and personal life[32]. The analyzed studies highlighted a negative correlation between depression symptoms and HRQoL[20,26]. In 15.3% of patients, the symptoms were severe or very severe if they had concurrent depression. The authors also emphasize that PAH patients are not routinely screened for anxiety, despite the reported symptoms. The few available studies do not draw from the literature on the subject. In a study by Vanhoof et al[26], anxiety was found in 27% of patients, and subjects in this group had difficulties relaxing, were often nervous and irritated, and tended to overreact. Patients with depression have been demonstrated to have more

severe disease and a higher NYHA class, and take more medication, which also suggests a more severe disease course. Likewise, patients with anxiety also had more severe disease and a higher NYHA class, as well as worse 6MWD test results; conversely, patients with better 6MWD test results had fewer symptoms of depression and a better NYHA functional class[20]. What is more, a decrease in blood oxygen saturation affects the MCS (Mental Component Summary of SF-36). Researchers have also established a negative correlation between depression and anxiety, and physical HRQoL. Of note, affective disorders are considerably more common in the population of PAH patients than among those with other chronic conditions[20,26]. Most patients use problem-focused strategies to cope with stress and depression and more information strategies to cope with the disease[20,26].

Study Limitations

Despite the relatively large number of patients assessed, the most important limitation of our meta-analysis was the small number of studies included. This is partly due to the fact that some original papers did not meet the inclusion criteria, as described in the introduction. Another limitation of the study is associated with different PAH treatment regimens and different duration of follow-up periods used in the analyzed studies, which may limit the results of our work. Another limitation of the study is the heterogeneity of the study group, which makes it very difficult to compare outcomes and state greater improvement in one study *vs.* another.

Conclusions

Our meta-analysis demonstrated that PAH patients tend to have a poor HRQoL, mainly in the physical functioning domain, less so in the psychological functioning domain.

HRQoL may be improved by therapeutic interventions, mainly pharmaceutical ones.

Patients with PAH also tend to suffer from depression, anxiety, stress, or sleep disorders. All these factors are significantly correlated with poorer HRQoL. Depression and anxiety have a negative impact on functional capacity determined using the 6MWD test.

Factors correlated with HRQoL include the NYHA functional class, gender, and developing heart failure.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Ethics Approval and Consent to Participate

Not applicable. According to the regulations of the Bioethics Committee at the Wroclaw Medical University, only medical experiments and research projects are the subject of the committee's evaluation (https://www.umed.wroc.pl/bioetyka-regulamin).

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Authors' Contribution

All authors (KS, NŚL, KD, KJ, GK, JG, BJP) contributed equally to this manuscript. All authors have read and approved the manuscript.

Authors' Contribution

The Authors declare that they have no conflict of interests.

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