Thorax Online First, published on November 7, 2006 as 10.1136/thx.2006.062026

Quadriceps strength predicts mortality in patients with moderate to severe Chronic Obstructive Pulmonary Disease

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Keywords: mortality, quadriceps weakness, COPD

Abstract

Background: Prognosis in chronic obstructive pulmonary disease (COPD) is poorly predicted by indices of airflow obstruction, because other factors which reflect the systemic nature of the disease also influence prognosis. This study was undertaken to test the hypothesis that a reduction in quadriceps maximal voluntary contraction force (QMVC), is a useful predictor of mortality in patients with COPD.

Methods: A mortality questionnaire was sent to the primary care physician of 184 COPD patients who had undergone quadriceps strength measurement over the last five years. QMVC was expressed as a % of the patients' body mass index. The endpoint measured was death or lung transplantation and median (range) follow up was 38 (1-54) months.

Results: Data was obtained for 162 patients (108 male, 54 female) with a mean FEV_1 % predicted of 35.6(16.2) giving a response rate of 88%. Transplant free survival of the cohort was 93.5% at 1 year and 87.1% at 2 years. Cox regression models showed that the mortality risk increased with increasing age and with reducing QMVC. Only age, Hazard ratio 1.72 (95% CI 1.14-2.60), p=0.01 and QMVC, HR 0.91 (0.83-0.99), p=0.036 continued to be statistically significant predictors of mortality when controlled for other variables in the multivariate analysis.

Conclusion: Quadriceps MVC is simple and provides more powerful prognostic information in COPD than that provided by age, Body Mass Index and FEV_1.

Introduction

Chronic obstructive pulmonary disease (COPD) is the 4th leading cause of death in the world (1) but prognosis is only poorly predicted by indices of airflow obstruction. Given this limitation, a new severity classification, the BODE index (2), has been proposed which takes into account the multicomponent nature of COPD with significant emphasis being placed on the body mass index (BMI) as an indicator of poor prognosis (3) (4) (5) (6). However, many investigators consider that it is, more specifically, the loss of skeletal muscle mass which confers a poorer prognosis in COPD patients (7) (8) (9) (10). Muscle mass depletion is associated with reduced exercise performance (11) (12), increased dyspnoea (13) and worse health related quality of life (14). Similarly skeletal muscle weakness is a common finding in COPD and is associated with reduced exercise capacity (15) (16) (17). As exercise capacity is thought to be a significant factor determining mortality in COPD (18) it perhaps follows that muscle weakness should also predict mortality.

In a recent paper by Marquis et al (7) computerised tomographic (CT) scanning was used to measure the mid-thigh cross-sectional area ($MTCSA_{CT}$) in patients with COPD. This radiological measure of quadriceps bulk was shown to predict mortality better than BMI and this was particularly so in patients with more severe COPD (forced expiratory volume in one second, FEV_1<50%). This measure is attractive as a single reproducible predictor of COPD mortality but there are some obvious drawbacks which would limit its more widespread use. In particular the use of CT scanning has resource implications as well as involving a significant radiation exposure. We therefore hypothesized that a simple functional measure of strength, the quadriceps maximum voluntary contraction force (QMVC), might also predict mortality in patients with COPD.

Methods

The study cohort was 184 patients with COPD, recruited without further selection from outpatient clinics at the Royal Brompton Hospital, a tertiary referral centre, and King's College Hospital, in whom quadriceps strength measurements had been performed in the preceding five years. All patients underwent baseline anthropometric measurements including bioelectrical impedance analysis and pulmonary function tests, as well as quadriceps strength measurement. The primary endpoint was time to death or lung transplantation (termed transplant-free survival, TFS), calculated from the date when quadriceps strength was measured until the reference date of July 20th 2005 when the analysis was performed. The status of the patient (alive, dead or lung transplant recipient) was ascertained by a questionnaire sent to the patients' primary care physician. We also enquired about exacerbations of COPD which required hospital admission, smoking status, comorbidities, drug treatments and whether they had undergone a course of pulmonary rehabilitation. Patients were excluded from this study if they had significant comorbidity. The Royal Brompton Hospital Research Ethics Committee approved the study.

Pulmonary Function testing
All patients had COPD diagnosed according to international guidelines (19). Pulmonary function testing was performed by standardised techniques in the lung function departments of the Royal Brompton and King's College Hospitals. Patients were subdivided into GOLD stages on the basis of their FEV_1.

Fat free mass measurements
Fat free mass (FFM) was determined using bioelectrical impedance analysis (Bodystat 1500, Bodystat, Isle Of Man, UK) and a disease specific regression equation (20).

Quadriceps Measurements
Quadriceps maximum voluntary contraction force (QMVC) was measured using the technique of Edwards *et al* (21). Subjects sat in a purpose built chair with an inextensible strap connecting the ankle of their dominant leg to a strain gauge (Strainstall Ltd, Cowes, UK). The force signal was amplified and passed to a computer running LabView 4 software (National Instruments, Austin, Texas). The linearity of the strain gauge is factory certified from 0 to 100Kg. The equipment was calibrated using a suspended weight prior to testing each subject. Care was taken to ensure that subjects' knees were flexed to 90 degrees and that the strain gauge and couplings were all aligned to ensure that the contraction was isometric. Subjects performed at least 3 sustained maximal isometric quadriceps contractions of between 5 and 10 seconds duration. The force produced was visible online to both subject and investigator to allow positive feedback and vigorous encouragement was given. There was a gap of 30-60 seconds between each contraction to allow time to recover from each effort. The best QMVC was then expressed as a function of the patient's body mass index.

Statistical analysis
Transplant-free survival (TFS) distribution was estimated using Kaplan-Meier product moment estimator. A univariate analysis, based on the Cox proportional hazards model where survival status at 20th July 2005 was used as the dependent variable, was performed to identify prognostic factors for TFS. Variables considered were age

(divided into 10-year groups), body mass index (BMI), fat free mass index (FFMI), FEV_1 (% predicted) and QMVC (as a % of BMI). A multivariate Cox model was then fitted, in which all factors were considered. A stepwise backward variable selection procedure was implemented to remove the non-significant variables from the multiple models. The validity of the proportional hazards assumptions was assessed using Grambsch and Therneau goodness of fit test (22) and the validity of the log-linearity assumptions by fitting generalized additive models with splines to the residuals. Additionally, the discriminative ability of different multiple models was compared using the *D* measure of Royston and Sauerbrei (23), as well as the *D*-based version of Kent and O'Quigley's measure of dependence (R-squared measure) (24). Data are expressed as mean (SD) values unless otherwise stated.

Results

The response rate to the questionnaire was 88%, and therefore the data expressed in this paper is for 162 patients (108 male, 54 female). Patient demographics are shown in Table 1 and it can be seen that there were no significant differences between the patients in whom we obtained outcome data and patients in whom we did not. During follow up, 36 deaths occurred as well as 2 lung transplants, and 31 patients had at least one hospital admission due to an exacerbation of COPD (3 followed by death and one by a lung transplant).

All patients received standard therapy for COPD with 20 patients taking long term oral steroids at the time of quadriceps measurement. Nineteen patients were continuing smokers at the time of measurement. Seventy four patients had completed or subsequently completed a course of pulmonary rehabilitation. Patients with serious comorbidity were excluded from the analysis (i.e. their primary care physician was not sent a questionnaire) and of the remaining cohort, eleven patients had treated hypertension , eight suffered with mild ischaemic heart disease and one patient had non insulin dependant diabetes mellitus.

Most of the patients had moderate to severe COPD which reflects the type of patients seen in hospital outpatient clinics in the UK. The cohort transplant-free survival curve is shown in Figure 1. As only two patients were followed up for more than 4 years, one of whom died, the data were censored at 4 years. Median length of follow up was 38 months, with a range of 1-54 months. Transplant-free survival of the cohort was 93.5% at 1 year and 87.1% at 2 years. The transplant-free survival curves for patients with normal and reduced quadriceps strength (QMVC $\geq$ or $<$ 120% of BMI respectively) were significantly different (p=0.017) and are displayed in Figure 2. The transplant-free survival separated by GOLD stage can be seen in Figure 3 which shows that mortality increases with worsening lung function. Although the curves show the expected trend they do not reach statistical significance, Stages 0-2 *vs.* 3-4 p=0.17.

The results of univariate and multivariate Cox models are presented in table 2. The univariate analysis shows that the mortality risk increased with increasing age and with reducing QMVC. Among all factors in the multivariate analysis, only age and QMVC wielded a significant association with survival. DLCO was not considered in the multivariate analysis as data was missing from 23 patients. Being on oral steroids is a strong predictor of mortality: HR 3.68 (1.84-7.34), p=0.0002. No significant association was found between an acute exacerbation with the hazard of death or transplantation (HR 0.65, 95%CI 0.23 to 1.88, p=0.43). In fact, only 3 of the 32 patients who had exacerbations died, *vs.* 32 of the 130 who did not. When compared to a model including age, gender, BMI and FEV_1 (% predicted), the selected model using only QMVC, gender and age yielded an explained variation (R^2) of 0.29 *vs.* 0.26, indicating improved prognostic power. The *D*-measure of prognostic discrimination for these models was 1.02 *vs.* 0.93, in agreement with the previous result.

Review of the hazard ratios for individual variables (Figure 4) did not challenge the linearity hypotheses of the Cox models, nor Grambsch and Therneau's goodness of fit test (all p<0.25). The relationship between the risk of death and increasing age and

reducing QMVC appears approximately linear, whereas the relationship between BMI and FEV_1 and the risk of death seemed, to visual inspection, flatter when considering a BMI between 20 and 30 kg/m^2 or an FEV_1 below 50% of predicted, suggesting poorer prognostic power in these ranges for these variables.

Discussion

We found that, in patients with COPD, quadriceps muscle strength adds prognostic information to that provided by age, Body Mass Index and FEV_1. We believe that, in common with $MTCSA_{CT}$, QMVC reflects quadriceps muscle bulk and can be indicative of skeletal muscle dysfunction, but this physiological measurement is cheap and radiation free and may have greater functional relevance. Measurement of quadriceps strength could be used to identify high-risk COPD patients who have peripheral muscle weakness and who may obtain greater benefit from rehabilitation or nutritional supplementation.

Critique of the Method

Our questionnaire did not specify the cause of death so the data reflect all cause mortality. The mortality rate in our study, an annual death rate of approximately 7%, is similar to other studies on comparable patients, ranging from 5% in the study by Marquis to 9% in the study by Slinde. We had a response rate of 88% from the questionnaires and this was in part due to some patients no longer being registered with their original primary care physician. However we doubt that the incompleteness of the data jeopardises our conclusions since both groups were similar with respect to baseline characteristics. We also acknowledge that since the Brompton Hospital acts as a tertiary referral centre that our patients may not be wholly typical of the generality of COPD patients; our hypothesis should be retested in a primary care setting.

A further limitation of the study is that we measured only whole body fat free mass rather than regional muscle bulk. Thus we are unable to identify whether the poorer prognosis conferred by weakness is specifically due to a reduction in quadriceps bulk or a reduction in quadriceps specific force. Whilst this could be an interesting area for future study is does not detract from the finding that QMVC has strong prognostic power.

Quadriceps strength in normal humans bears a reasonably close relationship with total body weight and Edwards *et al* recommended that quadriceps strength be normalised against body weight (21). This approach relied on an unstated assumption that BMI did not vary greatly within his healthy population and therefore that quadriceps muscle strength enjoyed a reasonably constant relationship with body weight (as a surrogate for height); in fact Edwards and colleagues reported neither the height nor BMI of their subjects. In patients with severe COPD, selective loss of quadriceps muscle bulk occurs, and since we hypothesized that it was this mechanism that confers the poor prognosis, it seemed to us inappropriate to discount the effect of height (and by inference femur length) on QMVC. For this reason we expressed QMVC as a function of BMI. In addition we performed analyses expressing QMVC as a function of body weight or fat free mass and this did not materially alter our conclusions, although the predictive power was slightly diminished with the former and increased with the latter.

QMVC is a non-invasive test, is simple to perform and gives a functional assessment of muscle bulk. Although we could additionally have performed magnetic stimulation of the femoral nerve, using the rationale that volitional measures are open to the

criticism that weakness is due to reduced motivation or aptitude (25), we did not do this in most patients. The fact that QMVC emerged as a powerful prognostic indicator suggests these reservations do not detract from the value of the measurement.

We did not have exercise capacity or dyspnoea scores available on these patients so we were unable to calculate our cohort's BODE index and therefore could not compare our predictive model with that of Celli and associates (2). However exercise capacity is associated with quadriceps strength and the data show that our model which includes only age, gender and quadriceps strength is a useful predictor of mortality and is easier to perform. In the BODE grading system, the four variables which had the strongest association with one-year mortality; BMI, FEV_1, modified Medical Research council (MMRC) dyspnoea score and six minute walk distances, had a generalized R^2=0.21, whereas in our study a model including age, gender and QMVC yielded an explained variation over the time course of the study of R^2=0.29. Although direct comparison of the prognostic value of these two models is difficult as we are unable to compute the same data, the power of our model is at least of a similar order of magnitude.

Significance of the findings

In the general population quadriceps weakness has been shown to be a predictor of mortality (26) so our results are consistent with the hypothesis that factors which contribute to quadriceps weakness, such as inactivity may also lead to reduced survival. However the magnitude of the weakness observed in our patients with moderate to severe COPD is more marked than observed in the normal population. Indeed we have previously shown that COPD patients had a mean quadriceps MVC of 34.4 Kg compared with 43.8 Kg in the healthy age-matched controls (27); therefore we do no think our data simply reflect ageing

Our findings suggest that quadriceps strength is a better marker at predicting mortality than either BMI or FFMI. In the study of Marquis *et al* the subjects' mean BMI was in the normal range (mean 26 kg/m^2) yet the mid thigh $MTCSA_{CT}$ values were 72% of normal which indicates that quadriceps muscle mass rather than body weight is the important physiologic variable predicting survival. This suggests that the loss of muscle mass has more ominous implications for prognosis than the loss of other body compartments. Consistent with these data we did not find that FFMI was predictive of mortality which is in contrast to other studies (8, 10) although absolute values for FFMI are not greatly different between these studies. The discordance between changes in fat free mass and quadriceps strength seem to support the importance of local rather than systemic factors in producing weakness.

In COPD systemic factors such as inflammation, hypoxia and nutritional depletion may interact with local factors such as muscle activity level or perfusion to produce muscle weakness. The question remains as to the extent to which muscle weakness is a generalised, systemically determined phenomenon or one that predominantly affects the lower limbs as a result of disuse. The "compartment theory" is based on the premise that changes in muscle function depend on the demands placed on the muscle in question and is supported by the observation that different changes are found in different muscle groups (28). Thus it is argued that patients walk less because of

dyspnoea, which leads to disuse atrophy and quadriceps weakness. Upper limb strength is relatively maintained in patients with COPD because there is a preservation of upper body activity and the shoulder girdle muscles are accessory muscles of respiration (17). Adductor pollicis twitch force is normal whereas quadriceps twitch is reduced in COPD patients (29). Therefore it is interesting that mid arm circumference, which reflects upper limb muscle bulk has been shown to predict mortality (9). We have also recently shown that the expiratory muscles (which are active in patients with COPD) have at least normal strength in a cohort of patients with COPD (30). We therefore believe that the predominance of published data is in favour of the characteristic abnormality in COPD being an isolated locomotor muscle weakness.

The prognostic value of QMVC does not establish a causal relationship. Our study suggests that reduced quadriceps strength predicts mortality however it does not help in elucidating the reasons for this decline or when this begins in patients with COPD. We are not sure whether the natural history of quadriceps weakness is a slow deterioration with disease progression or reduced activity, or, as suggested by the data of Spruit *et al* (31) a stepwise decline associated with exacerbations. Only 17% of our cohort had an exacerbation requiring hospital admission during follow up indicating that the majority were not frequent exacerbators, despite most of the patients having quadriceps weakness. This suggests that serious exacerbations may not be necessary to cause quadriceps muscle deterioration. It is possible that quadriceps weakness is a surrogate marker for a patients' reduced generalised performance status but it may also be a systemic manifestation of generalised inflammation in COPD. It has been shown that reduced physical activity in itself is an independent risk factor for hospital admission (32). We do not know the effect of improving muscle strength on mortality although our group has shown that early pulmonary rehabilitation following hospitalisation does improve quality of life and exercise capacity and reduces further hospital attendances (33).

In conclusion quadriceps strength measured by a maximal voluntary isometric contraction is useful in predicting mortality of patients with COPD. This easily performed measurement could be widely performed in the lung function laboratory and could serve to identify patients at higher risk of death.

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Table 1: Subject demographics. There were no significant differences between the patients in whom outcome data were available and those for whom it was not.

	Complete patient data n=162 (108 male, 54 female) Mean (SD)	No outcome data available n=22 (12 male, 10 female) Mean (SD)
Age when tested	63.7(9.3)	66.7(9.5)
Height (m)	1.70(0.09)	1.67(0.09)
Weight (kg)	70.2(16.3)	70.4(15.7)
BMI (kg/m^2)	24.4(5.0)	25.2(4.7)
FFMI (kg/m^2) male	17.1(2.3)	17.9(2.5)
FFMI (kg/m^2) female	15.8(2.3)	15.7(1.7)
FEV_1(L)	0.98(0.44)	1.02(0.3)
FEV_1% predicted	35.6(16.2)	42.2(9.3)
DLCO % predicted	37.3(17.6)	41.2(12.1)
GOLD stage		
Stage 0	0(0%)	0(0%)
Stage 1	2(1.2%)	0(0%)
Stage 2	29(17.9%)	3(13.6%)
Stage 3	56(34.6%)	9(40.9%)
Stage 4	75(46.3%)	10(45.5%)
QMVC (kg)	32.4(11.5)	35.7(13.3)
QMVC as a % of BMI	135.5(46.7)	142.7(50.5)

BMI – body mass index, FFMI – fat free mass index, FEV_1 – forced expiratory volume in one second, QMVC – quadriceps maximal voluntary contraction, DLCO – carbon monoxide diffusion capacity

Table 2: Assessment of prognostic factors using Cox proportional hazard models. (DLCO was not included in the multivariate analysis as data was missing on 23 patients.)

	Univariate analysis		Multivariate analysis	
Variable	HR (95% CI)	p	HR (95% CI)	p
Male gender	1.30 (0.64-2.62)	0.47	1.61 (0.71-3.64)	0.25
Age (per 10 ys)	1.68 (1.19-2.36)	0.0031	1.72 (1.14-2.60)	0.010
BMI (per kg/m²)	0.96 (0.90-1.03)	0.30	0.91 (0.80-1.05)	0.21
FFMI (per kg/m²)	0.96 (0.82-1.11)	0.58	1.08 (0.81-1.45)	0.60
FEV_1 (% predicted)	0.99 (0.97-1.01)	0.17	0.98 (0.96-1.01)	0.13
DLCO (%)	0.97 (0.95-0.99)	0.016		
QMVC (per 10% of BMI)	0.92 (0.85-0.99)	0.022	0.91 (0.83-0.99)	0.036
Currently smoking	1.79 (0.82-3.93)	0.14	2.06 (0.85-5.00)	0.11
Pulmonary Rehabilitation	0.95 (0.50-1.80)	0.88	1.57 (0.75-3.30)	0.23

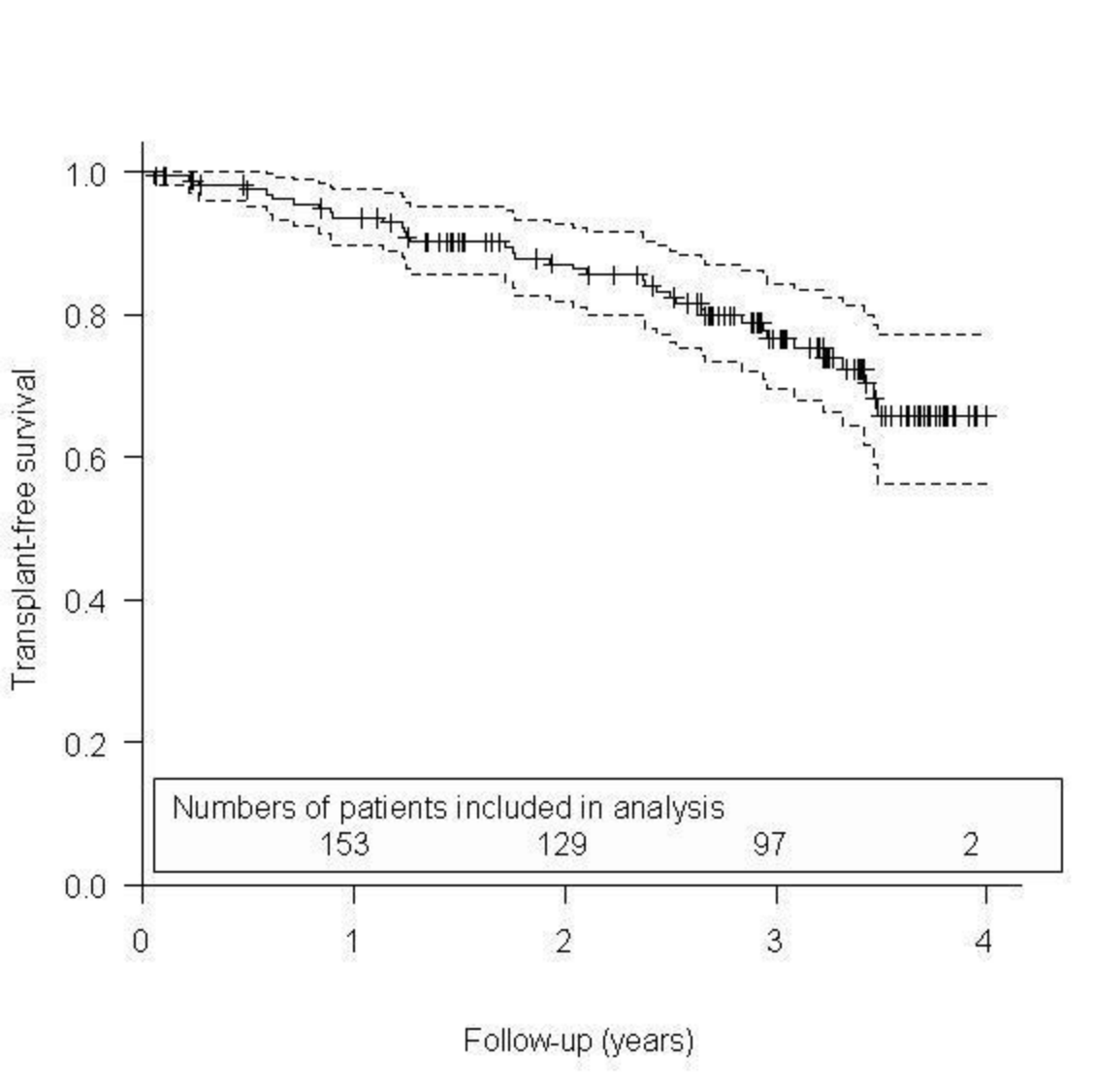
BMI – body mass index, FFMI – fat free mass index, FEV_1 – forced expiratory volume in one second, QMVC – quadriceps maximal voluntary contraction, DLCO – carbon monoxide diffusion capacity

Figure Legends:

Figure 1: Transplant–free survival for the whole COPD cohort (solid curve) with 95% confidence interval (dashed line). Censoring times are represented by crosses (+).
Figure 2: Transplant-free survival for patients with normal and reduced quadriceps strength, as defined by a QMVC greater or less than 120% of BMI. The curves are significantly different, p=0.017.
Figure 3: Transplant-free survival separated by GOLD stage. The curves were not statistically different, Stages 0-2 *vs.* 3-4 p=0.17.
Figure 4: Test of functional form for age (a), BMI (b), FEV_1 % predicted (c) and quadriceps MVC (d) data. The y axis shows the spline estimates of log-hazard ratios for death (solid lines) with 95% confidence interval (dashed lines) for each variable. The small lines on the x axis show where individual patients lie within the range.

Competing Interest Statement

None of the authors have any relevant competing interests.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Transplant-free survival
Numbers of patients included in analysis
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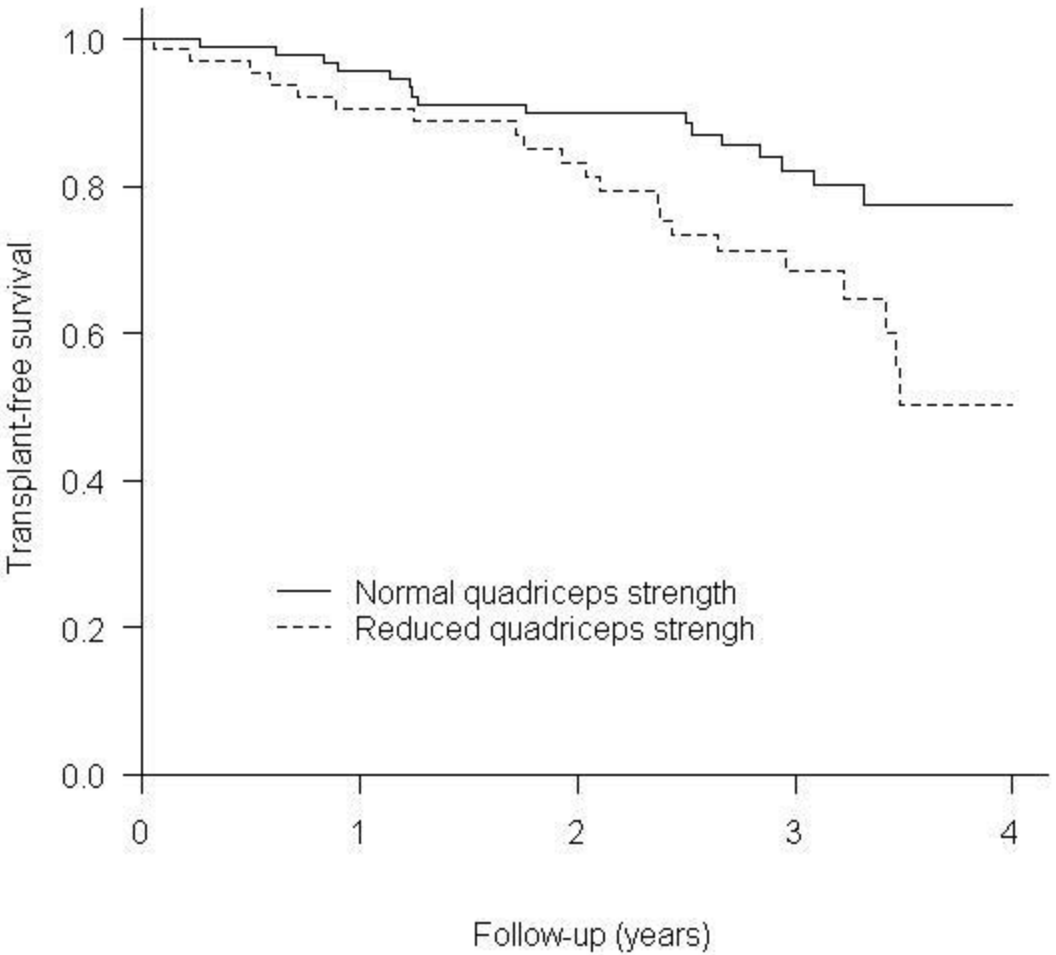
Follow-up (years)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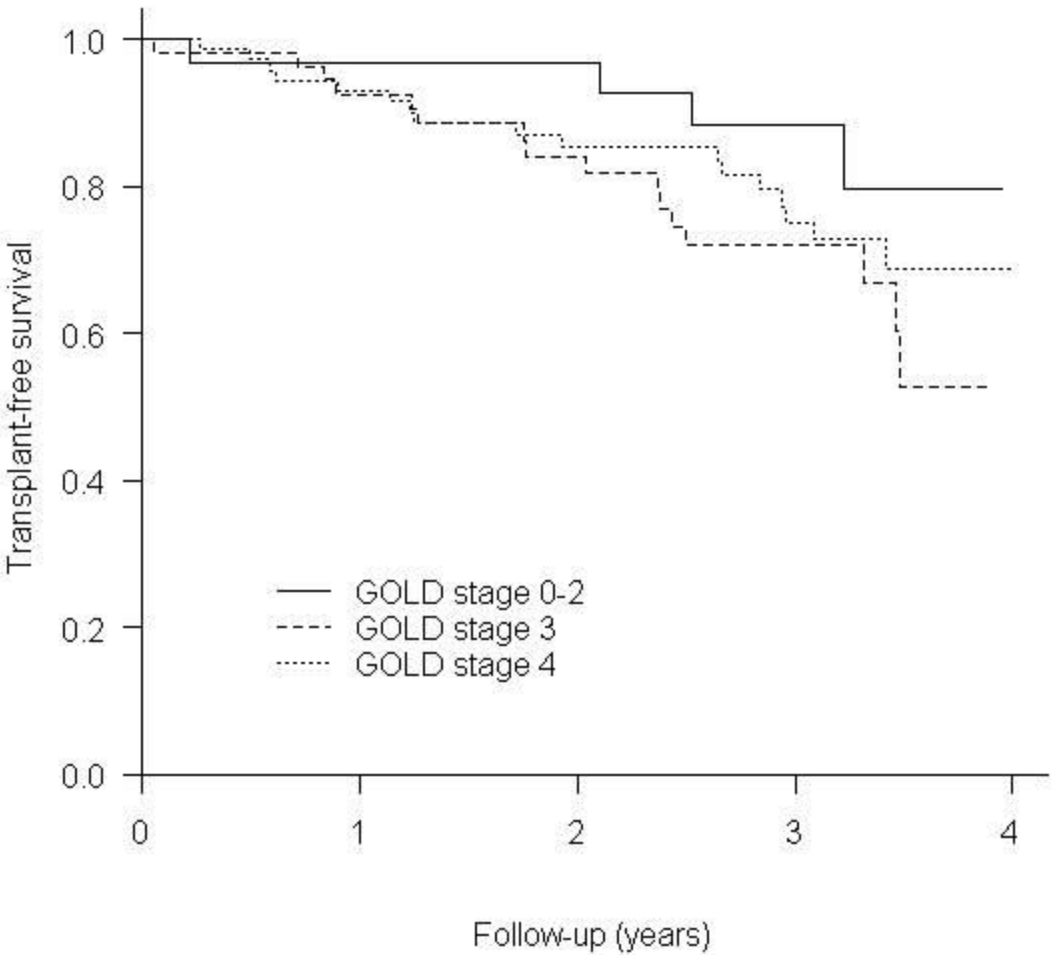
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Transplant-free survival
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GOLD stage 3
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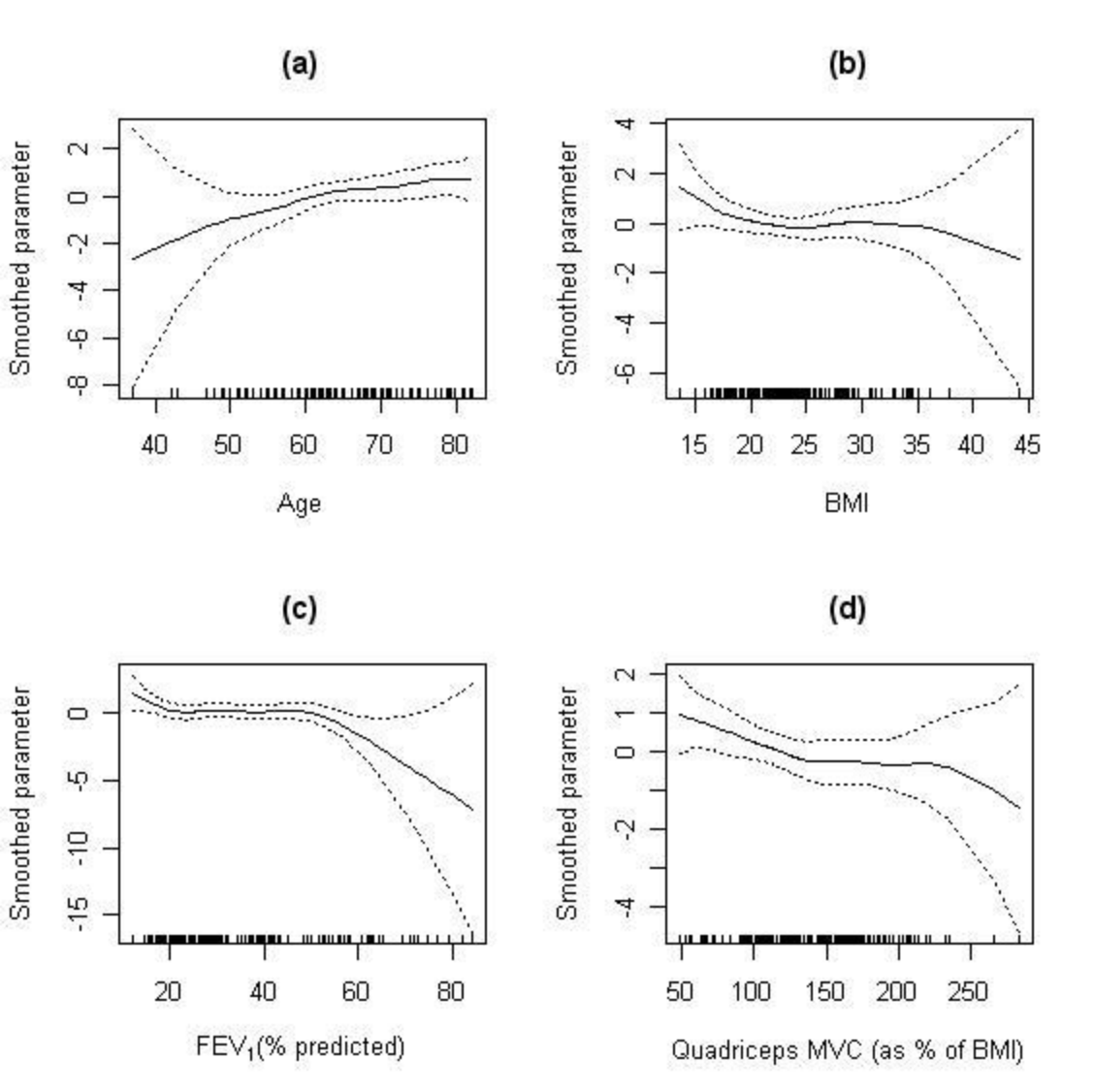
4
Follow-up (years)


(a)
Smoothed parameter
-8 -6 -4 -2 0 2
40 50 60 70 80
Age
(b)
Smoothed parameter
-6 -4 -2 0 2 4
15 20 25 30 35 40 45
BMI
(c)
Smoothed parameter
-15 -10 -5 0
20 40 60 80
FEV1(% predicted)
(d)
Smoothed parameter
-4 -2 0 1 2
50 100 150 200 250
Quadriceps MVC (as % of BMI)