ORIGINAL RESEARCH

# Cardiopulmonary Exercise Testing Provides Prognostic Information in Advanced Cystic Fibrosis Lung Disease

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## Abstract

**Rationale:** Cardiopulmonary exercise testing (CPET) provides prognostic information in cystic fibrosis (CF); however, its prognostic value for patients with advanced CF lung disease is unknown.

**Objectives:** To determine the prognostic value of CPET on the risk of death or lung transplant (LTX) within 2 years.

**Methods:** We retrospectively collected data from 20 CF centers in Asia, Australia, Europe, and North America on patients with a forced expiratory volume in 1 second ($FEV_1$) $\leq$ 40% predicted who performed a cycle ergometer CPET between January 2008 and December 2017. Time to death/LTX was analyzed using mixed Cox proportional hazards regression. Conditional inference trees were modeled to identify subgroups with increased risk of death/LTX.

**Results:** In total, 174 patients ($FEV_1$, 30.9% $\pm$ 5.8% predicted) were included. Forty-four patients (25.5%) died or underwent LTX. Cox regression analysis adjusted for age, sex, and $FEV_1$ revealed percentage predicted peak oxygen uptake ($\dot{V}O_{2peak}$) and peak work rate ($W_{peak}$) as significant predictors of death/LTX: adjusted hazard ratios per each additional 10% predicted were 0.60 (95% confidence interval, 0.43–0.90; $P = 0.008$) and 0.60 (0.48–0.82; $P < 0.001$). Tree-structured regression models, including a set of 11 prognostic factors for survival, identified $W_{peak}$ to be most strongly associated with 2-year risk of death/LTX. Probability of death/LTX was 45.2% for those with a $W_{peak} \leq 49.2\%$ predicted versus 10.9% for those with a $W_{peak} > 49.2\%$ predicted ($P < 0.001$).

**Conclusions:** CPET provides prognostic information in advanced CF lung disease, and $W_{peak}$ appears to be a promising marker for LTX referral and candidate selection.

**Keywords:** CF; lung transplantation; peak work rate; peak oxygen uptake; survival.

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Cystic fibrosis (CF) is a life-limiting disease caused by mutations in the gene encoding for the CF transmembrane conductance regulator (CFTR) protein, characterized by progressive lung destruction leading to respiratory failure in the majority of individuals (1). Lung transplantation (LTX) is a treatment undertaken to improve the quality of life and survival in carefully selected patients with advanced CF lung disease (ACFLD) (2, 3). Various predictors of LTX have been identified in CF, including poor lung function (forced expiratory volume in 1 s [$FEV_1$]), low body mass index (BMI), hypoxemia, infection with *Burkholderia cepacia* complex, oxygen supplementation, number of hospitalizations for pulmonary exacerbations, and functional exercise capacity (4–10). The changing demographics in CF and remarkable improvements in overall survival (11, 12), also seen in those with ACFLD (9), pose challenges to clinicians with respect to the optimal timing of LTX evaluation and candidate selection.

$FEV_1$ remains an important prognostic marker in CF (9); however, more dynamic, physiological markers of disease severity, such as cardiopulmonary exercise testing (CPET) outcomes (13), may prove valuable in a patient population that lives longer despite ACFLD (14). Several studies have demonstrated that exercise testing provides prognostic information in CF (8, 15–17). The CF Foundation recommends annual exercise testing using the 6-minute-walk test (6MWT) in those with $FEV_1 < 40\%$ predicted (3). Our group recently demonstrated that CPET-derived outcomes provide important prognostic information on the combined outcome death/LTX in CF even after controlling for other predictors (17). Although our previous study focused on long-term (≥10-year follow-up) outcomes, little information is available on the value of CPET-derived outcomes on short-term mortality and LTX predictions, particularly regarding those with ACFLD. The previous study was not designed and powered to assess the impact of CPET outcomes on short-term survival, although an exploratory analysis with a limited number of cases revealed significant associations between CPET outcomes and 2-year risk of death/LTX (17). To build on this preliminary evidence (17), the objective of the present study was to evaluate the prognostic value of CPET outcomes on 2-year risk of death/LTX in patients with ACFLD. Some of the results of this study have been previously reported in the form of an abstract (18).

## Methods

### Study Design and Subjects

We retrospectively collected health-related data from patients with ACFLD (18) aged ≥10 years and with $FEV_1 \leq 40\%$ predicted, who had performed CPET between January 1, 2008 and December 31, 2017 and for whom follow-up information on death or LTX was available 2 years (730 d) after CPET. We excluded patients who left their CF center within 2 years after CPET and for whom information on survival status was unavailable. Ethical approval was obtained from contributors' respective research ethics committees, if required (*see* data supplement).

### Clinical Characteristics

We collected anthropometric characteristics, *CFTR* genotype, CF-related comorbidities, presence of pathogens, concomitant medications, lung function, and 6MWT data at the time of CPET. In addition, we collected the numbers of hospitalizations, days in the hospital, days on intravenous antibiotics, and episodes of hemoptysis and pneumothorax during the 2-year follow-up period. We categorized CFTR mutations into minimal function mutations (i.e., both *CFTR* alleles in either class I, II, or III) and residual function mutations (i.e., at least one mutant *CFTR* allele in class IV or class V) (19–21).

### Cardiopulmonary Exercise Testing

CPET data collected were restricted to cycle ergometry tests using minute-by-minute increments or ramp protocols (22). Details on CPET equipment, reference equations, and test protocols (*see* Table E1 in the data supplement) and criteria for maximal effort are presented in

the data supplement. For each individual patient, one test was included in the analysis. All tests were performed without oxygen supplementation. If multiple tests were available within the period of interest for an individual, we requested data from the most recent valid test. We report peak oxygen uptake ($\dot{V}O_{2peak}$) (23) and peak work rate ($W_{peak}$) (24) values as percentage predicted using reference equations that have been previously used in studies investigating the prognostic value of CPET in patients with CF (15, 17).

All data were collected with REDCap (Research Electronic Data Capture, Vanderbilt University) (25). Database entries were monitored to minimize errors. The manuscript was prepared according to the Strengthening the Reporting of Observational Studies in Epidemiology statement (26).

### Statistical Analysis and Sample Size Calculation

Data are presented as *n* (%) or mean ± SD (minimum, maximum). We converted data from spirometry and CPET to percentage predicted values and/or *z*-scores (11–13). The primary composite endpoint for survival was LTX or death within 2 years after CPET, which we assessed as a binary variable as well as using the time between CPET and the event. Exploratory outcomes were 6MWT distance (6MWD) and numbers of hospitalizations, days in the hospital, days on intravenous antibiotics, and episodes of hemoptysis and pneumothorax during follow-up.

We used receiver operating characteristic (ROC) curves to establish cutoff values for $\dot{V}O_{2peak}$ and $W_{peak}$ by maximizing the sum of sensitivity and specificity. In a second step, we used the cutoff values to visualize survival rates (i.e., herein referred to as rates of death/LTX) for different groups in Kaplan-Meier curves. In addition, we computed multivariable mixed Cox proportional hazard regression models to predict 2-year risk of death/LTX adjusted for age, sex, $FEV_1$% predicted and either $\dot{V}O_{2peak}$% predicted or $W_{peak}$% predicted as continuous variables. Furthermore, we ran mixed Cox models using binary variables based on the proposed $\dot{V}O_{2peak}$ and $W_{peak}$ cutoff values from ROC curves instead of the measured values. Because we expected differences in patient characteristics between CF centers (Table E2), the mixed Cox models included a random intercept for each study center.

In an additional analysis, we modeled conditional inference trees (27) aiming to identify subgroups of patients with CF with increased risk of death/LTX. Details about the analysis are presented in the data supplement. The model included the following 11 candidate variables: $\dot{V}O_{2peak}$, $W_{peak}$ (both percentage predicted), sex, age, BMI ($kg \cdot m^{-2}$), $FEV_1$% predicted, CF-related diabetes, oxygen supplementation (i.e., continuous or at night) at the time of CPET, and *Pseudomonas aeruginosa* infection, *B. cepacia* complex infection, or *Nontuberculosis mycobacteria* infection in the 12 months before CPET.

Moreover, we conducted two sensitivity analyses. First, we excluded patients with a potential submaximal effort during CPET and compared all results with those from the primary study population. Second, we felt that using rounded cutoff values for $\dot{V}O_{2peak}$ and $W_{peak}$ would enhance their practicality in clinical settings. Therefore, we evaluated sensitivity and specificity values corresponding to 40% predicted $\dot{V}O_{2peak}$ and 50% predicted $W_{peak}$ and compared survival curves and Cox model outputs to the results obtained with the data-driven ROC curve cutoff values.

Overall, the numbers of missing outcome data for relevant prognostic factors included in the Cox models and conditional inference tree models were low and balanced between survivors and cases (Table E3). We did not perform an *a priori* sample size calculation. Missing outcome data were not imputed.

All statistical analyses were undertaken using R, Version 4.0.5. The statistical code is available in the data supplement.

## Results

Between July 14 and August 19, 2019, we contacted potential study collaborators via email using the membership list of the European CF Society Exercise Working Group and by searching PubMed for publications on CPET in CF over the last 12 years using MeSH terms "exercise testing" and "cystic fibrosis." We contacted 53 centers, of which 39 responded to the survey (74% response rate). Finally, 20 centers from Asia ($n = 2$), Australia ($n = 2$), Europe ($n = 11$), and North America ($n = 5$) contributed data from 180 patients with CF. Among those, six had an $FEV_1 > 40\%$ predicted (28) and were excluded, leaving 174 patients (41% female) for the final analysis. A flow chart is provided in the data supplement (Figure E1).

During the 2-year follow-up period, 11 patients died of respiratory failure and 33 underwent LTX (44/174, 25.3%). Tables 1 and 2 summarize patient characteristics and CPET data, stratified by survival status. Patients who died or underwent LTX had worse lung function and lower exercise capacity, were more frequently infected with *P. aeruginosa*, and more frequently had CF-related diabetes (Tables 1 and 2). Tables E4 and E5 present patient characteristics and CPET data for survivors stratified by highly effective modulator therapy (HEMT) and cases. Among survivors, the subgroup of patients receiving HEMT ($n = 9$) were older, had similar $FEV_1$% predicted, and had slightly lower percentage predicted $\dot{V}O_{2peak}$ and $W_{peak}$ than those not receiving HEMT ($n = 121$). The data must be interpreted with caution because of the small number of patients on HEMT.

### ROC Curves

ROC curves for $\dot{V}O_{2peak}$ and $W_{peak}$ are displayed in Figure 1. A comparison of the two ROC curves revealed no statistically significant difference (bootstrap test, $P = 0.19$). The area under the curve and sensitivity values were slightly higher for $W_{peak}$ than $\dot{V}O_{2peak}$, whereas specificity values were slightly higher for $\dot{V}O_{2peak}$ (Figure 1). The cutoff values for percentage predicted $\dot{V}O_{2peak}$ and $W_{peak}$ were 39.4% and 49.2%, respectively.

### Kaplan-Meier Survival Curves

The Kaplan-Meier curves show probabilities of death/LTX among patients categorized into two groups based on $\dot{V}O_{2peak}$ and $W_{peak}$ cutoffs from ROC curve analyses (Figure 2). The median time till death or LTX was not reached in either of the groups. Survival rates were significantly lower for the group of patients with $\dot{V}O_{2peak} \leq 39.4\%$ predicted than for those with $\dot{V}O_{2peak} > 39.4\%$ predicted (56.9% vs. 86.1%; $P < 0.0001$). Similarly, survival rates were lower for those with $W_{peak} \leq 49.2\%$ predicted than those with $W_{peak} > 49.2\%$ predicted (54.8% vs. 89.1%; $P < 0.0001$). Clinical characteristics and CPET data among groups of patients based on $\dot{V}O_{2peak}$ and $W_{peak}$ cutoffs from ROC curve analyses are provided in the data supplement (Tables E6–E9).

**Table 1.** Comparison of lung function, genotype, pathogens, and CF–related comorbidities among survivors and cases at the time of cardiopulmonary exercise testing

| Variable | Survivors (*n* = *130*) | Death/LTX (*n* = *44*) |
|---|---|---|
| Age, yr | 29.8 ± 9.7 (11.8, 53.0) | 30.5 ± 9.2 (17.5, 47.0) |
| Sex, female | 51 (39.2) | 21 (47.7) |
| BMI, $kg \cdot m^{-2}$ | 20.6 ± 3.5 (13.1, 35.9) | 19.3 ± 3.0 (14.2, 27.3) |
| Lung function | | |
| $FEV_1$% predicted | 32.1 ± 5.1 (15.7, 39.9) | 27.3 ± 6.1 (13.3, 39.7) |
| $FEV_1$, *z*-score | −5.3 ± 0.4 (−6.6, −4.4) | −5.6 ± 0.4 (−6.3, −4.6) |
| FVC% predicted | 54.3 ± 12.4 (20.2, 89.5) | 46.1 ± 13.6 (23.0, 73.5) |
| FVC, *z*-score | −3.9 ± 1.1 (−7.1, −0.9) | −4.6 ± 1.2 (−6.8, −2.2) |
| Genotype | | |
| CFTR, both alleles from classes I–III | 112 (86.2) | 38 (86.4) |
| CFTR, at least one allele from classes IV–V | 15 (11.5) | 3 (6.8) |
| CFTR, at least one allele unknown/not available | 3 (2.3) | 3 (6.8) |
| *CFTR* modulator therapy | | |
| At the time of CPET | 20 (15.4) | 4 (9.1) |
| After CPET | 10 (7.7) | 1 (2.3) |
| Ivacaftor | 7 (5.4) | 0 (0) |
| Lumacaftor/ivacaftor | 20 (15.4) | 4 (9.1) |
| Tezacaftor/ivacaftor | 1 (0.8) | 0 (0) |
| Elexacaftor/tezacaftor/ivacaftor | 2 (1.5) | 0 (0) |
| CF-related pathogens* | | |
| *P. aeruginosa* | 88 (67.7) | 42 (95.5) |
| *B. cepacia* complex | 12 (9.3) | 1 (2.3) |
| *N. mycobacteria* | 5 (3.9) | 3 (6.8) |
| Comorbidities | | |
| Pancreatic insufficiency | 107 (82.3) | 39 (88.6) |
| CF-related diabetes | 58 (44.6) | 23 (52.3) |
| Cardiac disease | 2 (1.5) | 2 (4.5) |

*Definition of abbreviations*: *B. cepacia* = *Burkholderia cepacia complex*; BMI = body mass index; CF = cystic fibrosis; CFTR = cystic fibrosis transmembrane conductance regulator; CPET = cardiopulmonary exercise testing; $FEV_1$ = forced expiratory volume in 1 second; FVC = forced vital capacity; LTX = lung transplantation; *N. mycobacteria* = *Nontuberculosis mycobacteria*; *P. aeruginosa* = *Pseudomonas aeruginosa*.
Data are mean ± standard deviation (minimum, maximum values) or *n* (%) of the study sample.
*Presence of infection(s) in the last 12 months before CPET.

**Table 2.** Comparison of cardiopulmonary exercise testing outcomes among survivors and cases

| Variable | Survivors (*n* = *130*) | Death/LTX (*n* = *44*) |
|---|---|---|
| Duration of exercise, s | 392 ± 123 (60, 980) | 318 ± 123 (120, 570) |
| $\dot{V}O_{2peak}$, $L \cdot min^{-1}$ | 1.3 ± 0.5 (0.6, 2.8) | 1.0 ± 0.3 (0.6, 2.2) |
| $\dot{V}O_{2peak}$, $ml \cdot min^{-1} \cdot kg^{-1}$ | 22.5 ± 7.4 (9.0, 48.5) | 18.5 ± 5.3 (9.5, 34.5) |
| $\dot{V}O_{2peak}$% predicted | 48.2 ± 13.7 (21.7, 98.1) | 38.2 ± 10.6 (20.6, 73.7) |
| $W_{peak}$, W | 101.5 ± 39.2 (25.0, 247.9) | 69.2 ± 25.9 (30.0, 141.0 |
| $W_{peak}$, $W \cdot kg^{-1}$ | 1.8 ± 0.6 (0.6, 4.2) | 1.3 ± 0.4 (0.6, 2.8) |
| $W_{peak}$% predicted | 56.3 ± 17.3 (20.9, 127.3) | 39.9 ± 12.7 (17.0, 72.7) |
| $HR_{peak}$, $beats \cdot min^{-1}$ | 152 ± 19 (105, 196) | 143 ± 18 (116, 186) |
| $HR_{peak}$% predicted | 82.4 ± 11.5 (35.0, 135.0) | 78.2 ± 8.8 (63.0, 100.0) |
| $\dot{R}ER_{peak}$ | 1.1 ± 0.1 (0.8, 1.6) | 1.1 ± 0.2 (0.7, 1.5) |
| $\dot{V}_{Epeak}$, $L \cdot min^{-1}$ | 45.7 ± 15.0 (20.0, 89.0) | 36.1 ± 14.0 (17.0, 80.0) |
| $fR_{peak}$, $breaths \cdot min^{-1}$ | 42.9 ± 10.7 (16.0, 76.0) | 41.6 ± 8.7 (28.0, 67.0) |
| $V_{Tpeak}$, L | 1.3 ± 0.5 (0.3, 3.4) | 1.0 ± 0.5 (0.4, 2.4) |
| $\dot{V}_{Epeak}/MVV_{pred}$, % | 95.9 ± 22.3 (46.0, 170.1) | 91.5 ± 23.0 (49.7, 173.6) |
| $Sp_{O_{2peak}}$, %* | 91 ± 5 (72, 99) | 87 ± 7 (69, 97) |

*Definition of abbreviations*: $fR_{peak}$ = breathing frequency at peak exercise; $HR_{peak}$ = peak heart rate; MVV = maximum voluntary ventilation (calculated as forced expiratory volume in 1 s × 40); $\dot{R}ER_{peak}$ = respiratory exchange ratio at peak exercise; $Sp_{O_{2peak}}$ = oxygen saturation at peak exercise; $\dot{V}_{Epeak}$ = peak minute ventilation; $\dot{V}_{Epeak}/MVV_{pred}$ = breathing reserve; $\dot{V}O_{2peak}$ = peak oxygen uptake; $V_{Tpeak}$ = tidal volume at peak exercise; $W_{peak}$ = peak work rate.
Data are mean ± standard deviation (minimum, maximum values) or *n* (%) of the study sample.
*Data were available for 141 patients (*n* = 106 survivors, *n* = 35 cases).

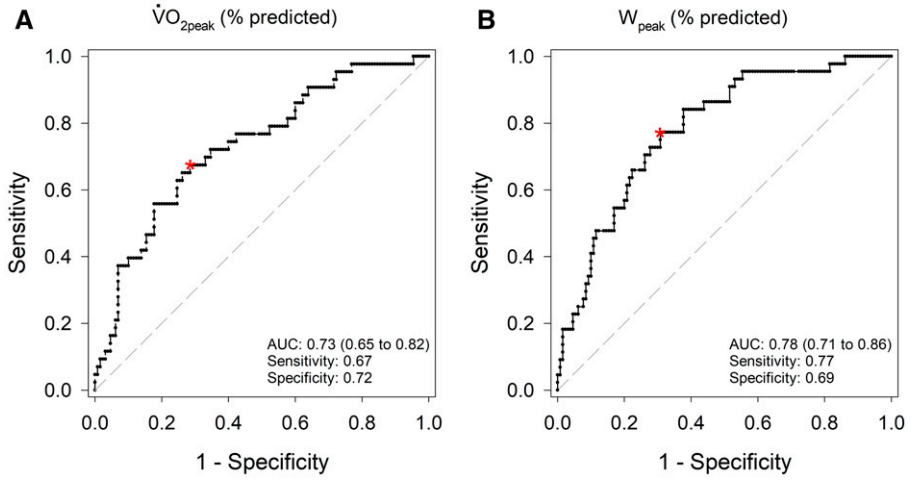


**Figure 1.** Receiver operating characteristic curves for (*A*) percentage predicted peak oxygen uptake ($\dot{V}O_{2peak}$) and (*B*) percentage predicted peak work rate ($W_{peak}$). The optimal cutoff values for $\dot{V}O_{2peak}$ and $W_{peak}$ were 39.4% and 49.2% predicted, respectively. Area under the receiver operating characteristic curve (AUC) and 95% confidence intervals are shown. The gray dashed line indicates no discriminatory ability (AUC = 0.5). The red asterisk displays the optimal cutoff value for 2-year risk of death/lung transplant. Sensitivity = true-positive rate; 1 − specificity = false-positive rate.

### Mixed Cox Proportional Hazard Regression Models

In mixed Cox regression models adjusted for age, sex, and $FEV_1$% predicted, both percentage predicted $\dot{V}O_{2peak}$ and $W_{peak}$ were significant predictors of death/LTX (Table 3). For each additional 10% predicted $\dot{V}O_{2peak}$ or $W_{peak}$, the risk of death/LTX within 2 years is reduced by ~40% (i.e., adjusted hazard ratio, 0.60 in both models). Both $\dot{V}O_{2peak}$ and $W_{peak}$ remained significant predictors of death/LTX when we used a binary variable stating being below or above the proposed cutoff values from the ROC curve analyses (Table E10). Patients with a "high" $\dot{V}O_{2peak}$

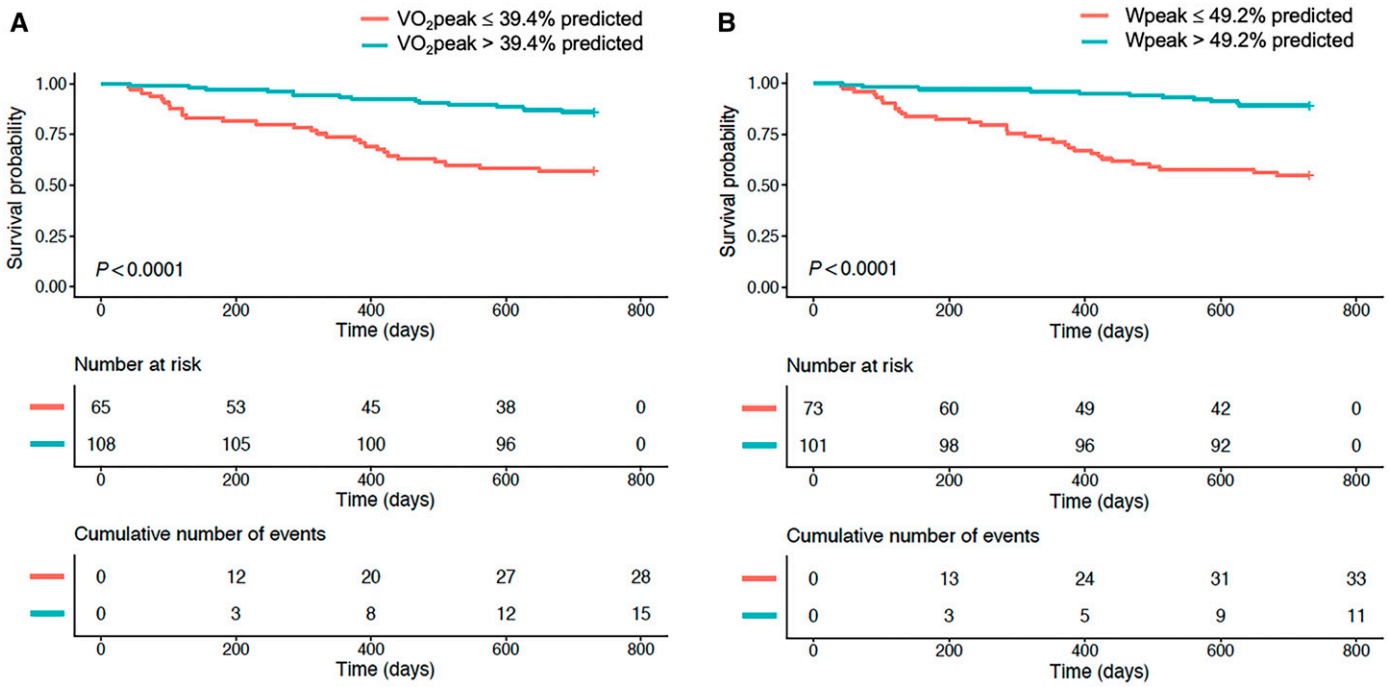


**Figure 2.** Kaplan-Meier survival curves for percentage predicted peak oxygen uptake ($\dot{V}O_{2peak}$) and peak work rate ($W_{peak}$). The figure shows the probability of death/lung transplant within 2 years (herein referred to as survival probability) after cardiopulmonary exercise testing for different groups of patients categorized according to $\dot{V}O_{2peak}$ and $W_{peak}$ cutoff values from receiver operating characteristic curves. The blue curves represent the groups of patients with (*A*) $\dot{V}O_{2peak} >$ 39.4% predicted, or (*B*) $W_{peak} >$ 49.2% predicted. The red curves represent the group of patients with (*A*) $\dot{V}O_{2peak} \leq$ 39.4% predicted or (*B*) $W_{peak} \leq$ 49.2% predicted. One patient had a valid $W_{peak}$ test, but gas exchange data including oxygen uptake values were not valid (number of patients at risk at start of observation: $n = 173$ for $\dot{V}O_{2peak}$, $n = 174$ for $W_{peak}$).

**Table 3.** Results of multivariable mixed Cox proportional hazard regression models including $\dot{V}O_{2peak}$ (model 1) or $W_{peak}$ (model 2) for 2-year risk of death/lung transplant

| | HR | 95% CI | *P* Value |
|---|---|---|---|
| Model 1 | | | |
| Age, yr | 1.00 | 0.97–1.03 | 0.94 |
| Male sex | 0.65 | 0.35–1.21 | 0.17 |
| $FEV_1$% predicted | 0.93 | 0.88–0.98 | 0.008 |
| $\dot{V}O_{2peak}$% predicted | 0.95* | 0.92–0.99 | 0.008 |
| Model 2 | | | |
| Age, yr | 1.00 | 0.97–1.04 | 0.78 |
| Male sex | 0.73 | 0.39–1.35 | 0.31 |
| $FEV_1$% predicted | 0.92 | 0.88–0.98 | 0.004 |
| $W_{peak}$% predicted | 0.95* | 0.93–0.98 | <0.001 |

*Definition of abbreviations*: CI = confidence interval; $FEV_1$ = forced expiratory volume in 1 second; HR = hazard ratio; $\dot{V}O_{2peak}$ = peak oxygen uptake; $W_{peak}$ = peak work rate.
Mixed Cox regression models contained a random intercept for study center. Sex is coded as 1 = male and 0 = female.
*Adjusted HRs per each additional 10% predicted were 0.60 (95% CI, 0.43–0.90) for $\dot{V}O_{2peak}$ and 0.60 (95% CI, 0.48–0.82) for $W_{peak}$.

or $W_{peak}$ had a 66% (95% confidence interval [CI], 83–30%) or 74% (95% CI, 78–45%) lower risk to die or to receive a lung transplant within 2 years after CPET when compared with those with a "low" $\dot{V}O_{2peak}$ or $W_{peak}$ (Table E10).

### Conditional Inference Trees

Among 11 prognostic factors, conditional inference trees identified percentage predicted $W_{peak}$ as the variable that was most strongly associated with 2-year risk of death/LTX (Figure 3), with a cutoff value for $W_{peak}$ of ⩽49.2% versus >49.2% predicted allowing for dichotomization into two subgroups with maximized differences in respect to the outcome. This proposed cutoff is identical to the cutoff derived from the ROC curve analyses. Rates of death/LTX

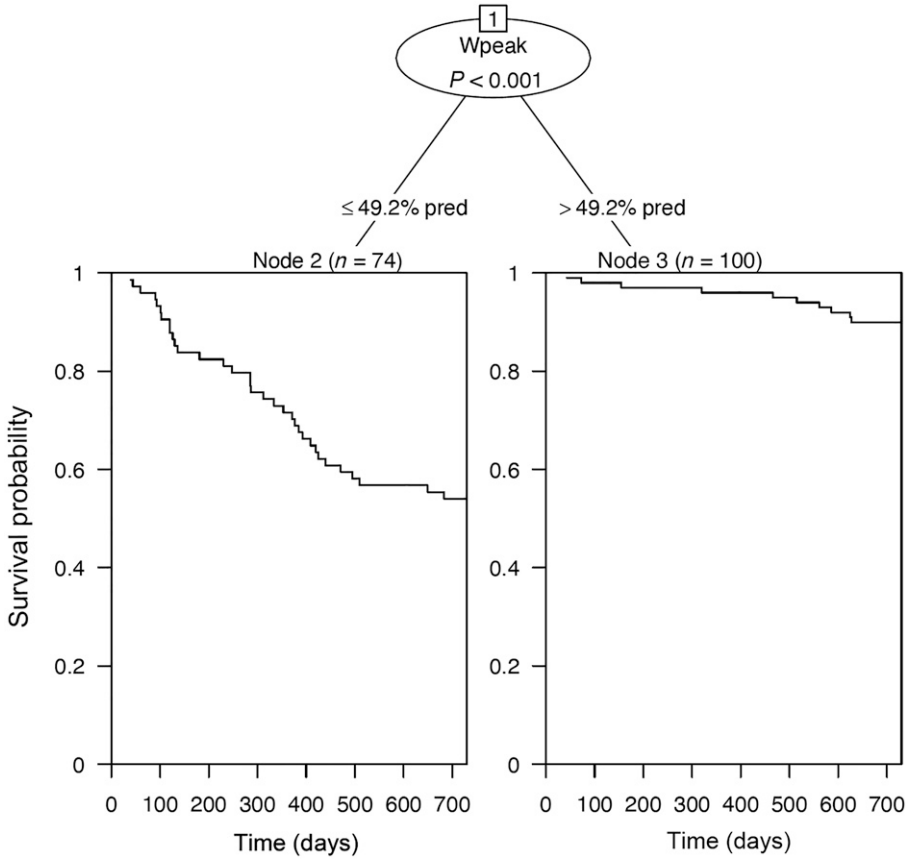


**Figure 3.** Conditional inference tree. The original cutoff values for $W_{peak}$ were ⩽49.15% and >49.15% predicted, respectively. For ease of reading, we rounded the cutoff values to one decimal place. $W_{peak}$ = peak work rate.

were significantly higher for the group with lower $W_{peak}$ than the group with higher $W_{peak}$ (45.2% vs. 10.9%; Figure 3). In a second step, we discarded $W_{peak}$ from the model and only added $\dot{V}O_{2peak}$ to the list of candidate variables. In this case, $FEV_1$% predicted was selected as the primary variable and, in a second step, $\dot{V}O_{2peak}$% predicted to derive two subgroups that are as distinct as possible with respect to the composite endpoint death/LTX (Figure E2). The cutoff values that best discriminated groups with respect to death/LTX were again identical to cutoffs established with ROC curve analyses.

### Exploratory Analyses

A descriptive analysis of survivors and cases as well as groups of patients categorized according to percentage predicted $\dot{V}O_{2peak}$ and $W_{peak}$ cutoff values from the ROC curve analysis are shown in Tables E11–E13. In an analysis adjusted for observation time, survivors spent fewer days in the hospital (28 ± 27 vs. 88 ± 81 d/yr) and received fewer days of intravenous antibiotics (39 ± 41 vs. 106 ± 90 d/yr) than cases during the 2-year follow-up period (Table E11). A similar pattern was observed when comparing groups of patients with low vs. high $\dot{V}O_{2peak}$ or $W_{peak}$, although the magnitude of between-group difference was smaller than for the comparison between survivors versus cases (Tables E12 and E13).

In addition, 31 patients had 6MWT data available (Tables E14–E17). Mean (±SD) 6MWD was 424 ± 127 m among cases and 537 ± 89 m among survivors (Table E14). Six of 16 (38%) patients who died or received a lung transplant within the 2-year follow-up period had a 6MWD < 400 m (3), and 11/16 had a walking distance < 475 m (8) (Tables E14–E16).

### Sensitivity Analyses

The analysis restricted to patients who met predefined maximal effort criteria during CPET ($n = 153$; *see* data supplement for details) resulted in similar ROC areas under the curve for $\dot{V}O_{2peak}$ and $W_{peak}$ compared with the overall study population, whereas sensitivity increased for $W_{peak}$. All other ROC curve characteristics were comparable (Figure E3). A comparison of clinical characteristics and CPET outcomes between those with maximal effort versus possible submaximal effort are given in Tables E18 and E19. Results of mixed Cox regression models and Kaplan-Meier curves were comparable to results from the primary study population (Table E20 and Figure E4). Moreover, conditional inference tree analysis again revealed $W_{peak}$ as most strongly associated with death/LTX, with minimal differences in $W_{peak}$ cutoff values for subgroups with different rates of death/LTX during the 2-year follow-up (Figure E5).

Repeating analyses, using more user-friendly cutoffs (40% predicted for $\dot{V}O_{2peak}$ and 50% predicted for $W_{peak}$), revealed a slightly lower specificity for $\dot{V}O_{2peak}$ (0.72 vs. 0.68) and $W_{peak}$ (0.69–0.62), whereas sensitivity remained unchanged compared with the original ROC curve cutoff values. Descriptive analyses comparing groups based on $\dot{V}O_{2peak}$ and $W_{peak}$ cutoffs are provided in Tables E21–E24. Overall, survival curves and effect estimates from Cox models were similar compared with the original ROC curve cutoffs for $\dot{V}O_{2peak}$ and $W_{peak}$ (Figure E6 and Table E24).

## Discussion

This international multicenter study investigated the prognostic value of CPET outcomes on 2-year risk of death/LTX in patients with ACFLD. In both univariate and adjusted analysis, we found that $\dot{V}O_{2peak}$ and $W_{peak}$ provide prognostic information. Using a data-driven analytical approach including a set of 11 prognostic factors, $W_{peak}$ was selected as the variable with the strongest association to 2-year rates of death/LTX. Our data highlight the potential for $W_{peak}$ to be a promising marker for LTX referral and candidate selection.

This study builds on and enhances our previous findings regarding the long-term prognostic value of CPET-derived outcomes on the combined endpoint death/LTX in CF (17). Our previous study reported ⩾10-year follow-up data from children and adults with a broad range of disease severity. An exploratory analysis, restricted to 2-year follow-up data and including a small number of patients with ACFLD, revealed promising findings on the prognostic role of CPET-derived variables, although generalizability of these data to a larger population with ACFLD was clearly limited (17). The current study focused on 2-year survival in patients with ACFLD, the typical time window used to make transplant predictions. We found that $\dot{V}O_{2peak}$ and $W_{peak}$ provide prognostic information beyond $FEV_1$. Herein, we provide evidence that maximal aerobic exercise capacity, a dynamic and physiological measure integrating oxygen consumption during exercise with the function of multiple organ systems (i.e., heart, lungs, muscles), adds prognostic information in ACFLD. In adjusted Cox regression models, the magnitude of association between $\dot{V}O_{2peak}$ and $W_{peak}$ and 2-year risk of death/LTX was similar. For each additional 10% predicted increase in $\dot{V}O_{2peak}$ or $W_{peak}$, the cumulative 2-year probability of death/LTX decreased by 40%. Using ROC curve analysis, cutoff values for $\dot{V}O_{2peak}$ and $W_{peak}$ that best discriminated with respect to 2-year risk of death/LTX were 39.4% and 49.2% predicted, respectively. It could be argued that cutoffs of 40% and 50% predicted for $\dot{V}O_{2peak}$ and $W_{peak}$, respectively, might be easier to use in clinical practice and, indeed, those cutoffs yield similar survival probabilities with no discernible differences in ROC curve–derived sensitivity and specificity values. Of note, the cutoffs established with the reference equations used in this study (23, 24) may differ when other reference equations are used to derive percentage predicted values.

Using conditional inference tree analyses, $W_{peak}$, and not $\dot{V}O_{2peak}$, was the CPET-derived variable that showed the strongest association with 2-year risk of death/LTX. Interestingly, two different data-driven analytical approaches (ROC curve analysis and conditional inference trees) resulted in identical cutoffs for percentage predicted $W_{peak}$ to discriminate between groups at increased risk of death/LTX, demonstrating the robustness of our novel findings. An important practical implication is that $W_{peak}$ can be measured using a maximal cycle ergometer test without the need for gas exchange measurements, which offers several advantages in a clinical setting. It is less laborious and expensive (i.e., does not require a metabolic cart), less time-consuming (i.e., no gas and volume calibration required), does not require special expertise for test conduct and interpretation, readily allows testing with supplemental oxygen, and allows evaluation of patients with chronic pulmonary infections (e.g., *Mycobacterium abscessus*) that prohibit them from being tested with gas exchange measures. From a patient perspective, it is less burdensome for those with severe lung disease, as they do not need to wear a facemask or mouthpiece during the test (22).

As stated, for each additional 10% predicted $W_{peak}$ in a person with ACFLD

(~10 W on average), 2-year risk of death/LTX is reduced by around 40% (hazard ratio, 0.60; Cox regression model). This model would be important to validate prospectively and may also serve to aid in the design of exercise intervention studies for patients with ACFLD, to test the hypothesis of whether risk of death and LTX can be reduced with a training program (e.g., does improvement in exercise capacity [$W_{peak}$] in patients with ACFLD lower subsequent risk of death/LTX).

Traditionally, measurement of exercise performance by 6MWT has formed part of LTX evaluation for patients with CF (3). The CF Foundation recommends LTX referral—regardless of $FEV_1$—when 6MWD is <400 m (3). The lung allocation score used in several countries to select candidates for LTX also includes data on 6MWD (29). The 6MWD cutoff value of <400 m was derived >20 years ago and comprised a diverse study population, including a small group ($n = 41$) of individuals with CF (30). In our study, 6MWT data were only available for 18% of participants, meaning that direct comparison with CPET outcomes and evaluating prognostic value of 6MWD on 2-year risk of death/LTX was not possible. Interestingly, only 38% of patients who died or received a LTX within the 2-year follow-up period had a 6MWD < 400 m (sensitivity, 38%; specificity, 87%; *see* Table E15), indicating that the discriminative power of this cutoff is limited. Our findings are supported by Gambazza and colleagues (31), who reported a median (interquartile range [IQR]) 6MWD of 520 m (451–581) in a group of 38 individuals with ACFLD. More recent data on the prognostic value of 6MWD, including a median follow-up of 723 days (IQR, 384–1,496), showed that 6MWD < 475 m is associated with a higher risk of death/LTX in CF (8). Using this cutoff improved the sensitivity from 38% to 69% in our study sample (Table E16). The sensitivity to detect death/LTX is even higher, at 75%, when using a $W_{peak}$ cutoff value of <49.2% predicted (Table E17). Although the 6MWT reflects activities of daily living, a $W_{peak}$ test has several advantages over a 6MWT, including *1*) ease of standardization across centers (i.e., no need for a 30-m floor) including in resource-poor settings; *2*) less influence of disruptive factors while doing the test in a busy clinical setting; *3*) easier recording of safety parameters (e.g., electrocardiogram, blood pressure); *4*) continuous monitoring of oxygen saturation (32); *5*) ease of performing a test with oxygen supplementation (i.e., no need to carry oxygen during the test); and *6*) lower risk for transmission of pathogens compared with walking in a hospital floor. In some centers, both 6MWT and CPET are performed, which adds burden to clinical staff and patients, whereas the benefit of doing both tests sequentially is currently unclear. We believe it is time to design a prospective face-to-face comparison to study the predictive performance of the 6MWT versus $W_{peak}$ test to predict short-term survival in the era of highly effective modulator therapies.

### Strengths and Limitations

This study has strengths and limitations. This is the first international multicenter study investigating the prognostic role of CPET-derived outcomes on 2-year rates of death/LTX in patients with ACFLD. We noticed differences in patient characteristics and disease severity across CF centers, which we controlled for in the multivariable Cox regression models, but we cover a wide range of severity among patients with ACFLD ($FEV_1$ range, 13.3–39.9% predicted) for whom annual exercise testing is recommended (3). In addition to potential ascertainment bias within a center, there is a potential for selection bias due to study design. Essentially, we have a convenience sample taken from centers where CPET is regularly performed. There is, however, no suggestion that this cohort with ACFLD would differ from those in a center where CPET is not routinely performed. Differences between CF centers regarding the indication for CPET were at least partly covered by including a random intercept per center in the models. Moreover, our original findings may not be applicable to patients receiving highly effective CFTR modulator treatments (33–37); the long-term impact of these treatments on disease progression and LTX referral and listing criteria has yet to be determined (38–40). Nonetheless, our findings are applicable to those ineligible (by genotype) for HEMT therapy and the substantial proportion of people with CF living in countries where HEMT is unavailable (40–42). To validate our findings, a prospective study with external validation should be conducted, which, unfortunately, was not possible in the current study. Unfortunately, the originally assumed number of patients and cases was not reached, partly because of the coronavirus disease (COVID-19) pandemic, which affected recruitment rates. In addition, because of the limited number of study participants and cases in our study, we were limited in the number of covariates (prognostic factors) to be included in the Cox regression models to avoid overfitting. Furthermore, a limitation of the mixed Cox regression model is the potential presence of measurement error associated with each term in the regression, which can impact the overall precision of the prediction model. Bias that might arise from using data from many different centers is taken care of by using a random intercept per center, but random noise that may occur in each measurement is not incorporated in our models. An additional limitation arises from our inability to uniformly capture changes in lung function (e.g., $FEV_1$ slope), medication patterns, exercise routines, and airway clearance therapies among patients, preventing us from incorporating this information as a time-varying variable in the models. Finally, submaximal CPET-derived outcomes have been shown to provide prognostic information in CF (16), whereas our analysis was restricted to maximal exercise variables only.

### Conclusions

CPET provides additional prognostic information in patients with ACFLD. $W_{peak}$ provides similar prognostic information to $\dot{V}O_{2peak}$ regarding 2-year risk of death/LTX and can be easily measured in almost all settings. Our findings provide a compelling rationale for the prospective evaluation of $W_{peak}$ as a promising marker for LTX referral and candidate selection. ■

**Author disclosures** are available with the text of this article at www.atsjournals.org.

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