Pulmonary Function Predicting Confirmed Recovery From Lower-Respiratory Symptoms in World Trade Center-Exposed Firefighters, 2001 to 2010

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Background: We examined the relationship between pulmonary function (FEV_1) and confirmed recovery from three lower-respiratory symptoms (LRSs) (cough, dyspnea, and wheeze) up to 9 years after symptom onset.

Methods: The study included white and black male World Trade Center (WTC)-exposed firefighters who reported at least one LRS on a medical monitoring examination during the first year after September 11, 2001. Confirmed recovery was defined as reporting no LRSs on two consecutive and all subsequent examinations. FEV_1 was assessed at the first post-September 11, 2001, examination and at each examination where symptom information was ascertained. We used stratified Cox regression models to analyze FEV_1 , WTC exposure, and other variables in relation to confirmed symptom recovery.

Results: A total of 4,368 firefighters met inclusion criteria and were symptomatic at year 1, of whom 1,592 (36.4%) experienced confirmed recovery. In univariable models, first post-September 11, 2001, concurrent, and difference between first post-September 11, 2001, and concurrent FEV_1 values were all significantly associated with confirmed recovery. In adjusted analyses, both first post-September 11, 2001, FEV_1 (hazard ratio [HR], 1.07 per 355-mL difference; 95% CI, 1.04-1.10) and FEV_1 % predicted (HR, 1.08 per 10% predicted difference; 95% CI, 1.04-1.12) predicted confirmed recovery. WTC exposure had an inverse association with confirmed recovery in the model with FEV_1 , with the earliest arrival group less likely to recover than the latest arrival group (HR, 0.73; 95% CI, 0.58-0.92).

Conclusions: Higher FEV_1 and improvement in FEV_1 after September 11, 2001, predicted confirmed LRS recovery, supporting a physiologic basis for recovery and highlighting consideration of spirometry as part of any postexposure respiratory health assessment.

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Abbreviations: FDNY = Fire Department City of New York; FDNY-WTC-MMP = Fire Department City of New York World Trade Center Medical Monitoring Program; HR = hazard ratio; LRS = lower-respiratory symptom; WTC = World Trade Center

After the September 11, 2001, terrorist attack on the World Trade Center (WTC), rescue workers from the Fire Department City of New York (FDNY) experienced substantial and immediate reductions in pulmonary function,¹ particularly in FEV_1 . FDNY firefighters had an average adjusted FEV_1 decline of 355 mL in the first 6 months after September 11, 2001, which is > 10 times the average annual age-related decline of 27 to 30 mL.^{2,3} Declines were persistent, resulting in little or no average recovery during

the subsequent 6 years.³ During the same time, FDNY rescue workers reported increased upper-respiratory symptoms, lower-respiratory symptoms (LRSs), and gastroesophageal reflux symptoms,⁴ with an exposure-response gradient based on earliest arrival time⁵ and work duration.^{4,6}

Modest associations between decreased pulmonary function and increased respiratory symptoms have been described in the general adult population^{7,8} and in elderly persons⁹; after occupational, dust, or pollutant

exposures¹⁰; in tobacco smokers^{11,12}; and in respiratory patients.¹³⁻¹⁵ In WTC-exposed cohorts, we and others have shown significant associations between pulmonary function and respiratory symptoms.^{1,16-19}

Prior studies have focused on the incidence or prevalence of symptoms and declines in pulmonary function. To date, and to our knowledge, no longitudinal studies have examined whether FEV₁ measured soon after WTC exposure predicts symptom resolution. We also are unaware of any such studies after other environmental or occupational exposures. Here, we report a longitudinal symptom study of the association of FEV₁ with subsequent confirmed recovery from LRSs of cough, wheeze, or dyspnea over the 9-year period after September 11, 2001.

MATERIALS AND METHODS

Within 1 month of September 11, 2001, the FDNY Bureau of Health Services instituted the formal Fire Department City of New York World Trade Center Medical Monitoring Program (FDNY-WTC-MMP) for all FDNY rescue and recovery workers. These monitoring visits were scheduled for every 12 to 18 months and included physical examinations, spirometry, and completion of self-administered health questionnaires. Study participation required written consent and was approved by the institutional review board at Montefiore Medical Center (protocol #07-09-320).

Study Population

The population comprised all white and black male active and retired FDNY firefighters hired before September 11, 2001, and who arrived at the WTC site within the first 2 weeks after September 11, 2001 (n = 10,092). Study subjects were also required to have had a monitoring examination during the first year after September 11, 2001 (n = 7,974) and to have reported at least one LRS during that examination (n = 5,442). To ensure sufficient follow-up, we further limited the analytic cohort to individuals who had at least three monitoring examinations from years 1 to 9 after September 11, 2001, as follows: one during year 1 and at least two thereafter, with the last one between years 7 and 9 (n = 4,368).

Spirometry

We assess pulmonary function at every medical monitoring examination by spirometry as previously described,³ with technique,

quality assurance, and interpretation based on American Thoracic Society guidelines. EasyOne spirometers (nidd Medical Technologies) provide automated quality grading based on these guidelines.²⁰ We eliminated from analysis spirometry measurements that had quality assurance grades of C or lower or that were done within 60 days of a prior spirometry. We calculated FEV₁ % predicted using National Health and Nutrition Examination Survey equations,²¹ and limited the study population to white and black race because reliable prediction equations are not available for other races or ethnicities.

Symptoms

Symptom information was obtained from the self-administered health questionnaires, which were taken on the same day that spirometry was performed. We focused on the following three LRSs: cough, dyspnea, and wheeze. In the first year after September 11, 2001, symptom presence was determined by affirmative answers to the question, "Since the disaster, have you had any of the following new or worsening respiratory symptoms?" Multiple answers were allowed. In subsequent questionnaires, to determine the presence of current dyspnea or current wheeze, participants who indicated that they experienced either symptom were then asked whether their symptoms resolved or felt normal when on medication or treatment, improved, stayed the same, or worsened. Any response except resolved indicated current symptom presence. To determine the presence of current cough, we used a more stringent definition to approximate the clinical definition of cough. Participants were required to affirm a daily or almost daily cough when awake (apart from a cold) to be considered as having cough. We defined symptom recovery as reporting the absence of all LRSs on at least two consecutive surveys and reporting symptom absence on all subsequent surveys, including a final survey obtained in years 7 to 9 (confirmed recovery).

WTC Exposure

We used the FDNY-WTC-MMP Exposure Intensity Index to categorize exposure to the WTC site based on initial arrival time. Participants who arrived during the morning of September 11, 2001 (day 1) were categorized as arrival group 1, or the most exposed; those who arrived during the afternoon of September 11, 2001, were categorized as arrival group 2; those who arrived on day 2 were categorized as arrival group 3; and those who arrived any day between days 3 and 14 were categorized as arrival group 4, or the least exposed.⁴

Other Measures

The FDNY-WTC-MMP database includes date of birth, measured height, measured weight, self-reported race/ethnicity, smoking status, duty status (active or retired) and retirement date, and WTC exposure. Smoking status was self-reported as either current smoker, former smoker, or never smoker. Self-reported medication use was available from questionnaires beginning in August 2005 and for 100% of the analytic cohort. Individuals were asked, "Since 9/11/2001, have you received any of the following medications?" Those who reported using bronchodilators, inhaled corticosteroids, montelukast (Singulair; Merck & Co, Inc), or nebulized medications were considered to be using respiratory medication.

Data Analysis

We used the Cochran-Mantel-Haenszel test for trend for analysis of medication use by number of symptoms. To individually examine the relationship between demographic and other characteristics of the cohort in relation to confirmed recovery, we ran

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univariable Cox regression models. We also used Cox regression models to analyze FEV₁ or FEV₁ % predicted in relation to time to confirmed recovery in both univariable and multivariable analyses adjusted for demographic (age on September 11, 2001, and race) and other risk factors (WTC arrival group, smoking status, weight, and self-reported medication use). These analyses were performed separately for participants reporting a single symptom during year 1, two symptoms, and three symptoms. We then compared results from the three separate models to those from a single stratified Cox model that allowed each of the three groups a different baseline hazard function. Follow-up started on the date of a participant's monitoring examination during year 1. Date of confirmed recovery was defined as the date of the first monitoring examination during follow-up in which an individual reported the absence of all symptoms. Participants without confirmed recovery were censored on the date of their last survey (up to year 9).

Both FEV₁ and FEV₁ % predicted were included in models as predictors of confirmed recovery in three different ways. First, we used an individual's first FEV₁ after September 11, 2001, and FEV₁ % predicted taken during year 1. Second, we created a time-dependent, concurrent variable using the FEV₁ and FEV₁ % predicted values that were obtained on the same day that each symptom questionnaire was completed. Finally, we created a time-dependent difference variable with FEV₁ only, using the difference between an individual's concurrent FEV₁ and his first FEV₁ after September 11, 2001. This difference variable was calculated using only absolute and not FEV₁ % predicted because the predictive equations take age into account, and thus, the time-to-event models would adjust for age twice with such a variable. Smoking status and weight at the time of each monitoring examination were analyzed as time-dependent variables to account for change over time.

We stratified the analytic cohort by quartile of their first FEV₁ % predicted after September 11, 2001, and graphed the cumulative probability of confirmed persistent recovery over the 9-year follow-up period. All statistical analyses were performed using SAS version 9.2 (SAS Institute Inc), and S-Plus version 8.1 (TIBCO Software Inc) was used to graph the cumulative probability of confirmed recovery.

RESULTS

The analytic cohort included 4,368 WTC-exposed male firefighters who were symptomatic with at least one LRS during year 1 and had at least two follow-up visits as previously described, of whom 1,592 (36.4%) had confirmed recovery at some point during follow-up. At baseline, 1,856 (42.5%) had one LRS, 1,278 (29.3%) had two, and 1,234 (28.3%) had three, and mean $\pm$ SD FEV₁ was 4.0 $\pm$ 0.7 L. The average number of visits with corresponding FEV₁ measurements was four, with an average time between visits of about 2 years. The majority had FEV₁ substantially above the lower limits of normal for the population. Table 1 shows time to confirmed recovery for specific characteristics of the analytic cohort.

Table 2 shows medications that individuals reported using between years 1 and 9 by the number of LRSs they reported during year 1. Steroids were the most commonly reported medication. There was a dose-response gradient between the number of symptoms reported and medication use. For example, the use

of inhaled corticosteroids was reported by 33.5% reporting one symptom, 45.1% reporting two symptoms, and 54.5% reporting three symptoms ($P < .001$).

A total of 1,592 of 4,368 participants (36.4%) demonstrated confirmed persistent recovery, which occurred a mean of 4.5 years after September 11, 2001. Of the 2,776 participants (63.6%) without confirmed persistent recovery, mean follow-up time was 8.1 years after September 11, 2001. Individuals with a lower FEV₁ at baseline had a lower probability of recovery throughout the study period (Fig 1). Those in the first quartile (lowest baseline FEV₁ % predicted) had the lowest cumulative probability of recovery (about 25%) at the end of follow-up. In contrast, those in the fourth quartile (highest baseline FEV₁ % predicted) had the highest cumulative probability of recovery (about 45%) at the end of follow-up.

Table 3 shows separate univariable models predicting time to confirmed recovery using FEV₁ and FEV₁ % predicted. Hazard ratios (HRs) for FEV₁ are estimated for every 355-mL increase because 355 mL was found to be the average decline in FEV₁ for firefighters during the first 6 months after September 11, 2001.³ HRs for FEV₁ % predicted were estimated for every 10-percentage point increase. Because the HRs obtained from three separate models were similar (model 1 included those having only one symptom during year 1, model 2 included those having only two symptoms during year 1, and model 3 included those having all three symptoms during year 1), we present results from the combined stratified Cox model. We also performed analyses in three separate cohorts defined by the particular LRS (cough, dyspnea, or wheeze) that individuals reported experiencing during year 1. Again, the magnitude of the associations between FEV₁ and FEV₁ % predicted and confirmed recovery were similar across all three symptom cohorts (results not shown); therefore, we used any LRS to denote symptom presence.

We found consistent positive associations between FEV₁ and FEV₁ % predicted and confirmed recovery. Concurrent measures showed the strongest association with confirmed recovery (HR, 1.15 for every 355-mL difference in FEV₁; 95% CI, 1.12-1.18; HR, 1.17 for every 10% increase in FEV₁ % predicted; 95% CI, 1.12-1.22). The first post-September 11, 2001, spirometry predicted confirmed recovery in univariable analysis, showing a slightly larger association with FEV₁ % predicted (HR, 1.12 per 10% predicted difference; 95% CI, 1.08-1.17). The FEV₁ difference variable also was associated with confirmed recovery because individuals who improved from their first FEV₁ measurements after September 11, 2001, had a greater likelihood of recovery than those who did not improve (HR, 1.06 per 355-mL increase; 95% CI, 1.01-1.10).

Table 1—Univariate Models of Time to Confirmed Recovery for Selected Demographic and Other Characteristics

Demographic or Characteristic	Total (N = 4,368)	Recovered (n = 1,592)	HR (95% CI)	P Value
Ever smoked				.44
Yes	1,373 (31.4)	481 (30.2)	0.96 (0.86-1.07)	
No	2,995 (68.6)	1,111 (69.8)	Reference	
Arrival group				
1	828 (19.0)	263 (16.5)	0.75 (0.60-0.95)	.01
2	2,843 (65.1)	1,066 (67.0)	0.87 (0.71-1.06)	.16
3	464 (10.6)	159 (10.0)	0.73 (0.57-0.93)	.01
4	233 (5.3)	104 (6.5)	Reference	...
Race				
Black	80 (1.8)	37 (2.3)	1.21 (0.87-1.68)	...
White	4,288 (98.2)	1,555 (97.7)	Reference	.25
Retired by year 9				
Yes	1,724 (39.5)	474 (29.8)	0.57 (0.51-0.64)	< .01
No	2,644 (60.5)	1,118 (70.2)	Reference	...
Ever respiratory medication				
Yes	2,386 (54.6)	632 (39.7)	0.50 (0.45-0.55)	< .01
No	1,982 (45.4)	960 (60.3)	Reference	...
Age on September 11, 2001, y	39.9 ± 7.2	39.1 ± 7.4	0.98 ^a (0.97-0.98)	< .01
Height, cm	179.9 ± 6.3	179.7 ± 6.2	0.99 (0.97-1.00)	.12

Data are presented as No. (%) or mean ± SD. HR = hazard ratio.

^aAge was modeled per 10 y.

First post-September 11, 2001, and concurrent FEV₁ and FEV₁ % predicted were also analyzed in separate multivariable models that controlled for risk factors described in Tables 4 and 5, respectively. In Table 4, even after adjusting for variables, including WTC arrival group, first post-September 11, 2001, FEV₁ was predictive of confirmed recovery (HR, 1.07; 95% CI, 1.04-1.10). WTC exposure had a significant inverse association with confirmed recovery in that individuals in arrival group 1 (those who arrived during the morning of the collapse) were less likely to recover (HR, 0.73; 95% CI, 0.58-0.92) compared with those in arrival group 4. Age on September 11, 2001, and concurrent weight were also significantly associated with recovery. Older individuals were less likely to recover (HR, 0.82 for every 10 years; 95% CI, 0.77-0.89) as were those with higher weight (HR, 0.94 for every 10 lb; 95% CI, 0.93-0.96). Self-reported medication use was inversely associated with recovery (HR, 0.52; 95% CI, 0.47-0.57). The association of FEV₁ remained for concurrent measures in multivariate analyses (HR, 1.14 for every 355-mL difference in FEV₁; 95% CI, 1.10-1.18; HR, 1.11 for every 10% increase in FEV₁ % predicted; 95% CI, 1.06-1.16) (data not shown).

We found similar results with FEV₁ % predicted in adjusted analyses. Age, height, and race were excluded from this model because these factors are already incorporated into the National Health and Nutrition Examination Survey prediction equations for FEV₁. The first FEV₁ % predicted (HR, 1.08; 95% CI, 1.04-1.12) after September 11, 2001, was associated with confirmed recovery; however, arrival group was now only marginally associated with confirmed recovery. Smoking status was significantly associated with recovery in that current smokers were less likely to experience confirmed recovery than never smokers (HR, 0.79; 95% CI, 0.65-0.96). In both models, we found that individuals who had ever reported the use of respiratory medications during follow-up were less likely to recover than those who never reported medication use (HR, 0.52; 95% CI, 0.47-0.57 in both models with FEV₁ and FEV₁ % predicted).

DISCUSSION

Using strict criteria to define confirmed recovery, 1,592 of 4,368 (36.4%) of initially symptomatic individuals recovered completely during follow-up. Higher

Table 2—Medications That Participants Reported Ever Using

Medication	One LRS at Baseline (n = 1,856)	Two LRSs at Baseline (n = 1,278)	Three LRSs at Baseline (n = 1,234)	Total (N = 4,368)
Any respiratory	824 (44.4)	748 (58.5)	814 (66.0)	2,386 (54.6)
Bronchodilator	463 (25.0)	475 (37.2)	568 (46.0)	1,506 (34.5)
Inhaled steroids	621 (33.5)	576 (45.1)	672 (54.5)	1,869 (42.8)
Montelukast	181 (9.8)	223 (17.5)	263 (21.3)	667 (15.3)
Nebulized medications	157 (8.5)	190 (14.9)	201 (16.3)	548 (12.5)

Data are presented as No. (%). All *P* < .001. LRS = lower-respiratory symptom.

FIGURE 1. Cumulative probability of confirmed recovery over the 9-year follow-up period by quartile of the first post-September 11, 2001, FEV₁ % predicted (blue, > 103 [quartile 4]; green, 95-103 [quartile 3]; orange, 87-95 [quartile 2]; red, < 87 [quartile 1]).

FEV₁ and FEV₁ % predicted measured shortly after September 11, 2001, and an increase in FEV₁ since immediately after September 11, 2001, were each found to predict confirmed LRS recovery up to 9 years post-September 11, 2001. Confirmed LRS recovery was least likely to occur in those arriving at the WTC on the morning of September 11, 2001, all of whom were caught in the dust cloud. Further, smoking status was also important because never smokers were more likely to recover than current or former smokers. This highlights the need for ongoing support of smoking cessation programs for WTC-exposed cohorts because smoking is a potentially modifiable impediment to recovery.

Table 3—Univariable Models of Time to Confirmed Recovery With Three Different Measurements of FEV₁ and FEV₁ % Predicted

Measurement	HR (95% CI)	P Value
First post-September 11, 2001, FEV ₁	1.09 (1.06-1.12)	< .01
Concurrent FEV ₁	1.15 (1.12-1.18)	< .01
Difference between first post-September 11, 2001, and concurrent FEV ₁	1.06 (1.01-1.10)	.01
First post-September 11, 2001 FEV ₁ % predicted	1.12 (1.08-1.17)	< .01
Concurrent FEV ₁ % predicted	1.17 (1.12-1.22)	< .01

HRs for FEV₁ measurements are per 355-mL increase. HRs for FEV₁ % predicted measurements are per 10% increase. See Table 1 legend for expansion of abbreviation.

In WTC-exposed cohorts, previous studies have demonstrated associations between pulmonary function and LRS prevalence but have not investigated whether higher pulmonary function could predict resolution of LRS after exposure. In a recent study of non-FDNY WTC rescue and recovery workers, respiratory symptoms were associated with lower FEV₁, lower FVC, and larger bronchodilator responses.¹⁹ A study of New York City Police Department emergency service responders found declines in FEV₁ and FVC 6 years after September 11, 2001, which were associated with respiratory symptoms.¹⁸ A study of WTC-exposed area residents and area workers found significant associations between LRS and pulmonary function as determined by oscillometry.¹⁷ In WTC-exposed FDNY rescue workers, hyperreactivity on methacholine challenge testing 6 months after September 11, 2001, was also associated with LRS.¹⁶

Similar associations between FEV₁ and LRS have been found after other noxious and chronic exposures, such as exposures in US coal miners²² and in tobacco smokers.^{11,12} Reduced pulmonary function has also been associated with numerous illnesses, such as diabetes,²³ respiratory and cardiovascular disease,²⁴ and all-cause mortality.²⁵

To our knowledge, the current study is the first to longitudinally examine the association between FEV₁ and confirmed LRS recovery. Similar studies have not been published in other WTC-exposed cohorts or after other noteworthy occupational and

Table 4—Multivariable Models of Time to Confirmed Recovery With FEV₁ and Other Risk Factors

Variable	HR ^a (95% CI)	P Value
First post-September 11, 2001, FEV ₁ (per 355 mL)	1.07 (1.04-1.10)	< .01
Concurrent smoking status		
Former	0.96 (0.86-1.08)	.51
Current	0.82 (0.68-0.99)	.04
Never	Reference	...
Arrival group		
1	0.73 (0.58-0.92)	.01
2	0.80 (0.65-0.98)	.03
3	0.73 (0.57-0.94)	.01
4	Reference	...
Age on September 11, 2001 (per 10 y)	0.82 (0.77-0.89)	< .01
Height (per 10 cm)	0.97 (0.87-1.07)	.48
Concurrent weight (per 10 lb)	0.94 (0.93-0.96)	< .01
Black race	1.30 (0.94-1.82)	.12
Ever medication use	0.52 (0.47-0.57)	< .01

See Table 1 legend for expansion of abbreviation.

^aHRs are adjusted for all variables listed.

environmental exposures. We show that higher FEV₁ values after September 11, 2001, can predict recovery from LRS up to 9 years later. It is important to acknowledge that the magnitude of this association, although statistically and clinically significant, was not large. Adding bronchodilator responsiveness or methacholine challenge hyperreactivity might improve this association, but these measures were not available for most of the cohort and would typically not be available during a mass screening program postdisaster.

It should be noted that 63.6% of the analytic cohort did not recover from LRS reported in the first year after September 11, 2001. This is a surprisingly high rate, considering the end of follow-up was 7 to 9 years

Table 5—Multivariable Models of Time to Confirmed Recovery With FEV₁ % Predicted and Other Risk Factors

Variable	HR ^a (95% CI)	P Value
First post-September 11, 2001, FEV ₁ % predicted (per 10 percentage points)	1.08 (1.04-1.12)	< .01
Concurrent smoking status		
Former	0.92 (0.82-1.04)	.18
Current	0.79 (0.65-0.96)	.01
Never	Reference	...
Arrival group		
1	0.80 (0.63-1.00)	.05
2	0.88 (0.72-1.07)	.20
3	0.78 (0.61-0.99)	.04
4	Reference	...
Concurrent weight (per 10 lb)	0.95 (0.94-0.97)	< .01
Ever medication use	0.52 (0.47-0.57)	< .01

See Table 1 legend for expansion of abbreviation.

^aHRs are adjusted for all variables listed.

after symptoms were first reported. This finding highlights the necessity of continued follow-up of the FDNY and other WTC-exposed rescue and recovery workers that focuses on treatment, tobacco cessation, and prevention of additional exposures not just by using respiratory protection but also, when possible, by removal from duties that might lead to hazardous exposures.

There are limitations to our study. First, although we stratified our analysis by the number of symptoms individuals reported immediately after September 11, 2001, we did not take into account a change in the number of respiratory symptoms experienced between year 1 and confirmed recovery. However, we did find that associations between FEV₁ and individual symptoms, compared with the number of symptoms experienced, did not differ. That is, the magnitude of the HRs were similar for recovery from cough, recovery from dyspnea, and recovery from wheeze. Similarly, there was no difference between modeling any two symptom combinations or all three. In addition, confirmed recovery was no more likely if an individual experienced one, two, or three symptoms initially. A second limitation is that time to recovery may be inflated because some individuals may not have come in for monitoring examinations at regular intervals, and thus, their recovery would have been recorded only at the first time they completed a questionnaire. However, we do not believe that this was a serious problem because the mean number of follow-up visits does not differ by quartile ranking of FEV₁ at the first post-September 11, 2001 visit: The mean number of follow-up visits ranged from 3.9 to 4.2 in the four quartile groups. Finally, we could not clearly establish the role of treatment in confirmed recovery because we found that individuals who reported using respiratory medications were less likely to recover. We believe that this result suggests that medication use serves as a surrogate for symptom severity rather than as an indicator of treatment compliance or success in the population. In support of this, we also found that those with more symptoms were more likely to report taking medications, especially inhaled corticosteroids, which is consistent with National Heart, Lung, and Blood Institute guidelines. Understanding this complex relationship would require analysis of medication adherence records, which were not available.

In conclusion, higher FEV₁ was predictive of confirmed persistent LRS recovery. Given the ability to predict symptom resolution, spirometric measurements should be considered for inclusion as a regular part of any postexposure respiratory health assessment because both absolute and FEV₁ % predicted values can be important prognostic factors of recovery and can focus treatment on those most at risk.

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Ms Soo: contributed to the data analysis, preparation of the first draft of the manuscript, and review and final approval of the manuscript.

Dr Webber: contributed to the study design, data analysis, project management, and review and final approval of the manuscript.

Dr Hall: contributed analytic and statistical guidance and to the review and final approval of the manuscript.

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