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## ORIGINAL ARTICLE

# Neural respiratory drive predicts clinical deterioration and safe discharge in exacerbations of COPD

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## ABSTRACT

**Rationale** Hospitalised patients with acute exacerbation of COPD may deteriorate despite treatment, with early readmission being common.

**Objectives** To investigate whether neural respiratory drive, measured using second intercostal space parasternal muscle electromyography (EMG<sub>para</sub>), would identify worsening dyspnoea and physician-defined inpatient clinical deterioration, and predict early readmission.

**Methods** Patients admitted to a single-site university hospital with exacerbation of COPD were enrolled. Spirometry, inspiratory capacity (IC), EMG<sub>para</sub>, routine physiological parameters, modified early warning score (MEWS), modified Borg scale for dyspnoea and physician-defined episodes of deterioration were recorded daily until discharge. Readmissions at 14 and 28 days post discharge were recorded.

**Measurements and main results** 120 patients were recruited (age 70±9 years, forced expiratory volume in 1 s (FEV<sub>1</sub>) of 30.5±11.2%). Worsening dyspnoea, defined as at least one-point increase in Borg scale, was associated with increases in EMG<sub>para%max</sub> and MEWS, whereas an increase in EMG<sub>para%max</sub> alone was associated with physician-defined inpatient clinical deterioration. Admission-to-discharge change (Δ) in the normalised value of EMG<sub>para</sub> (ΔEMG<sub>para%max</sub>) was inversely correlated with ΔFEV<sub>1</sub> ( $r=-0.38$ ,  $p<0.001$ ) and ΔIC ( $r=-0.44$ ,  $p<0.001$ ). ΔEMG<sub>para%max</sub> predicted 14-day readmission (OR 1.13, 95% CI 1.03 to 1.23) in the whole cohort and 28-day readmission in patients under 85 years (OR 1.09, 95% CI 1.01 to 1.18). Age (OR 1.08, 95% CI 1.03 to 1.14) and 12-month admission frequency (OR 1.29, 1.01 to 1.66), also predicted 28-day readmission in the whole cohort.

**Conclusions** Measurement of neural respiratory drive by EMG<sub>para</sub> represents a novel physiological biomarker that may be helpful in detecting inpatient clinical deterioration and identifying the risk of early readmission among patients with exacerbations of COPD.

**Trial registration** NCT01361451.

## INTRODUCTION

Acute exacerbations of COPD (AECOPD) are common, accounting for 12.5% of emergency admissions in the UK<sup>1</sup> with an in-hospital mortality of up to 10%.<sup>2</sup> Eighteen percent of patients with AECOPD present to the emergency department with acute hypercapnic respiratory failure<sup>3</sup> and a further 5% will develop late respiratory acidosis.

## Key messages

### What is the key question?

- Can non-invasive measurement of neural respiratory drive identify clinical deterioration and the risk of early readmission in patients admitted with exacerbation of COPD?

### What is the bottom line?

- Neural respiratory drive, measured by second intercostal space parasternal muscle electromyography, is a physiological biomarker of worsening breathlessness and physician-defined clinical deterioration in COPD exacerbations, and may predict early readmission.

### Why read on?

- The results of a large physiological observational cohort study are presented, validating a novel physiological biomarker that represents the balance between the load and the capacity of the respiratory muscle pump during exacerbations of COPD.

Twenty percent of hospitalised patients with AECOPD are readmitted within 28 days,<sup>4 5</sup> and financial penalties are now in operation for acute care hospitals in the UK and USA for readmissions within 30 days.<sup>6 7</sup> It is a health economic priority to identify COPD treatment failure promptly and reduce readmissions, and biomarkers that can achieve this will therefore be of significant clinical value.

Previous studies have reported the patient characteristics that predict readmission among hospitalised patients with COPD,<sup>2 8–11</sup> but these are limited by their dependence on non-modifiable parameters, rather than on the trajectory of response to treatment. In addition, early-warning scores,<sup>12</sup> often used to track inpatient clinical deterioration and trigger escalation of care, vary in their ability to predict outcomes such as critical care admission and hospital mortality,<sup>13</sup> limiting the usefulness of these approaches.

More advanced physiological measurements of elastic and threshold respiratory load are difficult

during an acute exacerbation as invasive monitoring of pleural pressure is poorly tolerated. In addition, the measurement of ventilation in flow-limited patients characterised by neuroventilatory uncoupling, as a result of severe hyperinflation, has significant caveats and therefore the non-invasive measurement of neural respiratory drive (NRD), which is a direct reflection of the imbalance between respiratory muscle load and capacity, would be a preferred option. Indeed, NRD as an advanced physiological biomarker, provides a direct measure of the balance between respiratory muscle load and capacity,<sup>14</sup> and has gained increasing attention in the acute setting.<sup>15</sup>

Recently, surface electromyography (EMG) of the second intercostal space parasternal muscles (EMG<sub>para</sub>) has been used as a non-invasive alternative to the invasive oesophageal measurement<sup>16</sup> of NRD in patients with COPD, asthma and cystic fibrosis.<sup>15 17 18</sup> Murphy *et al*<sup>15</sup> previously showed, in a pilot feasibility study of this technique, that the change in NRD during hospital admission was a biomarker of physician-defined clinical deterioration, and furthermore, change in NRD from admission to discharge identified patients with COPD who were readmitted within 14 days. However, this previous study was in a small group of selected patients with COPD, with the majority of patients having only a single pair of NRD measurements made during their hospital admission.

We therefore hypothesised that, in a large, prospective observational cohort study of patients hospitalised with exacerbation of COPD, changes in daily measurements of NRD between hospital admission and discharge would predict readmission within 14 and 28 days. We further hypothesised that change in NRD would objectively identify worsening dyspnoea and physician-defined clinical deterioration.

## METHODS

### Patients

The study was approved by the London-Bentham Research Ethics Committee and participants provided written informed consent. The authors registered the study as an observational cohort study (NCT01361451). Patients with a physician diagnosis of acute exacerbation of COPD, defined according to clinical features and basic investigations,<sup>1</sup> were enrolled within 12 h of admission to a UK teaching hospital. The requirement for admission was determined by the attending physician. Patients were excluded if they had another cause for their acute

admission (eg, acute heart failure, PE), cognitive impairment, active cancer or significant psychosocial factors.

### Admission data

Demographic and anthropometric data were collected. FEV<sub>1</sub>, FVC and inspiratory capacity (IC)<sup>19</sup> were measured using a pneumotachometer (3830, Hans-Rudolph, Shawnee, USA) or a handheld spirometer (Micro, Carefusion, Basingstoke, UK) according to international standards.<sup>20</sup> Symptoms were assessed using the Medical Research Council (MRC) Dyspnoea scale,<sup>21</sup> the modified Borg scale for dyspnoea<sup>22</sup> and the COPD Assessment Test (CAT).<sup>23</sup> Standard physiological observations (respiratory rate, heart rate, oxygen saturation, body temperature and blood pressure) were collected; an aggregate score derived from these was recorded as the modified early warning score (MEWS), according to local protocol.

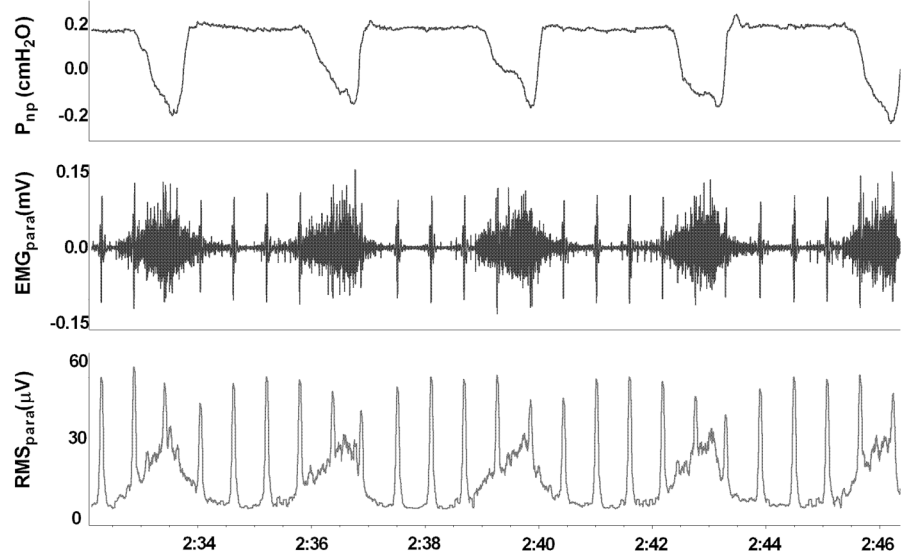
### EMG<sub>para</sub> measurement

EMG<sub>para</sub> was measured with patients in a semi-recumbent or seated position, as previously described.<sup>15</sup> After skin preparation, two surface electrodes (Blue Sensor Q, Ambu, St Ives, UK) were placed in the second intercostal spaces, immediately lateral to the sternum. The skin was marked to allow placement of electrodes in an identical position throughout the study. Nasal cannulae connected to a differential pressure transducer (Technical services, Lane Fox Respiratory Unit, London, UK) identified inspiration and expiration phases (figure 1). EMG<sub>para</sub> signals were amplified and sampled at 2 kHz (Dual Bioamp and Powerlab, AD Instruments, Chalgrove, UK). Signals were analysed using Labchart software (AD Instruments) on a personal computer. The peak root mean square EMG<sub>para</sub> activity for each inspiration was averaged over 1 min of tidal breathing and normalised to a value of EMG<sub>para</sub> obtained during a maximal inspiratory sniff manoeuvre, obtained before each measurement.<sup>15</sup> Two measures of NRD were derived, including (1) EMG<sub>para%max</sub>, the mean peak inspiratory tidal EMG<sub>para</sub> normalised to the maximal manoeuvre; and (2) NRDI (Neural Respiratory Drive Index), the product of EMG<sub>para%max</sub> and respiratory rate.<sup>15</sup>

### Study protocol

EMG<sub>para</sub>, modified Borg scale, FEV<sub>1</sub>, FVC and IC were measured at least daily, between admission and medical fitness for

**Figure 1** Representative trace of nasal pressure and second intercostal space parasternal electromyogram during tidal breathing in a patient with COPD during an exacerbation. P<sub>np</sub>, nasal pressure; EMG<sub>para</sub>, parasternal electromyogram; RMS<sub>para</sub>, root mean square of EMG<sub>para</sub>.



discharge, and at least 2 h after the last bronchodilator dose. Medical fitness for discharge was determined by the senior attending physician, which was either senior resident or consultant. Supplemental oxygen was provided as instructed by the attending physicians. Patients were settled at rest for 7 min before EMG<sub>para</sub> traces were acquired for analysis. Patients requiring non-invasive ventilation (NIV) had measurements taken after 10 min off NIV. The attending physicians, who were blinded to EMG<sub>para</sub> data, were asked to provide an opinion regarding clinical improvement or deterioration between successive assessments. EMG<sub>para</sub> data were analysed after patients' discharge from hospital. Data for readmissions and deaths were obtained from patients and their relatives, and from medical records. Admission-to-discharge changes in EMG<sub>para%max</sub> and NRDI were expressed as  $\Delta$ EMG<sub>para%max</sub> and  $\Delta$ NRDI, respectively. Changes in EMG<sub>para%max</sub> and NRDI between consecutive inpatient measurements were denoted  $\Delta$ EMG<sub>para%max,cons</sub> and  $\Delta$ NRDI<sub>cons</sub>, respectively.

### Primary endpoint and power calculation

Although this was an observational cohort study, an a priori primary endpoint of 28-day readmission was taken as this was considered to have major clinical relevance to the current financial penalty systems for readmission in the UK and USA. Secondary endpoints were 14-day readmission and clinical deterioration, defined by (1) at least one-point increase in Borg scale<sup>24</sup> between consecutive recordings, or (2) attending physician opinion. A sample size of 120 was determined from published pilot data<sup>15</sup> with a presumed 28-day readmission rate of 20% to detect a difference in NRDI of 203/min between readmitted and non-readmitted patients with a power of 80%.

### Statistical analysis

Paired data were analysed using t or Wilcoxon signed-rank tests. Readmitted and non-readmitted groups were compared using independent t or Mann–Witney U tests. Death after discharge without early readmission was analysed together with readmissions. Logistic regression and receiver-operator characteristic (ROC) analyses were used to identify, and test the utility of, predictors of readmission. Kaplan–Meier plots and log rank tests were used to analyse time to readmission. Generalised linear mixed model (GLMM) analyses were used to assess the association between  $\Delta$ EMG<sub>para%max,cons</sub> and episodes of worsening dyspnoea or with physician-defined deterioration. For the purposes of this study, death was analysed with the readmission data.

## RESULTS

### Admission, clinical course and readmission data

A total of 131 patients were enrolled between January 2011 and September 2013 (see online supplementary figure E1), and 120 patients completed the study between admission and discharge (table 1). Twenty (16.7%) patients were unable to perform FEV<sub>1</sub> and FVC manoeuvres at admission, while 27 (22.5%) patients could not perform admission IC manoeuvres. Three (2.5%) patients declined arterial blood gas sampling. Eight (6.7%) patients required NIV or high-dependency care following admission to hospital. There were no patients who received high-flow humidified oxygen therapy. A further three (2.5%) patients deteriorated more than 12 h after admission and required NIV. Median length of hospital stay was 3 (IQR 2–6) days. Median interval from the date of medical fitness for discharge to the date of discharge was 0 (IQR 0–1) days. One patient died 3 days after discharge from hospital.

**Table 1** Baseline characteristics at admission to hospital

Anthropometrics, smoking and previous exacerbations	
Age (years)	70 (9)
Male (%)	58 (48.3)
BMI (kg/m <sup>2</sup> )	25.3 (7.2)
Current smokers (%)	47 (39.2)
Smoking history (pack years)	40 (25–50)
Exacerbation frequency (/12 months)	3 (1–5)
Hospital admission frequency (/12 months)	1 (0–2)
Current exacerbation history	
Duration of symptoms (days)	4 (2–7)
Systemic steroids prior to admission (%)	26 (21.7)
Antibiotics prior to admission (%)	30 (25.0)
Comorbidities	
Ischaemic heart disease (%)	34 (28.3)
Cerebrovascular disease (%)	13 (10.8)
Hypertension (%)	53 (44.2)
Diabetes mellitus (%)	20 (16.7)
Disease severity	
GOLD stage 2 (%)*	4 (4)
GOLD stage 3 (%)*	36 (36)
GOLD stage 4 (%)*	60 (60)
MRC dyspnoea grade	4 (4–5)
Admission investigations	
Arterial blood gases†	
pH	7.39 (0.06)
p <sub>a</sub> CO <sub>2</sub> (kPa)	5.82 (1.39)
p <sub>a</sub> O <sub>2</sub> (kPa)	8.83 (2.98)
Bicarbonate (mEq/L)	25.7 (3.8)
Base excess (mmol/L)	0.63 (3.1)
Lactate (mmol/L)	1.7 (1.5)
Routine laboratory tests	
C-reactive protein (mmol/L)	65 (100)
Creatinine (μmol/L)	72 (45)
Fibrinogen (mmol/L)‡	4.6 (1.5)
Leucocytes (×10 <sup>3</sup> /μL)	11.9 (4.8)
Neutrophils (×10 <sup>3</sup> /μL)	8.4 (5.0)
Eosinophils (×10 <sup>3</sup> /μL)	0.3 (0.7)
Haemoglobin (g/dL)	13.8 (1.7)
Platelets (×10 <sup>9</sup> /L)	259 (87)
Radiographic consolidation	25 (20.8)
Length of hospital stay (days)	3 (2–6)
Deaths within 28 days (%)	1 (0.8)
Readmission within 28 days (%)	26 (21.7)
Deaths within 14 days (%)	1 (0.8)
Readmission within 14 days (%)	15 (12.5)

Mean (SD), Median (IQR) or N (%).

\*N=100.

†N=117.

‡N=68.

BMI, body mass index; GOLD, Global initiative for chronic Obstructive Lung Disease; MRC, Medical Research Council; P<sub>a</sub>CO<sub>2</sub>, arterial partial pressure of carbon dioxide; P<sub>a</sub>O<sub>2</sub>, arterial partial pressure of oxygen.

Fourteen-day and 28-day readmission rates were 12.5% and 21.7%, respectively. The single death was analysed with the readmission data.

**Early warning scores, symptom scores and physiological data**  
MEWS, modified Borg scale and CAT scores all improved from admission to discharge (table 2). FEV<sub>1</sub>, FVC and IC increased over this period, with a concomitant fall in EMG<sub>para%max</sub> and NRDI (table 2).

**Table 2** Physiological measurements at admission and discharge

	Admission	Discharge	p Value
<b>Spirometry</b>			
FEV <sub>1</sub> (L)*	0.69 (0.28)	0.75 (0.31)	<0.001
FVC (L)*	1.51 (0.56)	1.63 (0.54)	0.02
FEV <sub>1</sub> /%predicted (%)*	30.5 (11.2)	33.7 (12.2)	<0.001
FEV <sub>1</sub> /FVC ratio (%)*	47.4 (12.8)	48.9 (13.2)	0.184
Inspiratory capacity (L)†	1.39 (0.58)	1.56 (0.63)	<0.001
<b>Symptom scores</b>			
Modified Borg scale	3 (2–5)	2 (1–3)	<0.001
COPD assessment test	29 (24–32.75)	24 (17–29)	<0.001
<b>Routine observations</b>			
S <sub>p</sub> O <sub>2</sub> (%)	92.6 (3.5)	93.4 (2.8)	0.024
Temperature (°C)	36.5 (0.6)	36.3 (0.5)	0.023
Heart rate (/min)	97.2 (15.8)	84.8 (12.9)	<0.001
Respiratory rate (/min)	23.1 (4.3)	20.4 (2.4)	0.024
MEWS	3 (2–5)	2 (1–3)	<0.001
<b>Parasternal EMG parameters</b>			
Sniff (maximum) EMG (μV)	74.8 (37.3)	76.5 (39.1)	0.35
EMG <sub>para%max</sub> (%)	17.4 (8.2)	15.8 (7.3)	0.017
NRDI (/min)	372 (205)	329 (196)	0.018

Values are expressed as mean (SD) or median (IQR).

\*N=100.

†N=93.

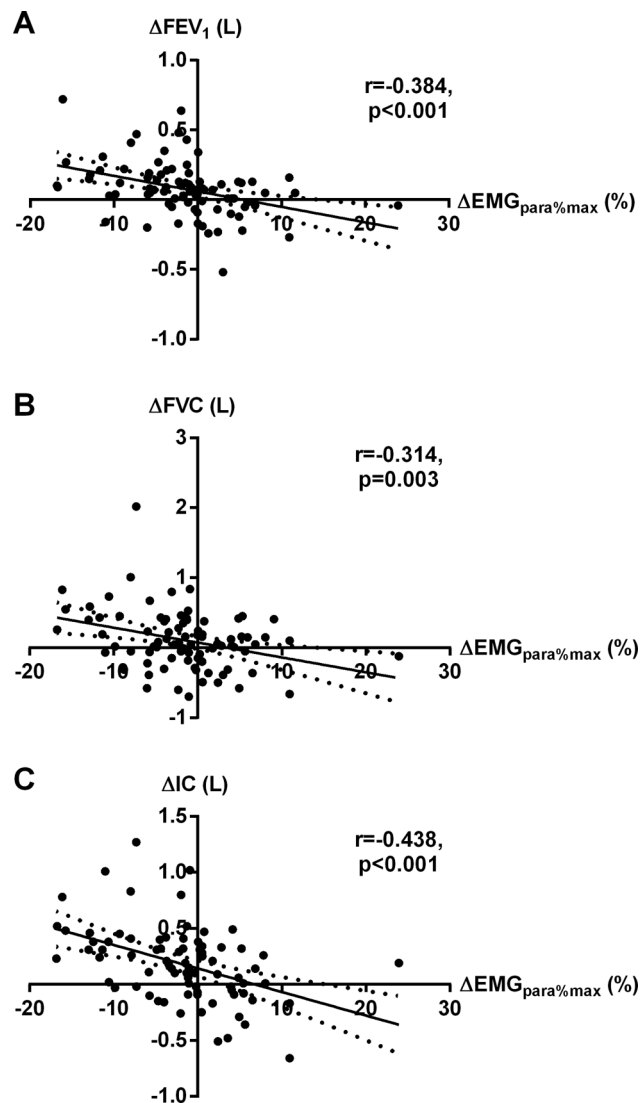
EMG, electromyography; MEWS, medical early warning score; NRDI, Neural Respiratory Drive Index; S<sub>p</sub>O<sub>2</sub>, transcutaneous oxygen saturation.

### Relationship between NRD, physiological parameters and dyspnoea

Admission-to-discharge change ( $\Delta$ ) in EMG<sub>para%max</sub> was inversely correlated with  $\Delta$ FEV<sub>1</sub> ( $r=-0.38$ ,  $p<0.001$ ),  $\Delta$ FVC ( $r=-0.31$ ,  $p=0.003$ ) and  $\Delta$ IC ( $r=-0.44$ ,  $p<0.001$ ) (figure 2). However, there was no correlation between  $\Delta$ EMG<sub>para%max</sub> and  $\Delta$ modified Borg scale,  $\Delta$ CAT score or  $\Delta$ MEWS. Increases in FEV<sub>1</sub> and IC were independently associated with reductions in EMG<sub>para%max</sub> on multiple linear regression analysis ( $\Delta$ FEV<sub>1</sub> standardised coefficient  $\beta=-0.36$ ,  $p=0.001$ ;  $\Delta$ IC  $\beta=-0.26$ ,  $p=0.019$ ).  $\Delta$ EMG<sub>para%max</sub> was weakly correlated with age ( $r=+0.24$ ,  $p=0.009$ ).  $\Delta$ NRDI was weakly inversely correlated with  $\Delta$ FEV<sub>1</sub> ( $r=-0.30$ ,  $p=0.004$ ),  $\Delta$ FVC ( $r=-0.29$ ,  $p=0.007$ ) and  $\Delta$ IC ( $r=-0.40$ ,  $p<0.001$ ), as well as with body mass index ( $r=-0.27$ ,  $p=0.005$ ). There were no correlations between  $\Delta$ NRDI and  $\Delta$ Borg scale or  $\Delta$ MEWS.

### Predictors of readmission within 28 days

Twenty-seven (22.5%) patients were readmitted or died within 28 days of hospital discharge. Independent sample analysis showed significant differences in age, MRC grade, admission haemoglobin levels, hospital admission frequency in the previous 12 months (admission frequency),  $\Delta$ EMG<sub>para%max</sub> and  $\Delta$ NRDI between readmitted and non-readmitted groups at 28 days (table 3). There were no significant differences in the values of EMG<sub>para%max</sub> and NRDI at discharge between the two groups. With the exception of the MRC grade, univariate analysis demonstrated that all of these parameters predicted readmission at 28 days (table 4). However, in multivariable stepwise logistic regression analysis, only age and admission frequency predicted 28-day readmission (adjusted OR 1.08, 95% CI 1.03 to 1.14,  $p=0.004$ , and adjusted OR 1.29, 95% CI 1.01 to 1.66;  $p=0.043$ , respectively). Change in EMG<sub>para%max</sub> between admission and discharge did not predict 28-day readmission in the whole cohort. The rate of radiographic



**Figure 2** Relationship between admission-to-discharge change in EMG<sub>para%max</sub> and changes in (A) FEV<sub>1</sub>, (B) FVC and (C) IC. EMG<sub>para%max</sub>, 1 min mean magnitude of rectified inspiratory parasternal EMG activity normalised to a maximal manoeuvre; IC, inspiratory capacity.

consolidation was not significantly different between the two groups (11.1% for the readmitted vs 23.7% for the non-readmitted group;  $p=0.16$ ).

In accordance with the correlation, albeit weak, between  $\Delta$ EMG<sub>para%max</sub> and age, a post hoc, exploratory analysis was performed among patients below an arbitrary age cut-off of 85 years ( $n=112$ ). There were 23 (20.5%) readmissions within 28 days among these patients. Under these circumstances, older age (adjusted OR 1.10, 95% CI 1.02 to 1.16;  $p=0.017$ ) and increasing EMG<sub>para%max</sub> between admission and discharge (adjusted OR 1.09, 95% CI 1.01 to 1.18,  $p=0.023$ ) were predictive of 28-day readmission. ROC analysis for the prediction of 28-day readmission in patients under 85 years produced an area under the ROC curve (AUC) of 0.70 for age and 0.66 for  $\Delta$ EMG<sub>para%max</sub>.

### Predictors of readmission within 14 days

Sixteen (13.3%) patients were readmitted or died within 14 days of discharge. There were differences in MRC grade and

**Table 3** Differences between readmitted and non-readmitted patients within 28 days

	28-day readmission N=27	Non-readmitted at 28 days N=93	p Value
Age (years)	75 (9)	68 (9)	0.001
MRC dyspnoea grade	5 (4–5)	4 (3–5)	0.013
Admission frequency (/12 months)	1 (1–3)	0 (0–2)	0.006
Admission haemoglobin (g/dL)	13.1 (1.8)	14.0 (1.7)	0.017
$\Delta$ EMG <sub>para%max</sub> (%)	+1.5 (8.4)	–2.4 (7.2)	0.018
$\Delta$ NRDI (/min)	+28 (217)	–64 (189)	0.032
$\Delta$ Modified Borg scale	–2 (–2.5 to –2)	–1 (–3 to –1)	0.58
$\Delta$ CAT	–7 (–12 to 0)	–5 (–9 to 0)	0.30
$\Delta$ Respiratory rate (/min)	–3.2 (5.3)	–2.6 (4.0)	0.50

Values are expressed as mean (SD) or median (IQR).  
CAT, COPD Assessment Test; EMG<sub>para%max</sub>, 1 min mean magnitude of rectified inspiratory parasternal EMG activity normalised to a maximal manoeuvre; MRC, Medical Research Council; NRDI, Neural Respiratory Drive Index.

$\Delta$ EMG<sub>para%max</sub> between the readmitted and non-readmitted groups (table 5), but MRC grade did not predict 14-day readmission in the univariate logistic regression model (table 6). Only admission-to-discharge increases in EMG<sub>para%max</sub> (adjusted OR 1.12, 95% CI 1.03 to 1.21,  $p=0.005$ ) predicted 14-day readmission on multivariable stepwise logistic regression analysis. ROC analysis for the prediction of 14-day readmission gave an AUC of 0.70 for  $\Delta$ EMG<sub>para%max</sub>. By contrast, AUC for  $\Delta$ FEV<sub>1</sub> and  $\Delta$ IC were 0.57 and 0.56, respectively (figure 3). The failure of  $\Delta$ EMG<sub>para%max</sub> to fall by more than 3.1% between admission and discharge had a sensitivity of 93.8% and a specificity of 41.3% to detect 14-day readmission, with a positive predictive value (PPV) of 19.7% and a negative predictive value (NPV) of 97.7%. Again, there was a non-significant difference in the rate of radiographic consolidation between the groups (6.25% for the readmitted vs 23.1% for the non-readmitted group,  $p=0.123$ ). Kaplan–Meier analysis showed that patients whose EMG<sub>para%max</sub> failed to fall by less than 3.1% between admission and discharge had a shorter time to readmission than those whose EMG<sub>para%max</sub> fell by more than 3.1% (log rank test  $p=0.03$ ) (figure 4).

When  $\Delta$ NRDI was used instead of  $\Delta$ EMG<sub>para%max</sub> in the regression model as a measure of NRD, it also predicted 14-day readmission or death ( $\Delta$ NRDI: OR 1.003, 95% CI 1.001 to

**Table 4** Univariate logistic regression analysis for predictors of 28-day readmission

	OR	p Value	95% CI
Age	1.09	0.002	1.03 to 1.15
Hospital admission frequency	1.35	0.013	1.07 to 1.71
Haemoglobin	0.73	0.020	0.56 to 0.95
$\Delta$ EMG <sub>para%max</sub>	1.08	0.022	1.01 to 1.15
$\Delta$ NRDI	1.002	0.036	1.000 to 1.005
$\Delta$ Modified Borg scale	1.07	0.49	0.88 to 1.29
$\Delta$ CAT	0.98	0.82	0.93 to 1.03
$\Delta$ Respiratory rate	0.97	0.50	0.88 to 1.07

CAT, COPD Assessment Test; EMG<sub>para%max</sub>, 1 min mean magnitude of rectified inspiratory parasternal EMG activity normalised to a maximal manoeuvre; NRDI, neural respiratory drive index.

**Table 5** Differences between readmitted and non-readmitted survivors and non-readmitted survivors within 14 days

	14-day readmission or death N=16	Non-readmitted at 14 days N=104	p Value
MRC dyspnoea grade	5 (4–5)	4 (4–5)	0.039
$\Delta$ EMG <sub>para%max</sub> (%)	+3.6 (8.3)	–2.3 (7.2)	0.003
$\Delta$ NRDI (/min)	+71 (221)	–61 (190)	0.012
$\Delta$ Modified Borg scale	–0.25 (–2 to 1)	–1 (–3 to 0)	0.12
$\Delta$ CAT	–8.5 (–11 to –2)	–5 (–9 to 1)	0.16
$\Delta$ Respiratory rate (/min)	–2.6 (3.5)	–2.8 (4.4)	0.87

Values are expressed as mean (SD) or median (IQR).  
CAT, COPD Assessment Test; EMG<sub>para%max</sub>, 1 min mean magnitude of rectified inspiratory parasternal EMG activity normalised to a maximal manoeuvre; MRC, Medical Research Council; NRDI, Neural Respiratory Drive Index.

1.006,  $p=0.01$ ). ROC analysis for the prediction of 14-day readmission gave an AUC of 0.70 for NRDI.

### Detection of in-hospital clinical deterioration

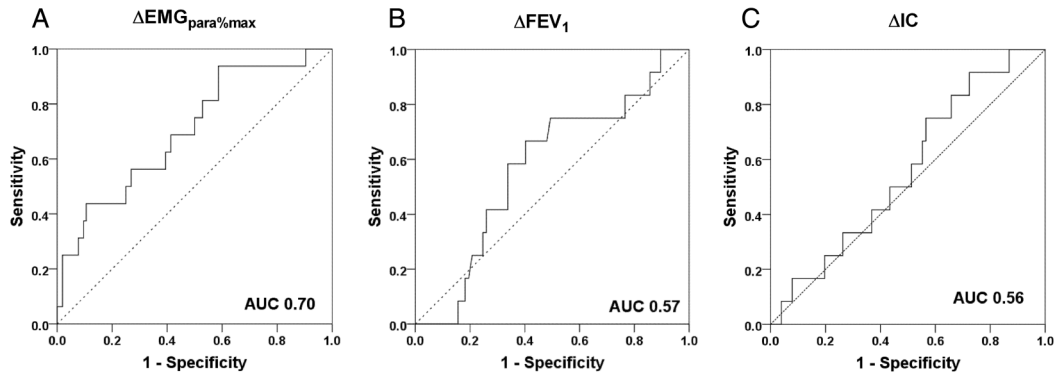
A total of 475 pairs of consecutive EMG<sub>para</sub> data were acquired from the 122 patients who provided at least one pair of analysable data; although 120 patients completed investigations between hospital admission and discharge, two further patients gave at least one pair of analysable data before withdrawal from the study. Patients had a median of three pairs of measurements (range 1–23) between admission and discharge. There were 116 episodes of worsening dyspnoea, defined as at least one-point increase in Borg scale. On univariate GLMM analysis, an increase in MEWS ( $\Delta$ MEWS<sub>cons</sub>) and in EMG<sub>para%max</sub> ( $\Delta$ EMG<sub>para%max,cons</sub>) between consecutive recordings was associated with symptomatic deterioration (table 7). Multivariable GLMM analysis showed that  $\Delta$ MEWS<sub>cons</sub> (adjusted OR 1.36, 95% CI 1.01 to 1.84,  $p=0.04$ ) and  $\Delta$ EMG<sub>para%max,cons</sub> (adjusted OR 1.07, 95% CI 1.01 to 1.14,  $p=0.027$ ) were independently associated with worsening of dyspnoea. Multivariable GLMM analysis showed that  $\Delta$ EMG<sub>para%max,cons</sub> (coefficient 0.05, 95% CI 0.01 to 0.09,  $p=0.024$ ) and  $\Delta$ IC<sub>cons</sub> (coefficient –1.11, 95% CI –2.19 to –0.03,  $p=0.044$ ) were independently associated with changes in Borg scale of any magnitude between consecutive recordings.

There were 35 episodes of physician-defined deterioration. Only an increase in EMG<sub>para%max</sub> between consecutive measurements was associated with physician-defined deterioration ( $\Delta$ EMG<sub>para%max,cons</sub> OR 1.030, 95% CI 1.003 to 1.055,  $p=0.03$ ).

**Table 6** Univariate logistic regression analysis for predictors of 14-day readmission

	OR	p Value	95% CI
MRC dyspnoea grade	1.86	0.09	0.92 to 3.76
$\Delta$ EMG <sub>para%max</sub>	1.12	0.005	1.03 to 1.21
$\Delta$ NRDI	1.003	0.014	1.001 to 1.006
$\Delta$ Modified Borg scale	1.23	0.10	0.96 to 1.57
$\Delta$ CAT	0.99	0.67	0.92 to 1.05
$\Delta$ Respiratory rate (/min)	1.01	0.87	0.89 to 1.15

Values are expressed as mean (SD) or median (IQR).  
CAT, COPD Assessment Test; EMG<sub>para%max</sub>, 1 min mean magnitude of rectified inspiratory parasternal EMG activity normalised to a maximal manoeuvre; MRC, Medical Research Council; NRDI, Neural Respiratory Drive Index.



**Figure 3** Receiver-operator curves for prediction of 14-day readmission for (A)  $\Delta\text{EMG}_{\text{para}\%_{\text{max}}}$ , (B)  $\Delta\text{FEV}_1$ , and (C)  $\Delta\text{IC}$ .  $\text{EMG}_{\text{para}\%_{\text{max}}}$ , 1 min mean magnitude of rectified inspiratory parasternal EMG activity normalised to a maximal manoeuvre; IC, inspiratory capacity; ROC, receiver-operator curve; AUC, area under the receiver-operator curve.

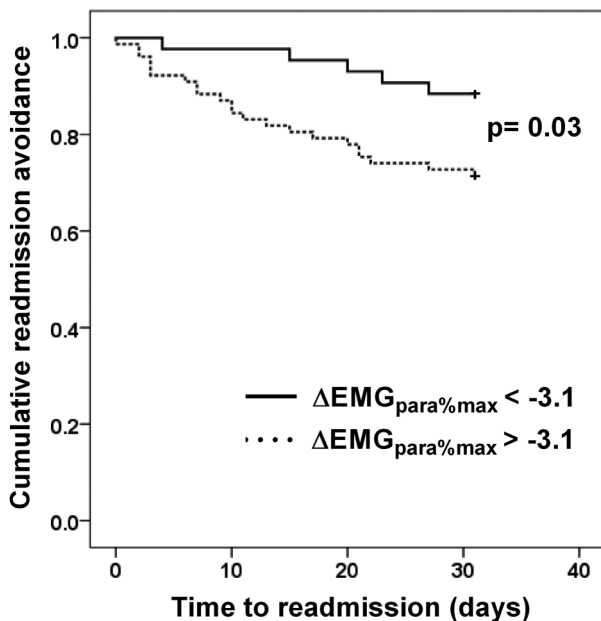
**DISCUSSION**

In this single-centre validation study of an advanced physiological biomarker performed in an unselected cohort of acutely unwell patients with COPD, the failure of NRD to fall between admission and discharge predicted readmission within 14 days of discharge. Furthermore, this failure was predictive of readmission within 28 days in those patients under 85 years of age, but not in the cohort as a whole. In addition to the utility of this test to predict clinical outcome following hospital discharge, an increase in NRD between consecutive daily measurements detected episodes of worsening dyspnoea and physician-defined in-hospital clinical deterioration. The physiological rationale of employing NRD was strongly supported by the relationship with change in respiratory muscle physiological load between admission and discharge.

**Critique of the method**

Every attempt was made to enrol consecutive eligible patients with a screening to recruitment ratio of 3.4:1 achieved, which is acceptable for such an observational detailed physiological study. Few of the patients enrolled into this study required non-invasive or invasive ventilation at admission, which adds to the generalisability of this study and indeed the current cohort was wholly representative of UK patients admitted to the acute medical wards.<sup>2</sup> Patients presenting in acute hypercapnic respiratory failure were frequently unable to provide written informed consent, and the study did not have ethical approval for proxy assent and retrospective patient consent.

In line with our previous work,<sup>15</sup> up to one-fifth of patients were unable to perform forced respiratory manoeuvres at admission, which supports the clinical rationale for non-invasive measurements, such as  $\text{EMG}_{\text{para}}$ , being performed during resting tidal breathing. This could be accommodated into the routine monitoring of acutely unwell patients with COPD as a measure of the respiratory load–capacity balance. The acquisition of respiratory EMG needs to be performed in a standardised manner as variations in electrode position and skin preparation can have a small influence on the magnitude of the signals; however, we have previously published data demonstrating the reproducibility of  $\text{EMG}_{\text{para}}$ .<sup>15 18</sup> Although there was variability in the value of the maximal EMG obtained during the sniff procedure between admission and discharge (see online supplementary figure E2), there was no overall increase during the course of the hospital stay and therefore it is unlikely that the reduction in  $\text{EMG}_{\text{para}\%_{\text{max}}}$  between admission and discharge was driven by a fall in the maximal  $\text{EMG}_{\text{para}}$ .



**Figure 4** Time-to-readmission Kaplan–Meier plots for patients whose  $\text{EMG}_{\text{para}\%_{\text{max}}}$  fell by more than 3.1% between admission and discharge (solid line), and those whose  $\text{EMG}_{\text{para}\%_{\text{max}}}$  fell by less than 3.1% (dotted line).  $\text{EMG}_{\text{para}\%_{\text{max}}}$ , 1 min mean magnitude of rectified inspiratory parasternal EMG activity normalised to a maximal manoeuvre.

**Table 7** Generalised linear mixed modelling analysis for factors associated with clinical deterioration in symptoms as defined by  $\geq 1$  point increase in Borg scale

	Adjusted OR	p Value	95% CI
$\Delta\text{MEWS}_{\text{cons}}$	1.157	0.048	1.001 to 1.338
$\Delta\text{EMG}_{\text{para}\%_{\text{max,cons}}}$ (%)	1.05	0.001	1.02 to 1.08

$\Delta\text{EMG}_{\text{para}\%_{\text{max,cons}}}$ , change in  $\text{EMG}_{\text{para}\%_{\text{max}}}$  between consecutive inpatient measurements;  $\text{EMG}_{\text{para}\%_{\text{max}}}$ , 1-min mean magnitude of rectified inspiratory parasternal EMG activity normalised to a maximal manoeuvre;  $\Delta\text{MEWS}_{\text{cons}}$ , change in modified early warning score between consecutive measurements.

### Clinical applicability of the findings

#### Readmission within 14 days

Although the cut-off level for  $\Delta\text{EMG}_{\text{para}\% \text{max}}$  of  $-3.1\%$  has a low PPV for 14-day readmission, the high NPV indicates that NRD has clinical utility as a risk-stratification tool for patients with COPD being discharged from hospital. Patients whose  $\text{EMG}_{\text{para}\% \text{max}}$  falls by more than  $3.1\%$  during hospital admission are at very low risk of 14-day readmission and indeed these patients have greater time to readmission. The selected cut-off value is similar in magnitude to the fall in  $\text{EMG}_{\text{para}\% \text{max}}$  observed amongst non-readmitted patients in the pilot study of Murphy *et al*,<sup>15</sup> indicating the reproducibility of this technique. Pharmacological and technological therapies could be used in future studies to target a reduction in  $\text{EMG}_{\text{para}}$ , with the aim of optimising pulmonary mechanics, which could potentially reduce readmission rates. The cut-off value of  $-3.1\%$  requires further prospective validation to become a useful clinical tool.

#### Readmission within 28 days

The admission-to-discharge change in NRD failed to predict 28-day readmission across all age groups. This is perhaps unsurprising as several previous studies have shown that age<sup>25 26</sup> and admission frequency<sup>8 27</sup> are strongly predictive of readmission. In elderly patients, functional impairment and the burden of chronic disease<sup>28</sup> play a major role in influencing readmission and, in the current study, it appears to be more influential than the failure to enhance the respiratory muscle load–capacity balance. The current data support the concept that the inpatient trajectory of NRD was a key factor influencing 14-day readmission in all age groups and 28-day readmission in those patients less than 85 years of age. Early readmission, under these circumstances, indicates a failure of the inpatient treatment to modify the airways obstruction and lung hyperinflation, and thereby to ameliorate the respiratory muscle load–capacity balance. Future studies should focus on strategies to modify the load–capacity balance and reduce NRD with the aim of promoting safe discharge. The authors acknowledge the limitations of the post-hoc application of an age cut-off of 85 years and wholly appreciate that this is an exploratory analysis and prospective validation will be required to assess 28-day readmission. However, this does not detract from the potential clinical implications of this approach and this analysis ensures that the appropriate target patient group are recruited into any future trials.

#### Clinical deterioration during admission

We have shown that increases in  $\text{EMG}_{\text{para}}$  predicted worsening of dyspnoea during hospital admission. NRD has the potential to be used to deliver enhanced monitoring for patients who are either unable to communicate their clinical condition effectively or those who fail to recognise the severity of their symptoms, which is a priority in healthcare systems where clinical resources, in terms of nursing and other clinical personnel, are increasingly being rationed. Although Murphy *et al*<sup>15</sup> found that  $\text{EMG}_{\text{para}}$  distinguished between physician-defined improvement and deterioration, this was only in a small number of episodes. We have reproduced these findings in a much larger unselected cohort. Importantly,  $\Delta\text{EMG}_{\text{para}\% \text{max}}$  was the only parameter that correlated with physician-defined deterioration, supporting NRD as a physiological biomarker for the early identification of treatment failure.

#### Physiological validity of NRD in the acute setting

In this cohort of acutely unwell patients with COPD, we observed a correlation between  $\Delta\text{EMG}_{\text{para}\% \text{max}}$  and  $\Delta\text{FEV}_1$ , supporting the hypothesis that  $\text{EMG}_{\text{para}}$  reflects the resistive

load imposed on the respiratory system during an acute exacerbation. Furthermore, there was a direct relationship between  $\Delta\text{EMG}_{\text{para}\% \text{max}}$  and  $\Delta\text{IC}$ , indicating that changes in the elastic and threshold loads imposed by hyperinflation can be detected by  $\text{EMG}_{\text{para}}$ . It appears therefore, that  $\text{EMG}_{\text{para}}$  reflects the changes in pulmonary mechanics that accompany an exacerbation of COPD. While the reduction in NRD with decreasing hyperinflation may be due, in part, to the increase in respiratory muscle length, rather than due to a reduction in NRD,<sup>29</sup> animal studies of parasternal intercostal muscle activation at high lung volume have shown that parasternal muscle EMG tends to remain stable despite acute lung hyperinflation.

### CONCLUSION

During recovery from an acute exacerbation of COPD requiring hospital admission, change in NRD from admission to discharge predicted 14-day readmission in all age groups and 28-day hospital readmission in patients under 85 years old. In addition, change in NRD between successive inpatient measurements was able to detect worsening dyspnoea and physician-defined clinical deterioration. Second intercostal space parasternal EMG is a novel advanced physiological monitoring tool that may be clinically useful in identifying treatment failure during hospital admission and for predicting safe discharge, which is a priority for all acute healthcare organisations.

**Contributors** Study concept and design: E-SS, PBM, MIP, NSH, GR, JM, NH. Acquisition, analysis or interpretation of data: E-SS, SM, MR, RH, MK, KO, KH, AD and NH. Drafting of the manuscript: E-SS, SM, PBM, NH. Critical revision of the manuscript for important intellectual content: RH, MR, MK, AD, MIP, KO, KH, NSH, GR, JM and NH. Statistical analysis: E-SS, SM, AD. Obtained funding: NH. Administrative, technical or material support: SM, RH, MR, KH, KO, GR. Study supervision: NH, JM.

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