Introduction: Anxiety and depression are common in pulmonary hypertension (PH) and health-related quality of life (HRQoL) is reduced. Sufficient analyses in incident and prevalent patients are lacking, so we provide a comparative analysis of these groups with focus on anxiety, depression and HRQoL.

Methods: Depression, anxiety and HRQoL were retrospectively analyzed by Hospital Anxiety and Depression Scale (HADS) and Short Form 36 questionnaire in 91 prevalent and 21 incident PH outpatients from a German tertiary care center specialized in PH. The acquired data as well as hemodynamic and functional parameters of prevalent and incident cases were compared.

Results: HRQoL was reduced in both cohorts of patients. Incident patients had significantly worse HRQoL in physical dominated scales than prevalent patients (physical component summary score: \(p = 0.02\); physical role performance: \(p < 0.01\)). Depression and anxiety were more pronounced in prevalent patients (elevated depression scales: 28.6% of incident group, 39.6% of prevalent group). The groups did not differ in hemodynamic data, but incident patients had significantly lower cardiac biomarkers such as NT-proBNP (\(p = 0.016\)) and hs-troponin (\(p = 0.017\)). The time since diagnosis was a predictor of the subscale physical role performance (\(p < 0.001\)).

Conclusion: Physical domains of HRQoL seem to be more limited in incident patients with PH. Anxiety and depression are frequent in both groups. A screening for anxiety and depression is important from the onset of the diagnosis, and patients should receive appropriate therapy to improve HRQoL, anxiety and depression.

Introduction

High prevalences of anxiety and depression for pulmonary hypertension (PH) are reported and both are strong predictors of health-related quality of life (HRQoL) in patients with PH [1–5]. Moreover, anxiety, depression and HRQoL have attributed a prognostic value in PH [6–8]. Patients with PH often suffer from dyspnea, fatigue and chest pain when the final diagnosis is set [9, 10]. May-
be due to these unspecific symptoms, there is often a delay in diagnosis. The time from beginning of symptoms to diagnosis of PH ranges on average from 18 months in chronic thromboembolic PH (CTEPH) [11] up to 47 months in idiopathic pulmonary arterial hypertension [10]. The delay in diagnosis leads to worsening of cardiac and pulmonary function reflected in an increase of symptoms and higher WHO functional classes [10]. It is unclear, if the delay in diagnosis could also increase the risk of developing anxiety and depression. On the contrary, mental disease and reduced HRQoL could accumulate throughout the course of disease, which would lead to a higher frequency of anxiety, depression and diminished HRQoL in prevalent patients.

To our knowledge, there is only one published analysis that deals with the comparison of anxiety and depression in incident and prevalent patients with PH. Somaini et al. [8] reported that incident PH patients suffered significantly more often from anxiety and depression than prevalent PH patients. As far as we know, other studies dealing with the questions of mental disorders and HRQoL in incident and prevalent PH patients are lacking.

We already analyzed the groups of PAH and CTEPH of the present cohort in an earlier published study and could show that anxiety and depression are very common in these subpopulations and that both groups suffer from poor HRQoL [12]. In the current study, we compared incident and prevalent patients with PH with the purpose of analyzing HRQoL, anxiety and depression in these groups.

Materials and Methods

Patients diagnosed with PH, including all groups of PH, were recruited when they had been initially diagnosed or presented for follow-up assessment between August 2010 and December 2011 at the Medical Mission Hospital, a tertiary PH center in Germany. A part of this cohort was partially analyzed before, regarding anxiety, depression and HRQoL in CTEPH and PAH patients in an earlier published study [12].

Recruited patients were to be at least 18 years old. For proper diagnostic approach and treatment, the assessment and therapy were conducted in accordance with current guidelines [13]. Diagnosis of PH was either confirmed or established for the first time by right heart catheterization as recommended [13, 14]. Patients with newly diagnosed PH according to right heart catheterization after first assessment were categorized as incident patients. Patients with the diagnosis of PH for at least 3 months were defined as prevalent patients.

Echocardiography (Vivid 7®, GE) and right heart catheterization were performed as recommended [13–15]. In addition, diagnosis of CTEPH included ventilation-perfusion scan, computed tomography angiography and conventional pulmonary angiography [13]. During follow-up or first assessment, anthropometric data, hemodynamic data and other recommended variables were obtained [13]. The current WHO functional class was assessed in prevalent and incident patients. For prevalent patients, the initial WHO functional class at the time of diagnosis was also recorded. The 6-min walking test (6MWT) was performed as suggested by ATS recommendations [16]. The assessment of dyspnea and exertion was made using the Borg Dyspnea and Exertion Scale, which ranges from 0 to 10 [16–19]. To complete measurement of functional capacity, cardiopulmonary exercise testing was performed including peak oxygen consumption [19, 20].

High-sensitive troponin (hs-Tn), uric acid and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) were detected using ECLI A (Elecsys 2010, Roche Diagnostics Mannheim, Germany). HRQoL was assessed by using the Short Form 36 (SF-36) questionnaire [21]. This tool consists of 36 items dealing with HRQoL. The 36 items are transformed to 8 subscales and 2 sum scales scoring from 0 to 100. A lower score represents a worse quality of life. Predefined criteria by manual guide were used to analyze the questionnaire [21].

The Hospital Anxiety and Depression Scale (HADS-D, German version) [22] was used to determine anxiety and depression. HADS-D contains in total 14 items, of which respectively 7 are used to represent the anxiety or depression scale. Each scale ranges from 0 to 21, and a cut-off score in HADS-D of 8 or more was used to define patients with elevated anxiety or depression scales [22].

In the prevalent population as well as in the incident population, right heart catheterization and other functional measures for disease severity were performed contemporaneously to HRQoL and HADS-D questionnaires. Survival was documented during the following regular visits at our specialized center and the probability of survival was analyzed according to Kaplan-Meier method.

Statistical analysis was performed using SPSS (Version 20; SPSS Inc., Chicago, IL, USA). Descriptive statistics were used for demographics, and HRQoL was expressed as mean ± standard deviation. Differences in mean scores between incident and prevalent patients were compared through unpaired t tests. Fisher’s exact test was used to analyze association in categorical data and Mann-Whitney U test was used to compare ordinal variables. The paired-sample sign test was used to determine a difference in WHO functional class in prevalent patients over time course. A stepwise multiple regression analysis was used to investigate if the time since diagnosis is a predictor of HRQoL.

Written informed consent was obtained from all patients. This study was approved by the local Ethics Committee of the Julius Maximilian University of Wuerzburg (Ethic Committee Number 253/12) and was performed according to the Declaration of Helsinki.

Results

The cohort consisted of 91 (81.3%) prevalent and 21 (18.7%) incident patients. Eighty-three percent of the whole collective suffered from either PAH or CTEPH. The remaining patients were part of other forms of PH
(PH due to lung diseases and/or hypoxia, PH with unclear and/or multifactorial mechanisms). The prevalent patients had been diagnosed for 19 months on average before analysis (median 13 months, range 156 months). The prevalent cohort consisted mainly of 64% of patients with PAH and 22% of patients with CTEPH. In the incident cohort, 57% of the patients were diagnosed PAH and 14% suffered from CTEPH. In the prevalent cohort, 70% (n = 64) were treated for PH with specific medication. Most patients received phosphodiesterase-5 inhibitors (68.8%) and endothelin-receptor-agonists (42.2%). There were 2 patients on calcium channel blocker therapy and 1 patient received inhaled iloprost next to an endothelin-receptor-agonist and phosphodiesterase-5 inhibitors. Two patients with CTEPH had undergone pulmonary endarterectomy with postoperative recurrent PH.

In the incident group, 3 patients (15.8%) were classified as WHO functional class II, whereas 16 patients (84.2%) belonged to WHO functional class III. In the prevalent group, 33 patients (37.1%) were defined as WHO functional class II and 56 patients (62.9%) were assigned to WHO functional class III. The distribution of WHO functional classes between incident and prevalent patients did not reach statistical significance (p = 0.28). Regarding the initial WHO functional class of the prevalent cohort at the time of the diagnosis, 12.6% were in WHO functional class II, 82.8% were in WHO functional class III and 4.6% were in WHO functional class IV. The WHO functional classes in the prevalent group were significantly different over time course measured by paired-samples sign test (z = −4.07; p < 0.001, n = 86).

The follow-up investigation revealed that survival probability in the prevalent group was 91.4% after 12 years.
months and 83.2% after 18 months. In the incident group, survival probability was 95.0% after both 12- and 18-month follow-up terms.

Anthropometric, hemodynamic and functional data are shown in Table 1. Sixty-three patients (69.2%) of the prevalent group and 14 patients (66.7%) of the incident group were female. Anthropometric data as well as functional data were not significantly different. Moreover, hemodynamic and echocardiographic parameters such as right atrial area and tricuspid annular plane systolic excursion (TAPSE) did not vary significantly across both cohorts. The cardiac biomarkers NT-proBNP ($p = 0.02$) and hs-Tn ($p = 0.02$) as well as thyroid-stimulating hormone (TSH) ($p = 0.03$) were significantly higher in the prevalent group.

Regarding mental disorders in both groups, 39.6% of the prevalent and 28.6% of the incident patients suffered from elevated anxiety scores in HADS-D. Elevated depression scores were present in 35.2% of prevalent and 28.6% in incident patient group. The comparison of frequency of anxiety and depression – defined by ≥8 points – in the incidence and prevalence group did not reach statistical significance ($p = 0.46$ and $p = 0.62$). Nevertheless, there is a trend toward prevalent patients having more often elevated depression and anxiety scores than incident patients (Table 2). In total, 8 patients in the prevalent group and 1 patient in the incident group had already been treated with psychoactive drugs before study analysis. Among the 36 prevalent patients with elevated anxiety scores, 8 patients had already been treated with psychoactive drugs before study analysis.

### Table 2. HADS score in incident and prevalent patients

| HADS-D anxiety score | Incident patients | Prevalent patients | $p$ value |
|----------------------|-------------------|-------------------|-----------|
| HADS score <8        | Patients, $n$     | 15                | 55        |
| In incident/prevalent patients, % | 71.4 | 60.4 |
| HADS score ≥8        | Patients, $n$     | 6                 | 36        |
| In incident/prevalent patients, % | 28.6 | 39.6 |
| $p = 0.46$           |                   |                   |           |

### Table 3. SF-36 scales in incident and prevalent patient groups

| SF-36 scale                        | Incident patients | Prevalent patients | $p$ value  |
|------------------------------------|-------------------|--------------------|------------|
|                                   | $N$ mean±SD       | $N$ mean±SD        |            |
| Physical functioning               | 19 39.36±17.78    | 87 40.62±29.42     | 0.81       |
| Physical role performance          | 18 16.67±29.70    | 80 40.52±44.82     | <0.01      |
| Bodily pain                        | 20 53.45±29.95    | 85 65.26±31.19     | 0.13       |
| General health perception          | 18 40.54±17.22    | 84 46.53±19.12     | 0.22       |
| Vitality                           | 19 43.16±11.69    | 85 46.27±20.78     | 0.37       |
| Social functioning                 | 20 73.75±22.54    | 88 70.88±25.34     | 0.64       |
| Emotional role performance         | 19 57.89±46.93    | 78 58.12±46.97     | 0.99       |
| Mental health                      | 19 71.16±15.41    | 84 65.12±18.99     | 0.20       |
| Physical component summary score   | 17 29.83±8.55     | 70 36.07±12.47     | 0.02       |
| Mental component summary score     | 17 50.86±9.60     | 70 48.11±11.10     | 0.35       |

Values are mean ± standard deviation. Significant values are given in bold.
scores, 5 patients (14%) had been under treatment with psychoactive drugs, whereas 2 patients (6%) were treated in the group with elevated depression score (n = 32). In the group of incident patients, none of the patients with elevated anxiety and/or depression scores had been treated pharmacologically due to the mental disorder.

HRQoL is reduced in both groups, which is demonstrated in Table 3. The comparison of the subscales between incident and prevalent patients showed that the incident group scored mostly lower than the prevalent group in physical scales. The difference was significant for both “physical role functioning” (p < 0.01) and “physical component summary score” (p = 0.02).

To evaluate the potential impact of the time of diagnosis on HRQoL, we conducted a stepwise linear regression with 6MWD, NT-proBNP, hs-Tn, age, number of PH-specific drugs and time since diagnosis as possible independent predictors. The stepwise regression analysis could show a correlation between “physical role functioning” and time since diagnosis (in months). Time since diagnosis did not serve as a predictor for the other subscales of HRQoL. Among the other variables, 6MWD was a predictor of HRQoL in almost every scale (Table 4).

**Discussion**

Data about anxiety, depression and HRQoL in incident and prevalent cohorts with PH are rare. In our cohort, hemodynamic data did not differ across the groups. Laboratory parameters such as hs-Tn and NT-proBNP were significantly higher in the prevalent group. Nevertheless, incident patients showed a worse WHO functional class than prevalent patients in our cohort. Previous comparisons of incident and prevalent patients reported that mean pulmonary arterial pressure (PAPm) tends to be higher in the prevalent cohort [23–25]. In the Czech cohort, prevalent patients with PAH also had a higher pulmonary vascular resistance (PVR) than incident patients [24]. Regarding literature, incident patients have even worse WHO functional class status than prevalent patients [8, 23–25]. Our data could also show this trend, but the comparison did not reach statistical significance. The fact that prevalent patients tend to be in a better WHO functional class, even when they had worse cardiac biomarkers in comparison with incident patients, can possibly be explained by the fact that there is a selection of patients with better prognosis and long-term survivors in the prevalent group. Regarding the initial WHO functional class of the prevalent patients, WHO functional class did improve over the time course.

Strange et al. [10] showed that during the diagnostic period of more than 3 years from the onset of symptoms to diagnosis in idiopathic pulmonary arterial hypertension, WHO functional classes deteriorated up to the time of diagnosis. During this delay, adequate medical therapy is lacking until diagnosis is made. The widespread use of special PAH medication in the prevalent group could therefore result in better WHO functional class [26, 27].

The survival analysis revealed that the probability of survival of the incident patients was slightly higher than the probability of the prevalent group. But an adequate

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**Table 4. Regression analysis of SF-36 scales**

| Dependent variables                  | Predictors | B   | p value | Adjusted R² | df | F value | p value (associated with F value) |
|--------------------------------------|------------|-----|---------|-------------|----|---------|----------------------------------|
| Physical functioning                 | 6MWD       | 0.14| <0.001  | 0.36        | 1; 100| 56.9    | <0.001                           |
| Physical role performance            | 6MWD       | 0.14| <0.001  | 0.19        | 2; 91| 11.8    | <0.001                           |
|                                      | Time since diagnosis |       |         |             |     |         |                                  |
| Bodily pain                          | 6MWD       | 0.09| <0.001  | 0.12        | 1; 99| 14.0    | <0.001                           |
| General health perception            | 6MWD       | 0.06| <0.001  | 0.14        | 1; 97| 17.2    | <0.001                           |
| Vitality                             | 6MWD       | 0.06| <0.001  | 0.11        | 1; 99| 13.5    | <0.001                           |
| Social functioning                   | 6MWD       | 0.42| 0.036   | 0.17        | 2; 101| 11.1    | <0.001                           |
|                                      | hs-Tn      | −0.44| 0.003   |             |     |         |                                  |
| Emotional role performance           | 6MWD       | 0.09| 0.02    | 0.48        | 1; 91| 5.6     | 0.020                           |
| Mental health                        | 6MWD       | 0.03| 0.036   | 0.03        | 1; 98| 4.5     | 0.036                           |
| Physical component summary score     | 6MWD       | 0.06| <0.001  | 0.34        | 1; 82| 42.8    | <0.001                           |

Only significant models and predictors are shown. B, coefficient; df, degrees of freedom.
Anxiety, Depression and Quality of Life in Incident and Prevalent Patients with PH

In our cohort. One reason for this could be a lower cut-off orders is reported much higher for incident patients than from anxiety or depression. The prevalence of mental disorders in incident patients, prevalent patients scored higher in mental subscales than prevalent patients, which goes in line with the distribution of anxiety and depression in these groups in our study. Physical dimension scales were significantly higher for prevalent patients in our study, although 6MWD was similar in both groups. But prevalent patients tend to be more often in a better WHO functional class. As WHO functional class reflects physical activity and correlates well with physical domains in SF 36 [33, 34], the fact that prevalent patients scored higher in the physical dominated domains is comprehensible. The differences in physical domains of HRQoL may also be attributed to medical therapy of PAH, which is known to improve HRQoL [7, 35], and in particular the physical domains of HRQoL [36]. In our study, the newly diagnosed patients have not been receiving any PAH-specific medication so far. The 6MWD seems to be a strong predictor of HRQoL in patients with PH [37]. In the conducted multiple regression analysis, 6MWD was a predictor of HRQoL in every scale except the mental component summary score. For the mental component summary score, none of the independent variables could serve as a predictor in a significant model.

Hs-Tn is already known to be a predictor of outcome in PAH [38]. In our analysis, hs-Tn served as a predictor in HRQoL next to 6MWD in the subscale social functioning \( (p < 0.001) \).

The time since diagnosis was also a predictor of HRQoL in the scale “physical role functioning” \( (p < 0.001) \). 6MWD and time since diagnosis could explain 19% of the variance of physical role functioning. Regarding the comparison of the scale “physical role functioning” in prevalent and incident patients, prevalent patients scored higher than incident patients, which goes in line with the time of diagnosis serving as a predictor in the regression analysis of this subscale.
One limiting factor of the study is the use of a generic HRQoL measurement tool instead of a disease-specific assessment tool, which may reflect clinical status more adequately. Nevertheless, the first disease-specific HRQoL assessment tool at that time was CAMPHOR, which was generated in 2006, but was adapted for German-speaking countries not until 2012 [39, 40]. Therefore, we decided to use SF-36 questionnaire to assess HRQoL in PH as it is a very common HRQoL tool which was used worldwide at that time in patients with PH for evaluating HRQoL as study endpoints.

Another limitation of the study is that different forms of PH were included in this monocentric analysis. Perhaps, some effects could be superimposed by inhomogeneity of groups, as, for example, PH due to left heart disease or PH due to lung disease implies other pathophysiological mechanisms and symptom burden than PAH and CTEPH [27]. Another important fact implying the heterogeneity of the cohort is that PH-specific treatment is only available for patients with PAH and CTEPH and could therefore have an impact on the hemodynamic, functional and possibly HRQoL results of the prevalence group. Nevertheless, the heterogenic cohort represents the typical pattern of PH patients in our specialized tertiary care center. Moreover, the analysis mainly consists of PAH and CTEPH patients with 83%. But meanwhile, there are more treatment options for patients with PAH and CTEPH since the analysis contains data from August 2010 and December 2011. It could be possible that due to new therapeutic options, the prevalence of anxiety and depression could be reduced and HRQoL could be improved in treated patients. To gain further information about treatment possibilities and effects in this complex interaction, a longitudinal study with follow-up of the incident patients in a homogenic cohort of PAH or CTEPH patients could help.

**Conclusion**

This study shows that anxiety and depression can often be found in newly diagnosed patients with PH, which emphasizes the importance of screening for mental disease from the onset of diagnosis. We could also show that incident patients had worse scores on physical subscales of HRQoL than prevalent patients, which is in accordance with the distribution of higher WHO functional classes in the incident group. Moreover, the time of diagnosis is a predictor of HRQoL next to 6MWD and hs-Tn. These results suggest that a rapid diagnosis of PH and screening for mental disease with provision of PH-specific treatment and psychological intervention if needed may help improve anxiety, depression and quality of life in patients with PH.

**Statement of Ethics**

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the local Ethics Committee of the Julius Maximilian University of Wuerzburg (Ethic Committee Number 253/12). Consent to participate statement: informed consent was obtained from all individual participants included in the study.

**Conflict of Interest Statement**

Dr. Pfeuffer-Jovic reports fees for travel/accommodation from Actelion, Boehringer Ingelheim, Novartis and OMT, outside the submitted work. Dr. Joa has nothing to disclose. Dr. Krannich has nothing to disclose. PD. Dr. Halank reports personal fees for lectures and consultations and travel/accommodation, meeting expenses from Acceleron, Actelion, AstraZeneca, Bayer, Berlin-Chemie, GSK, MSD, Novartis and OMT, outside the submitted work. PD. Dr. Held reports grants from Actelion; honoraria for lectures from Actelion, Bayer HealthCare, Berlin-Chemie, Boehringer Ingelheim, GSK, Novartis and Pfizer; honoraria for advisory board activities from Actelion, Bayer HealthCare, GSK and MSD; and participation in clinical trials of Actelion, Bayer HealthCare, GSK, Pfizer and United Therapeutics, outside the submitted work.

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**Author Contributions**

Writing and original draft: Elena Pfeuffer-Jovic and Matthias Held. Writing and review and editing: Elena Pfeuffer-Jovic, Matthias Held, Franziska Joa, Michael Halank and Jens-Holger Krannich. All authors were actively contributing to interpretation of the results and discussion of the findings. They all approved the final version of the manuscript.

**Data Availability Statement**

All data analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.
Anxiety, Depression and Quality of Life in Incident and Prevalent Patients with PH

References

1 Lowe B, Grafe K, Ufer C, Kreonke K, Grunig E, Herzog W, et al. Anxiety and depression in patients with pulmonary hypertension. *Psychosom Med*. 2004 Nov-Dec;66(6):831–6.

2 Looper KJ, Pierre A, Dunkley DM, Sigal JJ, Langleben D. Depressive symptoms in relation to physical functioning in pulmonary hypertension. *J Psychosom Res*. 2009 Mar;66(3):221–5.

3 Badesch DB, Raskob GE, Elliott CG, Krichman AM, Farber HW, Frost AE, et al. Pulmonary arterial hypertension: baseline characteristics from the REVEAL registry. *Chest*. 2010 Feb;137(2):376–87.

4 Halank M, Einsle F, Lehman S, Bremer H, Ewert R, Wilkens H, et al. Exercise capacity affects quality of life in patients with pulmonary hypertension. *Lung*. 2013 Aug;191(4):337–43.

5 Harzheim D, Klose H, Pinado FP, Ehlken N, Strange G, Gabbay E, Kermeen F, Williams T, Somaini G, Hasler ED, Saxer S, Huber LC, Cenedese E, Speich R, Dorschner L, Ulrich S, Badesch DB, Raskob GE, Elliott CG, Kritharides L, et al. The delay between symptoms to definitive diagnosis of idiopathic pulmonary hypertension and chronic thromboembolic pulmonary hypertension. *Respir Res*. 2011 Oct 9;14:104.

6 Cenedese E, Speich R, Dorschner L, Ulrich S, Maggiorini M, Jenni R, et al. Measurement of quality of life in pulmonary hypertension and its significance. *Eur Respir J*. 2006 Oct;28(4):808–15.

7 Fernandes CJ, Martins BC, Jardim CV, Gioncilli RM, Morinaga LB, Breda AP, et al. Quality of life as a prognostic marker in pulmonary arterial hypertension. *Health Qual Life Outcomes*. 2014 Aug 30;12:111.

8 Somani G, Hasler ED, Saxer S, Huber LC, Lichtblau M, Speich R, et al. Prevalence of anxiety and depression in pulmonary hypertension and changes during therapy. *Respiration*. 2016;91(5):359–66.

9 Wilkens H, Grimminger F, Hooper M, Stahler G, Ehiken B, Plesnial-Frank C, et al. Burden of pulmonary arterial hypertension in Germany. *Respir Med*. 2010 Jun;104(6):902–10.

10 Exner U, Schadeler K, Krombach S, Carrington M, Stewart S, et al. Time from symptoms to definitive diagnosis of idiopathic pulmonary arterial hypertension: the delay study. *Pulm Circ*. 2013 Jan;3(1):89–94.

11 Held M, Grun M, Holl R, Walter F, Schafer HJ, Graeter T, et al. [Chronic thromboembolic pulmonary hypertension: time delay from onset of symptoms to diagnosis and clinical condition at diagnosis]. *Dtsch Med Wochenschr*. 2014 Aug;139(33):1647–52.

12 Pfeuffer E, Kranich H, Halank M, Wilkens H, Kolb P, Jany B, et al. Anxiety, depression, and health-related QOL in patients diagnosed with PAH or CTEPH. *Lung*. 2017 Dec;195(6):759–68.

13 Galie N, Hoepf MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension: the task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). *Eur Heart J*. 2009 Oct;30(20):2493–537.

14 Rosenkranz S, Behr J, Ewert R, Ghofrani HA, Grunig E, Halank M, et al. [Right heart catheterization in pulmonary hypertension]. *Dtsch Med Wochenschr*. 2011 Dec;136(50):2601–16; quiz 2617–20.

15 Rudsiki LG, Lai WW, Afiallo J, Hua L, Handshumacher MD, Chandrasekaran K, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr*. 2010 Jul;23(7):685–715; quiz 786–8.

16 ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med*. 2002 Jul 1;166(1):111–7.

17 Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc*. 1982;14(5):377–81.

18 Borg G. Borg’s perceived exertion and pain scales. *Human Kinetics; 1992.*

19 Meyer FJ, Borst MM, Buschmann HC, Ewert R, Friedmann-Bette B, Ochmann U, et al. [Exercise testing in respiratory medicine]. *Pneumologie*. 2013 Jan;67(1):16–34.

20 American Thoracic Society, American College of Chest Physicians. ATS/ACCP statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med*. 2003 Jan 15;167(2):211–77.

21 Bullinger M, Kirchberger I, SF-36, Fragebogen zum Gesundheitszustand: Handanweisung. Göttingen: Hogrefe; 1998.

22 Snith R, Zigmond AS, Buss U. *Hospital Anxiety and Depression Scale – Deutsche Version*. Ein Fragebogen zur Erfassung von Angst und Depressivität in der somatischen Medizin; Testdokumentation und Handanweisung. Bern: Verlag Hans Huber; 1995.

23 Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, et al. Pulmonary arterial hypertension in France: results from a national registry. *Am J Respir Crit Care Med*. 2006 May 1;173(9):1023–30.

24 Jansa P, Jarkovsky J, Al-Hiti H, Popelova J, Ambroz D, Zatocil T, et al. Epidemiology and long-term survival of pulmonary arterial hypertension in the Czech Republic: a retrospective analysis of a nationwide register. *BMC Pulm Med*. 2014 Mar 15;14:45.

25 Koecz G, Kurzyna M, Mroczek E, Chrzanowski L, Mularz-Kubedla T, Skoczylas I, et al. Characterization of patients with pulmonary arterial hypertension: data from the Polish registry of pulmonary hypertension (BNP-PL). *J Clin Med*. 2020 Jan 8;9(1):173.

26 Baldi F, Fuso L, Arrighi E, Valente S. Optimal management of pulmonary arterial hypertension: prognostic indicators to determine treatment course. *Ther Clin Risk Manag*. 2014;10:825–39.

27 Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the joint task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). Endorsed by:– Association for European Paediatric and Congenital Cardiology (AEPc), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J*. 2016 Jan;137(1):67–119.

28 Jaccobi F, Hofler M, Siegert J, Mack S, Gerischer A, Scholl L, et al. Twelve-month prevalence, comorbidity and correlates of mental disorders in Germany: the mental health module of the German health interview and examination survey for adults (DEGS1-MH). *Int J Methods Psychiatr Res*. 2014 Sep;23(3):304–19.

29 Wells KB, Golding JM, Burnam MA. Psychiatric disorder in a sample of the general population with and without chronic medical conditions. *Am J Psychiatry*. 1988 Aug;145(8):976–81.

30 Harter M, Baumeister H, Reuter K, Jacci F, Hofler M, Bengel J, et al. Increased 12-month prevalence rates of mental disorders in patients with chronic somatic diseases. *Psychosom Med*. 2007;69(6):354–60.

31 Oga T, Nishimura K, Tsukino M, Sato S, Hahiro T, Mishima M. Longitudinal deterioration in patient reported outcomes in patients with COPD. *Respir Med*. 2007 Jan;101(1):94–102.

32 Roman A, Barbera JA, Castillo MJ, Munoz R, Escobar P. Health-related quality of life in a national cohort of patients with pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension. *Arch Broncholog*. 2013 May;49(5):181–8.

33 Taichman DB, Shin J, Hud L, Archer-Chicko C, Kaplan S, Sager JS, et al. Health-related quality of life in patients with pulmonary arterial hypertension. *Respir Res*. 2005 Aug 10;6:92.

DOI: 10.1159/000524369

Respiration 2022;101:784–792
35 Mehta S, Sastry BKS, Souza R, Torbicki A, Ghofrani HA, Channick RN, et al. Macitentan improves health-related quality of life for patients with pulmonary arterial hypertension: results from the randomized controlled SERAPHIN trial. Chest. 2017 Jan;151(1):106–18.

36 Rival G, Lacasse Y, Martin S, Bonnet S, Provencher S. Effect of pulmonary arterial hypertension-specific therapies on health-related quality of life: a systematic review. Chest. 2014 Sep;146(3):686–708.

37 Mathai SC, Suber T, Khair RM, Kolb TM, Damico RL, Hassoun PM. Health-related quality of life and survival in pulmonary arterial hypertension. Ann Am Thorac Soc. 2016 Jan;13(1):31–9.

38 Heresi GA, Tang WH, Aytekin M, Hammel J, Hazen SL, Dweik RA. Sensitive cardiac troponin I predicts poor outcomes in pulmonary arterial hypertension. Eur Respir J. 2012 Apr;39(4):939–44.

39 McKenna SP, Doughty N, Meads DM, Doward LC, Pepke-Zaba J. The cambridge pulmonary hypertension outcome review (CAMPHOR): a measure of health-related quality of life and quality of life for patients with pulmonary hypertension. Qual Life Res. 2006 Feb;15(1):103–15.

40 Cima K, Twiss J, Speich R, McKenna SP, Grunig E, Kahler CM, et al. The German adaptation of the cambridge pulmonary hypertension outcome review (CAMPHOR). Health Qual Life Outcomes. 2012 Sep 13;10:110.