Bedside Assessment of Quadriceps Muscle by Ultrasound after Admission for Acute Exacerbations of Chronic Respiratory Disease

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Abstract

Rationale: Hospitalization represents a major event for the patient with chronic respiratory disease. There is a high risk of readmission, which over the longer term may be related more closely to the underlying condition of the patient, such as skeletal muscle dysfunction.

Objectives: We assessed the risk of hospital readmission at 1 year, including measures of lower limb muscle as part of a larger clinical trial.

Methods: Patients hospitalized with an exacerbation of chronic respiratory disease underwent measures of muscle function including quadriceps ultrasound. Independent factors influencing time to hospital readmission or death were identified. Patients were classified into four quartiles based on quadriceps size and compared.

Measurements and Main Results: One hundred and ninety-one patients (mean age, 71.6 [SD, 9.1] yr) were recruited. One hundred and thirty (68%) were either readmitted or died. Factors associated with readmission or death were age (odds ratio [OR], 1.05; 95% confidence interval [CI], 1.01–1.08; $P = 0.015$), Medical Research Council (MRC) dyspnea grade (OR, 4.57; 95% CI, 2.62–7.95; $P < 0.001$), home oxygen use (OR, 12.4; 95% CI, 4.53–33.77; $P < 0.001$), quadriceps (rectus femoris) cross-sectional area (Q_{csa}) (OR, 0.34; 95% CI, 0.17–0.65; $P = 0.001$), and hospitalization in the previous year (OR, 4.82; 95% CI, 2.42–9.58; $P < 0.001$). In the multivariate analyses, home oxygen use (OR, 4.80; 95% CI, 1.68–13.69; $P = 0.003$), MRC dyspnea grade (OR, 2.57; 95% CI, 1.44–4.59; $P = 0.001$), Q_{csa} (OR, 0.46; 95% CI, 0.22–0.95; $P = 0.035$), and previous hospitalization (OR, 3.04; 95% CI, 1.47–6.29; $P = 0.003$) were independently associated with readmission or death. Patients with the smallest muscle spent more days in hospital than those with largest muscle (28.1 [SD, 33.9] vs. 12.2 [SD, 23.5] d; $P = 0.007$).

Conclusions: Smaller quadriceps muscle size, as measured by ultrasound in the acute care setting, is an independent risk factor for unscheduled readmission or death, which may have value both in clinical practice and for risk stratification.

Keywords: chronic obstructive pulmonary disease; skeletal muscle; ultrasonography; risk factors; frail elderly

Hospitalization for exacerbations of chronic obstructive pulmonary disease (COPD) and other chronic respiratory diseases (CRDs) is associated with worse health status and higher risk of subsequent readmission and death (1, 2). Measurements obtained during routine clinical care during hospitalization can predict short-term outcomes (e.g., in-hospital mortality and length of hospital stay) (3), but identifying those at risk of readmission over the longer term has proved more challenging. In the stable COPD

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At a Glance Commentary

Scientific Knowledge on the Subject: Hospitalization, and subsequent readmission, for exacerbations of chronic respiratory diseases are associated with worse health status and higher risk of death. Systemic effects, such as skeletal muscle dysfunction, are known to be of prognostic importance in the stable state, but the long-term prognostic value of skeletal muscle dysfunction during severe exacerbations is unknown.

What This Study Adds to the Field: Skeletal muscle dysfunction, measured by ultrasound, is an independent risk factor for hospital readmission. Patients with smaller quadriceps are more likely to be readmitted to hospital.

population, previous exacerbations were the single most powerful predictor of subsequent events (4).

The risk of subsequent events after hospitalization over the longer term may be related more closely to the underlying condition of the patient, including known systemic features of the disease such as skeletal muscle function. Previous studies have indicated that assessments of skeletal muscle function and mass predict mortality and symptom burden in the stable state independently from the severity and character of lung function impairment (5, 6). However, the predictive value of these indices in patients who have been hospitalized for an acute exacerbation (the population most at risk of adverse outcomes) is unknown. This is in part because technologies for assessing muscle function and mass that could be used at the bedside in acutely unwell subjects were not available. Simple measurements of muscle strength can be performed at the bedside but may be limited in this setting by their reliance on patient effort. Studies have suggested that ultrasound assessment of quadriceps (rectus femoris) cross-sectional area (Q_{csa}) is a surrogate for lower limb muscle mass, can be performed at the bedside, and is independent of patient effort (7–9).

We hypothesized that measurements of lower limb muscle function (mass and strength) and functional exercise capacity performed during acute exacerbation of CRD would provide a way to assess the risk for hospital readmission in the subsequent 12 months. This was investigated prospectively by recording these assessments in a cohort of patients recruited within 48 hours of acute hospital admission to a clinical trial of early rehabilitation, where the 12-month readmission rate was the primary outcome. In this study no difference was seen in hospitalization rate, although a higher mortality rate was seen in those who received early rehabilitation compared with usual care (10).

Methods

Study Design and Population

Subjects were recruited to a randomized controlled trial of an early rehabilitation intervention initiated during hospitalization for acute exacerbation of CRD. The outcome of the trial, including recruitment, inclusion, and exclusion criteria, has previously been described (10). This was an observational analysis of a subgroup of participants recruited at one of the study centers (Glenfield Hospital, Leicester, UK) where ultrasound assessments of muscle mass were made. Eligibility for the current study was defined by the performance of Q_{csa} before randomization. Because the study intervention had no effect on hospital readmission or functional performance (10), the treatment and control groups were combined for this analysis. Ethics approval for the study was given by the National Research Ethics Service, Nottingham REC 1 committee (09/H0403/76), and the study was registered (ISRCTN 05557928).

Outcome Measures

Outcome measures were performed at recruitment (within 48 h of acute admission) apart from spirometry and shuttle walk tests, which were performed at hospital discharge because subjects were too unwell to perform them on admission. Demographics, including Medical Research Council (MRC) dyspnea grade when in a stable state (range, 1–5); maximal isometric quadriceps strength, measured with an isometric dynamometer (11); St. George's Respiratory Questionnaire (12); and Q_{csa} were taken at time of recruitment. Spirometry, measured to British Thoracic Society/Association of Respiratory Technicians and Physiologists standards (13), and functional exercise performance, measured using the incremental shuttle walk test (ISWT) (14) and endurance shuttle walk test (ESWT) (15), were performed at discharge. Previous hospitalization over the previous 12 months was identified from hospital and general practice records and patient recollection.

Rectus Femoris Cross-Sectional Area

Q_{csa} was measured by B mode ultrasonography (Hitachi Medical Systems, Wellingborough, UK). Images were captured with a 7.5-MHz 7-cm linear probe. The rectus femoris of the right leg was used as a single muscle of the quadriceps so as to allow whole muscle on a single image. Images were taken using the mid-distance between the greater trochanter and knee joint. This distance was measured on the anterior aspect of the thigh from the superior patellar border. The transducer was placed perpendicular to the leg, with minimal pressure to provide an adequate view to minimize muscle compression. Oblique images were minimized by placing the transducer perpendicular to the muscle and ensuring minimal cross-sectional area on the image. Images were frozen and the outline of the rectus femoris was traced to obtain cross-sectional area measurement. Q_{csa} was taken as the mean of three consecutive measurements within 10% from separate frozen images. To adjust for the size of the individual, Q_{csa} was standardized to height squared.

Hospitalization and Admission Data

The primary outcome of the study was hospital readmission at 12 months, which was collected from local hospital databases and general practice records. Date of admission and length of hospital stay were recorded at 12 months. Death was identified from hospital databases, general practice records, and death certificates at 12 months.

Statistical Analysis

A composite end point of either hospitalization or death in the follow-up year was used as the primary outcome measure in this study. Statistical analysis was

conducted with Stata/SE version 13 (StataCorp, College Station, TX). Factors associated with hospitalization were identified by univariate model, using logistic regression. Factors tested were any baseline characteristic or outcome measure tested during the index admission. Multivariate analyses with the selected factors identified from the univariate analysis were conducted by binary logistic regression using a backward stepwise approach, offset by exposure time. All analyses used the treatment allocation as a covariate. Quadriceps mass, corrected by height squared, was divided into quartiles and the groups compared. Times to hospitalization or death were compared by Cox regression. Total numbers of hospital days were compared by Kruskal–Wallis test. Last, the clinical characteristics of the various groups identified were compared by independent analysis of variance and Kruskal–Wallis test for parametric and nonparametric continuous data as appropriate. Categorical measures were compared by chi-squared test.

Results

Baseline Characteristics and Readmission

A total of 191 subjects underwent ultrasound to determine the Q_{csa} at baseline and were included in the analysis. This represented 96% of those enrolled at the Glenfield site in the original clinical trial (n = 200). Baseline characteristics and measures are shown in Table 1. One hundred and thirty (68%) of the subjects were either readmitted or died in the year after their index admission, of whom 121 were admitted and 9 died without readmission. Mean time to readmission or death was 120 (95% confidence interval [CI], 101–139) days. Test–retest correlation between left and right Q_{csa} was 0.92 and the intraclass correlation coefficient, or Cronbach's α, was 0.95, which is similar to previous data (7, 16).

Factors Associated with Time to Hospitalization or Death

In the univariate logistic regression analysis of all available in-hospital assessments, the risk of either hospitalization or death was calculated. Factors significantly associated with readmission were MRC grade, home oxygen use, quadriceps cross-sectional area, and previous hospitalization and age (Table 2).

Significant factors from the univariate analysis were entered into a multivariate model, using a backward stepwise approach. Factors associated independently with further hospitalization were MRC grade, quadriceps cross-sectional area, previous hospitalization, and home oxygen use. Age was not significantly associated ($P = 0.272$). Odds ratios are shown in Table 3.

Clinical Characteristics of Patients with Different Quadriceps Mass

Participants were grouped into quartiles based on their quadriceps mass (quartile 1 range, 0.816–1.407 cm^2/m^2; quartile 2 range, 1.408–1.722 cm^2/m^2; quartile 3 range, 1.731–2.053 cm^2/m^2; quartile 4 range, 2.059–3.500 cm^2/m^2). Baseline characteristics and demographics were compared between the groups (Table 4). Subjects with a smaller Q_{csa} were more likely to have a lower body mass index and weight, and to be weaker. There was a trend to worse FEV_1 in the smaller muscle groups and a longer index length of hospital stay.

Risk of Hospitalization

In the year after the index admission the mean numbers of admissions were as follows: quartile 1 (smallest muscle), 2.5 (95% CI, 1.4–3.2); quartile 2, 1.3 (95% CI, 0.8–1.7); quartile 3, 1.5 (95% CI, 1.0–2.0); and quartile 4 (largest muscle), 1.7 (95% CI, 1.0–2.4) ($P = 0.025$). Risk of hospitalization, using Cox regression, was significantly higher in the smallest muscle group compared with largest (hazard ratio, 1.99; 95% CI, 1.21–3.27; $P = 0.007$) (Figure 1).

Number of Hospital Days

The number of hospital days in the year after the original admission was significantly higher in the smallest muscle group ($P = 0.007$) with 28.1 (SD, 33.9) days per subject in quartile 1, 11.9 (SD, 19.0) in quartile 2, 12.9 (SD, 23.1) in quartile 3, and 12.2 (SD, 23.5) in the largest muscle group (quartile 4) (Figure 2).

Mortality

Thirteen (28%) in the smallest muscle group (quartile 1) died compared with 10 (21%) in quartile 2, 7 (15%) in quartile 3, and 5 (10%) in the largest muscle group (quartile 4), with no difference between groups at 12 months ($P = 0.145$). No difference in mortality was seen when correcting for MRC dyspnea grade, previous hospitalization, home oxygen use, and treatment allocation using Cox regression (smallest [reference variable] vs. largest muscle groups: hazard ratio, 0.43; 95% CI, 0.15–1.21; $P = 0.110$).

Mortality in the various quartiles was compared between the intervention and usual care groups to test whether the excess mortality observed in the intervention group

Table 1. Clinical Characteristics of Subjects at Time of Recruitment*

Age, yr	71.6 (9.1)
BMI, kg/m^2	26.0 (6.0)
Sex, % male	45.6
MRC grade when stable, median (IQR)	4 (1)
Smoking	
% current	22.1
Pack-years	46.0 (35.9)
Home oxygen use, %	28.3
Number of comorbidities, median (IQR)	2 (2)
Hospitalized in previous year, % yes	52.4
Cohabitation, % living alone	38.6
Principal diagnosis, %	
COPD	80.6
Chronic asthma	6.8
Interstitial lung disease	5.8
Bronchiectasis	6.8
SGRQ	
Symptoms	76.59 (18.14)
Activity	87.16 (11.77)
Impact	57.95 (18.51)
Total	70.06 (14.01)
Quadriceps strength, kg	15.5 (7.1)
Quadriceps cross-sectional area, cm^2	4.76 (1.41)
Heart rate, bpm	85.9 (17.8)
Incremental shuttle walk test, m	109 (86)
Endurance shuttle walk test, s, median (IQR)	112 (144)
FEV_1 on discharge, L	0.97 (0.44)
FEV_1% predicted	44 (19)
FEV_1/FVC, %	53 (15)
Medication, %	
Long-acting muscarinic antagonist	52
Long-acting β-agonist	56
Inhaled corticosteroid	77
Long-term oral steroids	14

Definition of abbreviations: BMI = body mass index; COPD = chronic obstructive pulmonary disease; IQR = interquartile range; MRC = Medical Research Council; SGRQ = St. George's Respiratory Questionnaire.
Data are shown as mean (SD) unless otherwise indicated.
*Unscheduled hospitalization, n = 191.

Table 2. Factors Associated with Rehospitalization or Death at 1 Year in Univariate Analysis*

Variable	OR	95% CI	*P* Value
Age	**1.05**	**1.01–1.08**	**0.015**
Sex (female)	0.67	0.35–1.28	0.226
BMI	0.96	0.91–1.02	0.164
Lives with (spouse)	0.56	0.27–1.16	0.118
MRC dyspnea score	**4.57**	**2.62–7.95**	**<0.001**
Main diagnosis (ILD)	1.47	0.36–6.03	0.589
Smoking (yes)	0.46	0.11–1.87	0.280
Pack-years	1.00	0.99–1.01	0.608
Long-term oxygen therapy (yes)	**12.36**	**4.53–33.77**	**<0.001**
Quadriceps strength	0.96	0.92–1.01	0.124
Q_{csa}	**0.34**	**0.17–0.65**	**0.001**
ISWT	1.00	0.99–1.00	0.077
ESWT	1.00	1.00–1.00	0.210
FEV_1 on discharge	0.49	0.23–1.05	0.066
Total number of comorbidities	0.87	0.69–1.12	0.282
Mobility-limiting comorbidity† (yes)	0.69	0.36–1.32	0.263
Initial length of hospital stay	1.06	0.99–1.14	0.092
Previous hospitalization‡ (yes)	**4.82**	**2.42–9.58**	**<0.001**
Treatment allocation (intervention)	1.31	0.69–2.49	0.416

Definition of abbreviations: BMI = body mass index; CI = confidence interval; ESWT = endurance shuttle walk test; ILD = interstitial lung disease; ISWT = incremental shuttle walk test; MRC = Medical Research Council; OR = odds ratio; Q_{csa} = quadriceps cross-sectional area over height squared.
*ORs are shown for each separate variable. Significant variables are shown in boldface. ORs are per unit increase for continuous variables. For categorical variables, the group for which the OR is shown is provided in parentheses.
†Defined as significant cardiac disease, musculoskeletal disease, or vascular disease.
‡Hospitalization in previous 12 months.

in the original trial was in a specific quadriceps size. The difference in mortality between intervention and usual care groups was similar in all quadriceps subgroups (*see* Table E1 in the online supplement; $P = 0.404$).

Discussion

In this study, we demonstrate that indices of muscle function measured early during hospitalization influence the risk of readmission over the subsequent 12 months. Q_{csa} but not muscle strength was independently associated with hospital readmission or death and in a multivariate model this association remained significant alongside MRC dyspnea grade, home oxygen use, and hospitalization in the previous 12 months. Other measures of functional exercise performance (field walking performance) were also not significantly associated with readmission or death when measured at time of discharge from hospital. Muscle strength could also be determined during acute illness but did not significantly influence readmission rate, possibly because the volitional component of the assessment of strength was affected by the acute illness.

Table 3. Multivariate Analysis of Variables Significantly Predictive of Hospitalization or Death in the 12 Months after Measurement*

Variable	OR	95% CI	*P* Value
Long-term oxygen therapy (yes)	4.80	1.68–13.69	0.003
MRC dyspnea grade	2.57	1.44–4.59	0.001
Admitted in previous year (yes)	3.04	1.47–6.29	0.003
Quadriceps cross-sectional area	0.46	0.22–0.95	0.035

Definition of abbreviations: CI = confidence interval; MRC = Medical Research Council; OR = odds ratio.
*ORs are per unit increase for continuous variables. For categorical variables, the group for which the OR is shown is provided in parentheses.

Q_{csa} measurement was used as a marker of muscle mass in the current study. This technique has been previously validated against computed tomography measurements of Q_{csa} (7) and dual-energy X-ray absorptiometry (9) in COPD populations and has practical usefulness in the acute setting because it is independent of patient effort and can be performed at the bedside. Q_{csa} has previously been shown to be related to quadriceps strength and physical activity in stable COPD (17, 18), and more recently has been used to demonstrate progressive wasting in the intensive care environment (8). It is likely to offer a more sensitive and reliable measure of muscle mass than other potential bedside measures such as bioelectrical impendence analysis, which may not be able to detect regional loss of muscle mass and is subject to variation because of shifts in hydration status, which will be more important during the acute illness.

The impact of an exacerbation of respiratory disease on an individual will be determined by a combination of the severity of the acute event and the premorbid condition of the patient. As expected, our data confirm that measures of the physical condition of the patient can predict longer term readmission risk but importantly indicate that nonvolitional measures such as ultrasound remain discriminatory for this long-term outcome even when performed during the acute event. This contrasts with volitional measurements such as muscle strength or walking performance, which were not predictive when performed in this setting, presumably because they were influenced by the acuity of the event.

Subjects in the smallest muscle group were more likely to be readmitted or die (as expected) but also had more days in hospital over the subsequent 12 months. The small muscle group was characterized by muscle strength, with a trend to worse lung function and increased mobility-limiting comorbidities, which might explain the differences in readmission rate although these factors were not significant in the multivariate regression analysis. It is possible that reduced Q_{csa} is a surrogate for general "frailty" in this population. Objective measurements of frailty (e.g., 4-m gait speed) may also be of

Table 4. Comparison of Clinical Characteristics of Smaller Muscle and Larger Muscle Groups*

Variable	Quartile 1 (Smallest) (*n* = 47)		Quartile 2 (*n* = 48)		Quartile 3 (*n* = 48)		Quartile 4 (Largest) (*n* = 48)		*P* Value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Age, yr	73	9	72	10	71	9	70	8	0.287
Weight, kg	**63.6**	**16.8**	**65.1**	**16.6**	**74.2**	**15.3**	**77.3**	**17.9**	**<0.001**
BMI, kg/m^2	**22.7**	**4.6**	**24.8**	**5.4**	**27.6**	**5.5**	**28.8**	**6.4**	**<0.001**
QMVC, kg	**12.6**	**7.1**	**13.9**	**5.7**	**18.1**	**7.7**	**17.1**	**6.6**	**<0.001**
ISWT, m	109	86	100	91	119	85	110	83	0.815
ESWT, s	103	82	133	202	127	97	131	99	0.725
Oxygen saturation, %	93	4	93	3	92	4	93	3	0.908
Heart rate, bpm	87	16	89	14	89	11	92	14	0.261
FEV_1, L	0.90	0.39	0.86	0.39	1.03	0.40	1.09	0.54	0.060
FEV_1% predicted	41	19	44	19	46	17	47	21	0.441
MRC dyspnea grade, median (IQR)	4	0	4	1	4	1	4	1	0.281
Number of comorbidities, median (IQR)	3	2	2	2	2	1.5	2	2	0.148
Index length of hospital stay, d, median (IQR)	7	7	5	6.5	6	5	5	5	0.070
Sex, % male	49		40		44		50		0.717
Lives with, % alone	46		40		47		23		0.158
Principal diagnosis, % COPD	74		85		88		75		0.541
Admitted in previous year, %	66		50		48		46		0.188
Admitted ⩾2 in previous year, %	32		29		19		17		0.217
Mobility-limiting comorbidity, % yes	51		35		50		29		0.074

Definition of abbreviations: BMI = body mass index; COPD = chronic obstructive pulmonary disease; ESWT = endurance shuttle walk test; IQR = interquartile range; ISWT = incremental shuttle walk test; MRC = Medical Research Council; QMVC = maximal isometric quadriceps strength.
*Smaller muscle group, quadriceps cross-sectional area (Q_{csa}) < 4.79 cm^2; larger muscle group, Q_{csa} ⩾ 4.79 cm^2. Significant differences are shown in boldface.

discriminatory value in predicting rehospitalization (19).

We observed a higher proportion in the mean number of hospital days between the smallest and largest muscle groups, compared with number of hospital admissions. This suggests that skeletal muscle dysfunction is not only important for admission to hospital but also for the severity and duration of the admission. Better physical condition, represented by larger muscle mass, may allow patients who have been admitted to hospital to be better able to cope with the insult of a severe illness and hospitalization (20, 21), resulting in a shorter length of stay. Interventions to support this concept include Griffiths and colleagues, who observed a decrease in hospital days, but no reduction in hospital admissions after pulmonary rehabilitation (22).

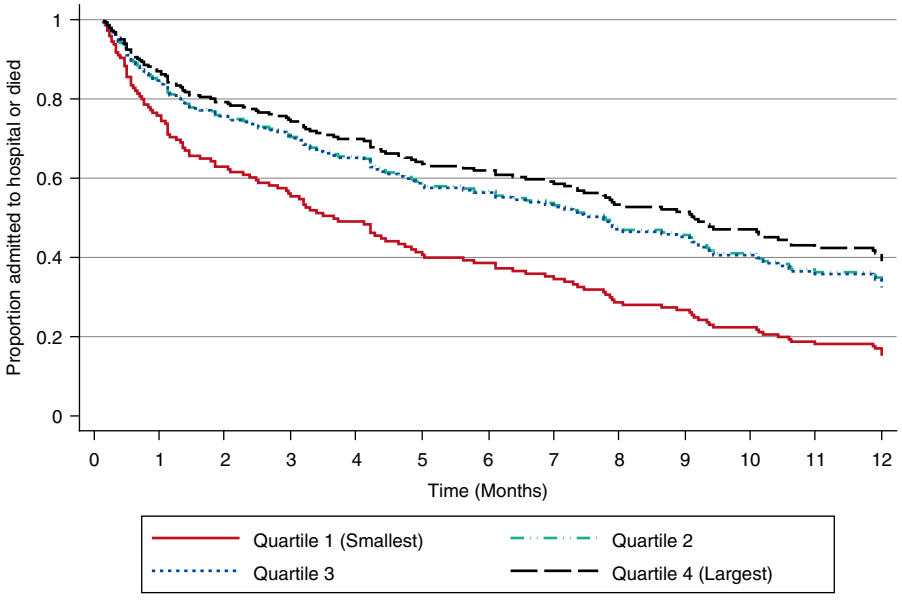

Figure 1. Cox regression curve of risk of hospitalization or death for quartiles of various quadriceps muscle size. Covariates in the model include hospitalization in the previous year, Medical Research Council dyspnea grade, and home oxygen use. Significant difference is present between smallest and largest muscle groups at 12 months ($P = 0.007$).

There was no statistically significant difference in mortality between the smallest muscle and largest muscle groups, although the absolute difference was 18% in favor of the largest muscle group. It is likely that this study was underpowered for this measure and that further research would be of benefit, as other studies have suggested that reduced muscle function (mass and strength) is an independent predictor of mortality in COPD (5).

This is the first study to report the predictive value of measurements of muscle function taken during hospitalization for exacerbations of CRD. Our data are in line with other studies suggesting that self-reported physical activity after discharge (23) and its recovery at 1 month predict the risk of readmission (24).

Our study suggests that measures of muscle function can be recorded during hospital admission and may provide an

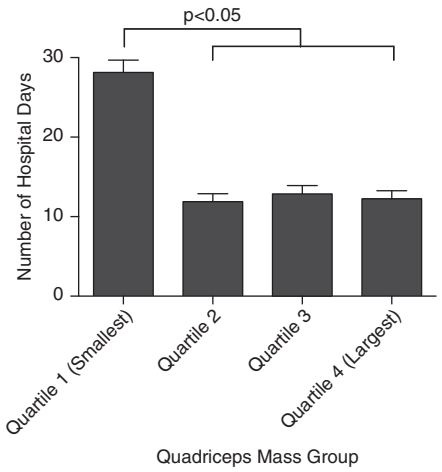

Figure 2. Mean number of days spent in hospital in the year after the index admission. Groups shown are quartiles of quadriceps size, measured by ultrasound and corrected for patients' height. *Error bars* represent the 95% Poisson confidence intervals.

opportunity for future risk stratification. The identification of such risk strata is of considerable interest because of the burden and cost of unscheduled hospitalization to patients and health care systems and may inform treatment decisions (e.g., prioritization of palliative or end-of-life care) or identify populations suitable for targeted interventions.

The original clinical trial for this study showed no difference in hospitalization rate between an early rehabilitation intervention and usual care, although an increase in mortality was seen in the intervention group. These data demonstrate, on the basis of quadriceps size, no difference in mortality or efficacy of the intervention in any particular subgroup. It is unknown whether other interventions, such as postexacerbation pulmonary rehabilitation or other targeted therapies, would be more effective or more acceptable in patients with a better prognosis (i.e., those with larger muscle) (25–27).

Limitations to the analysis described in this study are acknowledged. Although the data were collected prospectively, it is a secondary, subgroup analysis of a clinical trial and risk stratification was not the purpose of the investigation. In any multivariate analysis, limitations are posed by the range of measures that are available. Q_{csa}, using ultrasound, is not a routine measure. However, it is a simple measure to perform and bedside ultrasound equipment is already routinely available in the acute care setting for other indications, such as the investigation of pleural disease. We used the ISWT and ESWT as measures of maximal and submaximal exercise capacity. It is possible that other measures such as the 6-minute walk test may have been of prognostic use. However, both the ISWT and ESWT are well validated (28) and the ESWT and 6-minute walk test have similar exercise response profiles (29), although there have been limited data for any of these tests in the acute hospital setting.

In conclusion, smaller lower limb muscle mass in the acute care setting is a risk factor for subsequent unscheduled admission to hospital for exacerbations of CRD. Such measurements may have value in both clinical practice and as a risk stratification tool in these populations. ■

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

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