Patient-Reported Outcomes Assessed by the CAMPHOR Questionnaire Predict Clinical Deterioration in Idiopathic Pulmonary Arterial Hypertension and Chronic Thromboembolic Pulmonary Hypertension

Colm McCabe, MBBS; Maxine Bennett, MSc; Natalie Doughty, MSc;
Robert MacKenzie Ross, MBBChir; Linda Sharples, PhD; and Joanna Pepke-Zaba, PhD

Background: The Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) is a disease-specific assessment tool used for the evaluation and follow-up of patients with pulmonary hypertension (PH). We describe a novel use for this questionnaire in its potential to predict clinical deterioration (CD) in two patient cohorts with subtypes of PH, idiopathic pulmonary arterial hypertension (IPAH), and chronic thromboembolic pulmonary hypertension (CTEPH) during an 8-year period.

Methods: We retrospectively analyzed CAMPHOR scores obtained at baseline and at follow-up visits in patients under the care of our unit over an 8-year period to assess CD and survival, as well as 6-min walk distance (6MWD) and New York Heart Association (NYHA) class.

Results: Using Cox regression, we demonstrated a significant predictive effect of CD from total CAMPHOR scores at study enrollment in IPAH and CTEPH (hazard ratios, 1.03 [95% CI, 1.01-1.05] and 1.04 [95% CI, 1.02-1.06] per unit score increase, respectively), as well as from CAMPHOR subscales as independent predictors. This predictive effect is diluted after adjusting for the prognostic effect of 6MWD and NYHA class. Repeated CAMPHOR assessment over time appears not to add predictive value of CD to that obtained at diagnosis, although it still informs physicians of important changes in self-reported symptoms.

Conclusions: When emphasis is placed on the evaluation of patient perceptions, CAMPHOR may represent an alternative method of estimating the likelihood of CD. *CHEST* 2013; 144(2):522-530

Abbreviations: 6MWD = 6-min walk distance; CAMPHOR = Cambridge Pulmonary Hypertension Outcome Review; CD = clinical deterioration; CTEPH = chronic thromboembolic pulmonary hypertension; IPAH = idiopathic pulmonary arterial hypertension; mPAP = mean pulmonary artery pressure; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PEA = pulmonary endarterectomy; PH = pulmonary hypertension; PROM = patient-reported outcome measure; PVR = pulmonary vascular resistance; QoL = quality of life

Pulmonary hypertension (PH) is an “umbrella” condition associated with a number of diseases and is characterized by elevated pulmonary artery pressure, culminating in right-sided heart failure and death.¹ Two widely studied subtypes, idiopathic pulmonary arterial hypertension (IPAH) and chronic thromboembolic pulmonary hypertension (CTEPH), are rare conditions that, despite available treatments, display overall poor survival but have heterogeneity in individual prognoses.²

IPAH has been perceived traditionally as a progressive disease with uniformly poor outcome, but improving trends in survival are emerging, suggesting that advances in medical therapy or greater diversity in patient phenotype may be responsible.^{3,4} In CTEPH with a proximal distribution of thrombotic obstructions, pulmonary endarterectomy (PEA) strongly impacts survival with surgery that restores hemodynamics to normal levels almost analogous to cure in the most expert hands.⁵ However, in patients with a

distal distribution of disease and in those experiencing functional limitation and persistently abnormal hemodynamics following PEA, outcomes are less well characterized.

Prognostic factors, both invasive and noninvasive, form a cornerstone of pulmonary arterial hypertension (PAH) management and are relevant to both medical therapy and transplant referral.^{6,7} Individually, however, they behave inconsistently in estimating prognosis. As such, their use has been supplanted by examining panels of clinical data, which take into account multiple disease factors.⁸ None of these specifically include patient-reported outcome measures (PROMs) or measures of a patient's health-related quality of life (QoL). These are typically short, self-completed questionnaires that can be either generic or disease specific. In health-care services, they are perceived increasingly as a robust method of measuring treatment outcomes that are important from a patient perspective. Using PROMs for prognostic evaluation is an emerging area in PH,⁹ although there is a burgeoning interest in their use for other chronic lung diseases.¹⁰ Although generic PROMs may lack sensitivity in monitoring changes in single patients, there are advantages in applying disease-specific versions, including trying to better understand the complex relationship between treatment efficacy and patient outcomes particular to certain diseases.

The most widely studied PROM in PH is the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR), a PH-specific measure of health-related QoL. It is a questionnaire comprising three sections evaluating symptoms, activity levels, and QoL¹¹ that has undergone international validation in patients with PH of multiple causes.¹²⁻¹⁵ Furthermore, it has shown good correlation with the Medical Outcomes Study 36-Item Short Form Health Survey and the 6-min walk distance (6MWD).¹⁴

We were, therefore, interested in broadening the current clinical application of CAMPHOR because

patients with PAH possess specific QoL issues relative to other cardiopulmonary disease. We hypothesized that the scores would have prognostic value in both IPAH and CTEPH, two conditions known to overlap in pathomechanism and clinical progression. Our primary aim was to determine whether baseline CAMPHOR scores predicted clinical deterioration (CD) in these diseases. Our secondary aims were to evaluate its prognostic value when repeated over time and also the additional value it provided at diagnosis after adjustment for the prognostic influence of New York Heart Association (NYHA) class and 6MWD.

MATERIALS AND METHODS

This study was a retrospective analysis of data covering 2004 and 2012 obtained from the Pulmonary Vascular Disease Unit database at Papworth Hospital, corresponding to 8 years of CAMPHOR use in our practice. All patients provided written informed consent in completing questionnaires. Data collection for this study was under the approval of the local research ethics committee (Huntingdon), which approved the use of CAMPHOR in a PH population from 2004 (IRB reference H02/805).

Study Population

Inclusion Criteria: The study population consisted of incident cases of IPAH and CTEPH between May 2004 and the end of March 2012. All patients must have undergone right-sided heart catheterization satisfying the most contemporaneous World Symposium on Pulmonary Hypertension criteria at diagnosis and had to be > 16 years old. Patients with CTEPH consisted of two subgroups. The first subgroup comprised patients with a distal distribution unsuitable for PEA; the second comprised patients with continued functional limitation receiving targeted PH treatment when found to have persistently elevated mean pulmonary artery pressure (mPAP) (> 25 mm Hg) at right-sided heart catheterization at least 3 months after PEA. These patients are referred to as "residual" within the CTEPH group.

Exclusion Criteria: Patients were excluded in the following circumstances: a proximal distribution of CTEPH treated by PEA, a change in diagnosis following initial assessment, a prescription of targeted therapy predating the first CAMPHOR assessment, death during their first admission, failure to complete CAMPHOR with assessment of 6MWD and NYHA class, or failure to meet the threshold for treatment under the national guidelines.

Questionnaire

The CAMPHOR questionnaire contains 65 items in total, 25 relating to symptoms, 15 relating to activities, and 25 relating to QoL. It is negatively weighted; a higher score indicates worse QoL and greater functional limitation. Symptom and QoL items are both scored out of 25: "yes/true" scores 1 and "no/not true" scores 0. Activity items have three possible responses (score 0-2), giving a score out of 30. Each CAMPHOR assessment takes an average of 10 min.

Outcome Variables

The primary outcome was CD, defined as hospital admission with symptoms of right-sided heart failure, escalation of targeted

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Affiliations: From the Pulmonary Vascular Disease Unit (Drs McCabe, MacKenzie Ross, and Pepke-Zaba and Ms Doughty) Papworth Hospital NHS Trust; and the MRC Biostatistics Unit (Ms Bennett and Dr Sharples), Institute of Public Health, Cambridge, England.

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Correspondence to: Joanna Pepke-Zaba, PhD, Pulmonary Vascular Disease Unit, Papworth Hospital NHS Trust, Cambridge, CB23 3RE, England; e-mail: joanna.pepkezaba@papworth.nhs.uk
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FIGURE 1. Patient pathway showing numbers screened, excluded, enrolled, and those experiencing CD. CD = clinical deterioration; CTEPH = chronic thromboembolic pulmonary hypertension; IPAH = idiopathic pulmonary arterial hypertension; NYHA = New York Heart Association; PH = pulmonary hypertension.

therapy, transplant, atrial septostomy, or death. CD was quantified from time zero, taken as the first diagnosis of PH contemporaneous with initiation of targeted treatment of patients with IPAH and distal CTEPH. In the residual CTEPH group, time zero was taken from first the assessment at least 3 months following PEA. In total, five patients were lost to follow-up, and these patients were censored at the last visit date. All patients were treated as per National UK standards of care for PH,¹⁶ and follow-up continued until all patients clinically deteriorated or until they were censored at the end of data collection (March 23, 2012).

Statistical Analysis

Patients diagnosed with IPAH and CTEPH were analyzed. Baseline information at time zero was summarized as mean and SD or frequency counts and proportions. CAMPHOR scales were analyzed as total scores as well as scores for each subcategory. There are no standard cutoffs for categorizing total CAMPHOR scores or CAMPHOR subscales. For Kaplan-Meier plots, the total CAMPHOR score was split into four equal-sized categories (0-19, 20-39, 40-59, and 60-80), and subscales were split into three roughly equal-sized categories (0-8, 9-17, and ≥ 18 for symptom and QoL, and 0-9, 10-19, and ≥ 20 for activity).

Time from treatment initiation to CD/censoring in the different categories was summarized on Kaplan-Meier plots with comparisons among categories by log-ranks tests. Univariable and multivariable Cox regression was used to assess independent risk predictors. Hazard ratios and 95% CIs were calculated to a 5% significance level. The association between CD and longitudinal information from CAMPHOR and clinical measures at 4 months

and yearly intervals was analyzed using univariable Cox regression with time-updated covariates; for missing covariate values, the last measurement was carried forward. Twenty-four percent and 20% of patients with IPAH and CTEPH, respectively, had at least one prognostic factor missing at baseline. Missing baseline values were likely to be missing at random; therefore, missing values were imputed using multiple imputations to assess the robustness of the estimates from the complete case analysis. Because these analyses gave very similar results, only the complete case analysis is included here.

RESULTS

One hundred five patients with IPAH and 138 patients with CTEPH were screened, and 87 and 112, respectively, enrolled in the study. Patients were excluded for different reasons in the IPAH and CTEPH groups (Fig 1). Baseline demographics, CAMPHOR scores, and clinical data are shown in Table 1. Mean age in the IPAH group was lower, and pulmonary hemodynamics were more severe. Total CAMPHOR scores and all subscales were higher in the IPAH group, consistent with worse self-assessment of symptoms. Notably, 6MWD did not differ significantly at enrollment. Figure 1 shows the breakdown of CD for each group and demonstrates that most of the CD was a consequence of escalation of targeted therapies. In the

Table 1—Comparison of Baseline Characteristics

Variable	Patients With IPAH (n = 87)	Patients With CTEPH (n = 112)
Age, y		
Mean (SD)	55.7 (16.3)	61.4 (14.8)
Range	18-81	17-86
mPAP		
Mean (SD), mm Hg	49.6 (10.5)	45.8 (11.8)
Missing	9	2
PVR		
Mean (SD), dyn	13.8 (5.0)	10.5 (5.6)
Missing	22	14
Sex, No. (%)		
Male	35 (40)	44 (39)
Female	52 (60)	68 (61)
Total CAMPHOR score		
Mean (SD)	39.9 (17.2)	33.0 (16.8)
Missing	13	17
Symptom score		
Mean (SD)	13.8 (6.2)	11.7 (6.2)
Missing	12	15
Activity score		
Mean (SD)	13.9 (7.2)	11.5 (6.2)
Missing	12	16
QoL score		
Mean (SD)	12.0 (6.3)	10.0 (6.5)
Missing	13	17
6MWD		
Mean (SD), m	271.9 (112.7)	277.7 (119.0)
Missing	7	6
NYHA class, No. (%)		
II	8 (9)	22 (20)
III	61 (71)	83 (74)
IV	17 (20)	7 (6)
Missing	1	0
Type, No. (%)		
Distal	...	74 (66)
Residual	...	38 (34)

6MWD = 6-min walk distance; CAMPHOR = Cambridge Pulmonary Hypertension Outcome Review; CTEPH = chronic thromboembolic pulmonary hypertension; IPAH = idiopathic pulmonary arterial hypertension; mPAP = mean pulmonary artery pressure; NYHA = New York Heart Association; PVR = pulmonary vascular resistance; QoL = quality of life.

CTEPH group, 49 of the total of 62 CD events occurred in the distal group, and 13 in the residual group; 28 of 74 (38%) died in the distal group during the study, compared with seven of 38 (18%) in the residual group.

Neither sex nor age was associated with an altered risk of CD, nor did age significantly affect the interval to CD during follow-up. Freedom from CD was lower for patients with IPAH up to 5 years after enrollment, after which it was similar to that for patients with CTEPH (Fig 2). Survival was consistent with international registries, with no difference between the IPAH and the CTEPH cohort (Fig 3).^{17,18}

Univariable Analysis

In both the IPAH and the CTEPH groups, baseline measurements of total CAMPHOR scores, all sub-

*Logrank test P value

FIGURE 2. Kaplan-Meier plots displaying the cumulative proportion free from CD over the follow-up period. *Log-rank test P value. See Figure 1 legend for expansion of abbreviations.

scales, and a higher NYHA class were independent predictors of CD (Table 2). Hemodynamics, mPAP, and pulmonary vascular resistance (PVR) also showed some predictive value, but it was not as strong as that of total CAMPHOR. In patients with IPAH, CD was significantly associated with higher categories of total CAMPHOR score and symptom and activity scores (Fig 4A, e-Appendix 1). QoL scores between 0 and 8 and between 9 and 17 showed similar rates of CD, although QoL scores > 18 were associated with a significantly higher rate of CD (e-Appendix 1). In the CTEPH group, CD was significantly related to total CAMPHOR score and all CAMPHOR subscales (Fig 4B, e-Appendix 1). A higher baseline 6MWD predicted a reduced likelihood of CD in both the IPAH and the CTEPH group, with a 50-m increase associated with a significantly reduced hazard across

*Logrank test P value

FIGURE 3. Kaplan-Meier plot for overall survival for both the IPAH and the CTEPH group. *Log-rank test P value. See Figure 1 legend for expansion of abbreviations.

Table 2—Univariable Cox Proportional Hazards Models for Clinical Deterioration With Baseline Measurements as Covariates

Variable	Patients With IPAH		Patients With CTEPH	
	HR (95% CI)	P Value ^a	HR (95% CI)	P Value ^a
Total CAMPHOR, unit score increase	1.03 (1.01-1.05)	.001	1.04 (1.02-1.06)	< .001
Symptom, unit score increase	1.09 (1.04-1.14)	.001	1.12 (1.07-1.18)	< .001
Activity, unit score increase	1.06 (1.02-1.11)	.002	1.12 (1.07-1.17)	< .001
QoL ^b				
0-8	...	.046	1.07 (1.03-1.12)	.001
9-17	0.73 (0.38-1.40)	...	...	...
18-25	1.79 (0.90-3.53)	...	...	...
NYHA				
II	...	.007	...	.013
III	1.59 (0.62-4.07)	...	2.67 (1.25-5.70)	...
IV	4.00 (1.42-11.27)	...	3.57 (1.06-12.06)	...
6MWD, 50-m increase	0.84 (0.75-0.95)	.004	0.79 (0.70-0.89)	< .001
mPAP, 5 mm Hg increase	1.10 (0.96-1.25)	.170	1.15 (1.03-1.29)	.013
PVR, 200-dyn increase (2.5 Wood units)	1.20 (1.04-1.38)	.015	1.12 (0.99-1.27)	.075
Type				
Distal	...	...	...	< .001
Residual	...	...	0.37 (0.20-0.69)	...

HR = hazard ratio. See Table 1 legend for expansion of other abbreviations.

^aLikelihood ratio test P value.

^bQoL unit score increase for patients with CTEPH and categories for patients with IPAH.

the study population (Table 2). A total of 66 and 90 patients in the IPAH and CTEPH groups, respectively, had total CAMPHOR, NYHA class, and 6MWD at baseline.

Multivariable Analysis

The multivariable modeling adjusted for the effect of NYHA class and 6MWD at baseline is shown in Table 3. Only a high QoL score provides an independent predictive effect of CD for patients with IPAH. In the CTEPH group, baseline symptom score and total CAMPHOR were of independent value, with no significant effect seen from activity or QoL. CAMPHOR is correlated to 6MWD and NYHA class, but when both are adjusted for, the effect of each subscale is notably diluted. Further adjustment for mPAP and PVR increases the association of total CAMPHOR and its subscales with CD (e-Appendix 2), but these results should be interpreted with caution because of the low number of patients and CD events. Forty-seven patients in the IPAH group and 78 patients in the CTEPH group had total CAMPHOR, NYHA class, 6MWD, and hemodynamics at baseline.

Longitudinal Analysis

Longitudinal analysis of total CAMPHOR scores, its subscales, and 6MWD showed a direct association with CD (Table 4). NYHA class was not analyzed as a time-updated covariate because patients rarely changed class. The similar regression coefficients using

Cox regression (Table 2) and time-updated covariates (Table 4) suggest that isolated CAMPHOR assessments over time add little to its predictive effect on CD determined at enrollment and that the effect of CAMPHOR does not change over time.

DISCUSSION

The current clinical application of CAMPHOR focuses on the evaluation of patient perceptions in PH. We have shown, we believe for the first time, a novel use for the CAMPHOR questionnaire obtained at diagnosis in its ability to predict CD in patients with IPAH and CTEPH. Similar to NYHA class and 6MWD, with the univariable model, both total CAMPHOR score and its subscales appear to predict risk of CD in IPAH and CTEPH. Following adjustment for 6MWD and NYHA class, some predictive effect persists and further adjusting for hemodynamics increases the association of total CAMPHOR and its subscales with CD. This may be explained by the loss of heterogeneity between IPAH and CTEPH after adjustment for NYHA class, 6MWD, mPAP, and PVR, resulting in a clearer association between CAMPHOR and CD.

In keeping with existing knowledge, a lower 6MWD and a higher NYHA class at enrollment were associated with a greater risk of CD. Sex had no significant effect. Contrasting with the findings of other studies, age did not predict the rate of CD in either the IPAH or the CTEPH cohort.¹⁹⁻²¹ This is most likely explained

FIGURE 4. Kaplan-Meier plots displaying the cumulative proportion free from CD over the follow-up period for different categories of total Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) at baseline. A, patients with IPAH. B, patients with CTEPH. CD = clinical differential. See Figure 1 legend for expansion of other abbreviations.

by our definition of CD being different from that used in other interventional studies, in that we did not incorporate a reduction in 6MWD or maintenance of NYHA class within our CD criteria, both of which may act as more sensitive indicators of CD with advancing age.²² We intentionally chose our definition of CD because not all clinical measures were documented at each visit and because assessment of NYHA class is subject to interobserver variability. Additionally, CD could have occurred without a 6MWD being undertaken if patients were too unwell. Despite this, the survival trends were similar to those of large registries, which suggests that the observed rates of CD with advancing age are a genuine effect.^{23,24}

Although baseline total CAMPHOR scores demonstrated a significant predictive effect of CD in both IPAH and CTEPH, exceptions arise within the sub-

scales of CAMPHOR when analyzed in isolation. For QoL within the IPAH cohort, the hazard ratio behaved nonlinearly, with an inferred protective effect against CD for QoL scores between 9 and 17, which reverts to a detrimental effect for scores of ≥ 18 , in contrast to trends demonstrated by symptom and activity scores. This may be a reflection of the uncertain clinical meaning of small changes in subscale values. To put this in perspective, the complete CAMPHOR is an 80-point scale, in which an increase of 10 points produces a univariable hazard ratios of 1.37 (95% CI, 1.14-1.64) and 1.51 (95% CI, 1.27-1.79) for IPAH and CTEPH, giving a 37% and 51% increase in the incidence of CD, respectively.

Comparison between disease groups also suggests that different CAMPHOR subscales harbor different predictive values. This finding is difficult to explain, although the QoL of all three CAMPHOR subscales is the most likely to be subject to confounding. It is known that factors such as age, sex, education, and income may impact QoL, but the contributions of each could not be assessed in this study.²⁵ Similarly, feelings of depression, anxiety, and hopelessness are well captured within QoL.²⁶ Patients with IPAH experience more indolent symptom onset, in contrast to an often relatively abrupt onset of CTEPH precipitated by an acute embolic event. Conceivably, therefore, illness perceptions may differ at first presentation during a phase of patient adjustment.

Importantly, decisions to increase treatment would have been made following patient assessment using 6MWD and other assessment tools. CAMPHOR scores were collected and reviewed after any clinical decision was made, meaning that scores would not have affected treatment decisions and, thus, CD. Notably, the majority of CD events arose from escalation of targeted therapies in both the IPAH and the CTEPH cohort. Differing trends in the treatment of these diseases in the United Kingdom make cross-cohort comparison of rates of CD difficult to interpret; IPAH benefits from several licensed drug classes with more scope for escalation of treatment in the face of a poor response to an initial treatment agent but CTEPH has no specific licensed treatments, and treatment with PAH licensed therapy is recommended generally only within clinical drug trials. Furthermore, UK treatment guidelines differ from European guidelines because treatment in the United Kingdom is driven more by the clinical impression of PH physicians rather than targeted toward fixed goals in functional capacity.²⁰ Obtaining an equivalent prescription of targeted therapies may therefore be impossible to achieve between IPAH and CTEPH in the face of clinically apparent patient deterioration, although at baseline, data on targeted therapies prescribed within our cohorts (e-Appendix 3) suggest similar treatment strategies for IPAH and CTEPH.

Table 3—Multivariable Cox Proportional Hazards Models Adjusted for NYHA and 6MWD for Clinical Deterioration With Baseline Measurements as Covariates

Variable	Patients With IPAH		Patients With CTEPH	
	HR (95% CI)	P Value ^a	HR (95% CI)	P Value ^a
Total CAMPHOR, unit score increase	1.02 (0.99-1.05)	.158	1.03 (1.00-1.05)	.027
Symptom, unit score increase	1.05 (0.98-1.12)	.143	1.08 (1.02-1.15)	.006
Activity, unit score increase	1.04 (0.98-1.10)	.227	1.06 (1.00-1.13)	.067
QoL ^b				
0-8	...	.005	1.03 (0.98-1.09)	.210
9-17	0.37 (0.16-0.84)	...	...	...
18-25	1.14 (0.47-2.78)	...	...	...

See Table 1 and 2 legends for expansion of abbreviations.

^aLikelihood ratio test *P* value.

^bQoL unit score increase for patients with CTEPH and categories for patients with IPAH.

Survival did not differ significantly between the IPAH and the CTEPH cohort. Deaths contributed more toward CD in the CTEPH group, but a similar proportion of patients with IPAH died after an alternative CD event. Almost one-third of the CTEPH cohort consisted of patients after PEA, presenting with persistent functional limitation. It is our clinical experience that patients in this category exhibit more stable clinical courses compared with those with distal CTEPH and there are almost certainly differences in pulmonary circulatory responses that govern prognosis following major operative intervention.²⁷ Although combining these two groups may therefore seem artificial, our primary intention in this study was to evaluate the prognostic power of patient perceptions using CAMPHOR and, for this reason, their amalgamation is justifiable.

PAH therapies are generally licensed for symptomatic benefit based on studies using 6MWD as a surrogate for symptomatic change. The use of PROMs to monitor patients is appropriate because patients are treated primarily for symptoms; patients will often trade years of life for a good QoL. The finding that CAMPHOR may also offer prognostic information should therefore be seen as an added benefit. The use of CAMPHOR is patient centered in contrast to more traditional assessment tools, which, as a group, and may be subject to observer variability and confounding factors.

Despite a relatively large patient number, our study does have limitations. The Cox regression used in our statistical analysis assumes constant risk ratios for predictive variables throughout the duration of a patient's study, which may not clinically apply to the patients in our study. Clinical need determined follow-up intervals; hence, longitudinal analysis was hampered by a lack of time-updated covariate measurements. Finally, our definition of CD is only valid for the sequential addition of PH-targeted drug classes. Emerging trends toward up-front combination therapy in patients with NYHA class III/IV would need separate validation if our definition of CD were to be used.

CONCLUSIONS

Several international prognostic stratification tools now exist in PAH that may predict survival accurately, but these still rely on invasive tests.^{21,23,24} Increasing attention is now turning toward the physical and emotional implications of living with an incurable disease, and the IPAH and CTEPH populations should not be regarded as exceptional.²⁸ The relatively limited response to PAH-targeted treatments with persistent high mortality rates makes the clinical incorporation of patient perceptions into long-term care an attractive step forward in an emerging era of goal-oriented therapy. Future studies incorporating CAMPHOR into

Table 4—Univariable Cox Proportional Hazards Models With CAMPHOR Scores as Time-Updated Covariates

Variable	Patients With IPAH		Patients With CTEPH	
	HR (95% CI)	P Value ^a	HR (95% CI)	P Value ^a
Total CAMPHOR, unit score increase	1.04 (1.02-1.06)	<.001	1.04 (1.02-1.05)	<.001
Symptom, unit score increase	1.11 (1.06-1.16)	<.001	1.11 (1.06-1.15)	<.001
Activity, unit score increase	1.08 (1.04-1.12)	<.001	1.12 (1.07-1.16)	<.001
QoL, unit score increase	1.08 (1.03-1.13)	<.001	1.08 (1.04-1.12)	<.001
6MWD, 50-m increase	0.81 (0.73-0.91)	<.001	0.75 (0.67-0.84)	<.001

See Table 1 and 2 legends for expansion of abbreviations.

^aLikelihood ratio test *P* value.

the currently available prognostic tools may demonstrate equally useful effects.

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Author contributions: Dr Pepke-Zaba is the overall guarantor of the manuscript.

Dr McCabe: contributed to the creation of the figures and was the principal writer of the manuscript.

Ms Bennett: contributed to the statistical design and analyses, creation of tables and figures, and writing of the manuscript.

Ms Doughty: contributed to the data gathering from the patient database and analysis of baseline patient characteristics and manuscript preparation.

Dr MacKenzie Ross: contributed to the data analysis and manuscript preparation.

Dr Sharples: contributed to the statistical design and analysis, table and figure preparation, and writing of the manuscript.

Dr Pepke-Zaba: contributed to the review of the manuscript, rewriting of some paragraphs, and supervision of the writing and manuscript preparation.

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Additional information: The e-Appendixes can be found in the "Supplemental Materials" area of the online article.

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