ERJ Express. Published on August 29, 2013 as doi: 10.1183/09031936.00110913

Detection and severity grading of COPD exacerbations using the Exacerbations of Chronic Obstructive Pulmonary Disease Tool (EXACT)

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Running Title: EXACT to detect and grade COPD exacerbations

Key words: COPD, Exacerbations, Severity, Outcomes Assessment, Respiratory Questionnaire

Take home message:

The EXACT is an effective method to assess exacerbation severity but uncertainty remains over its ability to detect exacerbations.

Abstract

Background: Uncertainty exists over the ability of the Exacerbations of Chronic Obstructive Pulmonary Disease Tool (EXACT) patient-reported outcome diary to quantify exacerbation severity and frequency. To clarify this we investigated the ability of the EXACT to assess severity of exacerbations and examined the relationship between exacerbations diagnosed using London COPD cohort diary cards, physician review and symptom-defined events using the EXACT.

Methods: 58 patients enrolled in the London COPD cohort prospectively completed the EXACT during 128 cohort diary card-defined exacerbations between January 2010 and April 2012.

Results: Mean EXACT scores increased from 42.6 (SD 8.6) at baseline to 48.0 (8.6) at exacerbation onset ($p<0.001$), and rose further to a maximum score of 54.1 (8.9). Maximum EXACT scores were significantly higher in treated than untreated events. Time taken for EXACT scores to return to baseline was significantly related to symptom recovery time as judged by London COPD cohort diary cards, and to PEFR recovery. Approximately 50% of both diary card-defined and HCU exacerbations crossed the EXACT event threshold. However, only 27.9% of diary-card defined and 34.6% of HCU exacerbations fully met the criteria for an EXACT event. Patients exhibited smaller rises in EXACT score at exacerbation as baseline disease severity increased.

Conclusion: The EXACT is an effective method of evaluating COPD exacerbation severity. However, concerns remain about the ability of the EXACT to accurately detect exacerbations.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is associated with episodes of symptomatic deterioration termed exacerbations (1). COPD exacerbations are amongst the commonest causes of medical admission to hospital (2). Patients with frequent exacerbations (3) have accelerated lung function decline (4, 5), worse quality of life (6), are at increased risk of cardiovascular events (7) and have greater mortality (8).

Assessment of exacerbation severity is an important outcome measure in COPD and most clinical trials of preventive therapy to date have used a dichotomous approach to assigning severity levels, with outpatient drug therapy (antibiotics and/or steroids) categorized as "moderate" and hospitalisations labelled "severe". These outcome measures are limited by inaccurate reporting, lack of generalisability across different healthcare systems and their failure to capture unreported exacerbations. Unreported exacerbations are common (6, 9, 10) and important events, associated with worsening quality of life (6, 9) and increased risk of subsequent hospitalisation (11).

Exacerbation symptoms systematically recorded on daily diary cards accurately detect both reported and unreported exacerbations (6, 12), but most symptom diary cards are not sensitive enough to assess severity of these events. The FDA's patient-reported outcome (PRO) guidance document (13) offers recommendations for developing PRO instruments for use in medical product development, including symptom-based methods for standardizing the severity of reported and unreported exacerbations.

The Exacerbations of Chronic Obstructive Pulmonary Disease Tool (EXACT) is a PRO daily symptom diary developed to capture frequency, severity, and duration of exacerbations in clinical trials of COPD (14). Scores range from 0 to 100, with higher scores indicating more severe symptoms. To date, no published data have examined the relationship between EXACT scores and pulmonary function or markers of inflammation during exacerbations. Furthermore, the EXACT was designed to quantify the evaluation of exacerbations of COPD. Specifically, the intent was to capture unreported events, using a threshold-based definition of sustained symptomatic worsening, and provide a standardized metric for evaluating the severity of unreported and reported, healthcare utilisation (HCU) events. However, in published papers thus far, no data has been reported examining the relationship between symptom-defined events captured by the EXACT, exacerbations detected by London COPD cohort symptom diary cards, and HCU events.

We hypothesised that the EXACT can accurately assess the severity of both reported and unreported COPD exacerbations, defined by the London COPD cohort diary card, as measured by exacerbation length, lung function impairment and systemic inflammation. Furthermore, we sought to examine the relationship between exacerbations diagnosed using validated London COPD cohort diary cards (4, 6, 12) and physician review, and symptom-defined events captured by the EXACT. Therefore, we prospectively administered the EXACT to patients in a well characterised COPD cohort.

METHODS

Patient recruitment

This study involved 58 COPD patients enrolled in the London COPD cohort between January 2010 and April 2012. At annual review or recruitment between 01/04/2009 and 26/5/2012 a full medical history and examination was obtained. Patients were included if the post-bronchodilator forced expiratory volume in 1 second (FEV_1) was ≤80% predicted from age, height, and sex and FEV_1/forced vital capacity (FVC) ratio was <0.7 (15). Patients with a history of any other significant respiratory diseases were excluded, as were those unable to complete daily diary cards.

Ethical approval for the study was granted from the Royal Free Hospital research ethics committee and all patients gave written informed consent. Permission to use the EXACT questionnaire was obtained from United BioSource Company (UBC, Bethesda, MD, USA).

Monitoring and Definition of Exacerbations

Patients were asked to record daily peak expiratory flow rate (PEFR) and any increase in respiratory symptoms on London COPD cohort diary cards. An exacerbation was defined as an increase for two consecutive days in respiratory symptoms, with at least one major symptom (dyspnoea, sputum purulence or sputum volume) plus either another major or a minor symptom (wheeze, cold, sore throat, and cough), the first of which was defined as the day of onset of the exacerbation. Symptom counts were obtained by summating each increased respiratory symptom recorded on diary cards per day (12).

Exacerbation duration was defined as the number of days after onset that worsening symptoms persisted. The last day of recorded worsening symptoms before two consecutive symptom-free days defined the end of the exacerbation. Exacerbation recovery was not determinable if patients failed to record diary card symptoms or continuously recorded symptoms for more than 99 days after onset. Exacerbation frequency was calculated for each patient using diary card data obtained between 1/4/2010 and 1/4/2012. For recently recruited patients with less than one year diary data, exacerbation frequency was based on the number of exacerbations the patient recalled for the year prior to recruitment (16) (see online supplement for further details).

Exacerbation Assessment

Exacerbations were treated according to the prevailing guidelines and clinical judgment with increased inhaled therapy, antibiotics and/or oral steroids. Neither the magnitude of exacerbation EXACT score nor the diary card symptom score played any role in treatment decisions. When patients attended for an exacerbation, venous blood samples were taken and spirometry performed prior to commencing exacerbation treatment. Serum C-reactive protein (CRP) was measured using Modular Analytics E 170 Module (Roche, Burgess Hill, UK).

EXACT administration

Patients completed a paper version of the EXACT at least once under supervision in clinic and were instructed to complete the EXACT diary each evening before bedtime, based on their symptoms experienced that day. Patients prospectively completed the EXACT on a daily-basis when stable and continued long-term to enable capture of the exacerbation prodrome, the onset of the event, its nadir and recovery. Patients in the analysis completed at least one EXACT at both the symptomatic onset of an exacerbation and during a baseline

period -14 to -8 days before onset. The median number of EXACT questionnaires completed per person was 196 (IQR 106-311). Each patient's baseline value was represented by the mean value recorded during the stable state (median 7 days (IQR 7-7) of data recorded during baseline period). As specified in the User Manual, EXACT events were defined as a 12 point increase above baseline for 2 consecutive days or 9 point increase for 3 days. For the purposes of this study, we defined EXACT recovery as the time taken from exacerbation onset for the EXACT score to return to baseline value.

Statistical analysis

Data were analysed with STATA 8.2 (Stata Corporation, Texas, USA). Normally distributed data were expressed as mean and standard deviation (SD) and skewed data as median and interquartile range (IQR). Comparisons were made by paired Student t-test or Wilcoxon signed-rank test. The relationship between exacerbation frequency, determined using London COPD cohort diary cards, and baseline EXACT scores was examined with a negative binomial regression model, whilst Poisson regression was used to model exacerbation recovery and EXACT scores. Cross-sectional regression models were used to analyse the relationship between CRP levels during exacerbation and EXACT score as allowance could be made for repeated measures on the same patient. Total net EXACT recovery score of an exacerbation was created to give a novel measure of exacerbation severity which reflects the overall symptomatic intensity of an exacerbation. Total net EXACT recovery score of an exacerbation was calculated as the sum of daily mean change from baseline EXACT scores from exacerbation onset to symptomatic resolution as judged by London COPD cohort diary cards (see online data supplement for further explanation, **Figure E1**).

RESULTS

Patient Characteristics

Full baseline clinical characteristics of the 58 patients included in this analysis are reported in **Table 1**, which demonstrates that patients had moderate to severe COPD with a mean FEV_1 % predicted of 48.6%.

Baseline Studies

Baseline EXACT scores were significantly related to disease severity. These baseline EXACT scores in 58 patients were significantly correlated with London COPD cohort diary card exacerbation frequency (rho=0.38, p=0.003), FEV_1 (rho=-0.32, p=0.015) and FEV_1% predicted (rho=-0.30, p=0.020).

Exacerbation Studies

58 patients completed the EXACT during 128 London COPD cohort diary card exacerbations. 85 of 128 (66.4%) were treated with systemic therapy; 82 (64.1%) with antibiotics and 64 (50.0%) with oral corticosteroids. There were no hospitalised exacerbations.

The baseline mean EXACT score averaged over 7 days (-14 to -8 days before exacerbation onset) was 42.6 (SD 8.6). This increased to 48.0 (8.6) at London COPD cohort diary card exacerbation onset, 5.4 (7.1) above baseline ($p<0.001$), representing a 13% rise. EXACT scores increased further to a maximum score of 54.1 (8.9) or 11.4 (7.6) above baseline ($p<0.001$), during the 2 weeks following exacerbation onset (**Figure 1**). The median time from exacerbation onset to peak EXACT score was 3 days (IQR 1-5.5). No difference was seen in the maximum increase from onset in EXACT score between type 1 Anthonisen

exacerbations (events associated with increased sputum volume, purulence and dyspnoea) and other types (n=27, 6.6 (6.3) vs. n=101, 5.9 (5.4), p=0.541).

Relationship between EXACT score and systemic inflammation

EXACT score changes at exacerbation presentation were significantly related to concurrent levels of systemic inflammation. At exacerbation, $\log_{10}$CRP was related to the change in EXACT score from baseline to exacerbation (rho=0.30; p=0.041, **Figure 2**). The median exacerbation CRP score was 9 (IQR 4.3-16.8).

Evolution of EXACT scores during exacerbation recovery

EXACT scores accurately reflected exacerbation recovery. The time taken for EXACT scores to return to baseline (median 7 days, IQR 0-12; n=93) was significantly related (rho=0.44; p<0.001) to symptom recovery time as judged by London COPD cohort diary cards (median 8 days, IQR 4-12; n=114). Recovery in EXACT was also significantly correlated with lung function recovery as measured by PEFR (rho=0.32; p=0.003). Time course plots of recovery of EXACT score, London COPD cohort diary card symptom counts and peak expiratory flow rate (PEFR) generated using daily mean values of all 128 exacerbations are presented in **Figure 3(a), (b) and (c)** respectively.

Relationship between EXACT scores and exacerbation treatment

No difference was observed in exacerbation onset EXACT scores between treated (systemic therapy) and untreated (no systemic therapy) events (n=85, mean 48.2 (8.5) vs. n=43, 47.7

(9.0), p=0.762). However, maximum EXACT scores were significantly higher in treated than untreated events (n=85, mean 55.2 (9.1) vs. n=43, 51.8 (8.1), p=0.040, **Figure 4a**).

Time course of EXACT scores during treated and untreated exacerbations

Median time from exacerbation onset to initiation of systemic therapy for the 85 treated exacerbations was 2 days (1-4). Despite the higher maximum EXACT score following exacerbation onset, no significant difference was seen between treated and untreated exacerbations in EXACT recovery time (n=61, median 7 days (0-12) vs. n=32, 5.5 (2-12), p=0.656, **Figure 4b**) or total net EXACT recovery score (n=61, median 24.2 EXACT.day (0-75.3) vs. n=32, 13.1 (1.5-65.9), p=0.455).

EXACT Concordance

Relationship between EXACT scores and London COPD cohort diary card-defined exacerbations

58 patients had 128 London COPD cohort diary card defined exacerbations, 27 of which (21.1%) attained a 12 point increase in EXACT score above baseline for 2 consecutive days. 34 of 128 (26.6%) of exacerbations attained a 9 point increase for 3 consecutive days. 57 (44.5%) of 128 exacerbations attained a 12 point increase in EXACT score above baseline at least once during the 14 day period following exacerbation onset. On average this threshold score of 12 was breached 4.4 days after symptomatic onset. 59 of 128 exacerbations (46.1%) had a 9 point increase in EXACT score above baseline at least once during the 14 day period following exacerbation onset, on average 3.7 days after symptomatic onset.

Relationship between EXACT scores and healthcare utilisation (HCU) exacerbations

85 (66.4%) of 128 London COPD cohort diary card defined exacerbations were treated with additional systemic therapy (oral antibiotics and/or corticosteroids) by the study team, consistent with a moderate severity HCU exacerbation. 22 of 85 (25.9%) HCU exacerbations attained a 12 point increase in EXACT score above baseline for 2 consecutive days. 29 of 85 (34.1%) attained a 9 point increase for 3 consecutive days (see online for further threshold analysis). The 12 point threshold was breached at least once during the 14 day period following exacerbation onset in 43/85 (50.6%) of these HCU exacerbations and the 9 point threshold in 44/85 (51.8%).

Relationship between symptom-defined events using the EXACT and London COPD cohort diary card and HCU exacerbations

The scoring algorithm for a symptom-defined event using the EXACT is an increase of 12 points above the patient's mean baseline for 2 consecutive days or an increase of 9 points above the patient's mean baseline for 3 consecutive days. Previous analyses for the EXACT have examined the day of presentation of an HCU exacerbation ± 7 days for the presence of an EXACT event (Leidy & Murray, personal communication, 2013). In this study we analysed the period of exacerbation onset ± 7 days, as defined by London COPD cohort diary cards. 86 diary card defined exacerbations had a complete dataset of daily EXACT scores during this period. 24 (27.9%) of these exacerbations met the EXACT threshold for a symptom-defined event. Of these 86 exacerbations with a complete dataset, 52 were HCU exacerbations, 18 (34.6%) of which met the criteria for an EXACT event.

Relationship between exacerbation EXACT scores and baseline disease severity

Patients exhibited smaller rises in EXACT score at exacerbation as baseline disease severity (judged by baseline EXACT score) increased. **Figure 5** shows that change between maximum exacerbation and baseline EXACT score seen at London COPD cohort diary card exacerbation was significantly related to baseline EXACT score (rho =-0.61, $p<0.001$) allowing for repeated measures.

DISCUSSION

This novel study is the first to independently validate the EXACT as an effective tool to assess exacerbation severity. EXACT scores increase at COPD exacerbation, the magnitude of which reflects the severity of the event in terms of treatment, systemic inflammation, airflow limitation and symptom recovery time. For the first time we have studied the EXACT against the validated London COPD cohort daily symptom diary card (4, 6, 12) and thus uniquely examined the complex relationship between symptom-defined events using the EXACT and both healthcare utilisation (HCU) exacerbations and London Cohort diary-card identified, untreated exacerbations. Approximately 50% of both diary card-defined and HCU exacerbations crossed the EXACT event threshold but only approximately one third fulfilled the criteria for an EXACT event. Thus this study has highlighted important potential limitations of the EXACT in its ability to independently identify events which were captured by physician review (HCU) or London COPD cohort diary cards. Baseline disease severity appears to play an important role in symptom reporting and physician prescribing thresholds at exacerbation.

In this study we have shown that EXACT scores at exacerbation are significantly related to systemic inflammation, as measured by concurrent levels of serum CRP. This is an important asset for a successful outcome measure of exacerbation severity since elevated systemic inflammation during exacerbations relates to both clinical non-recovery and exacerbation recurrence (17). Furthermore, the time taken for EXACT scores to return to baseline was significantly related to recovery time as judged by London COPD cohort symptom diary cards and was also modestly correlated with lung function recovery as measured by PEFR. Thus our data supports the use of the EXACT as an effective tool to measure exacerbation

severity and assess recovery, particularly suited to trials of interventions to treat acute exacerbations. In this setting, the relative proportion of patients whose EXACT scores have returned to baseline (or fallen by a predetermined magnitude) by 7 days (the median recovery time in a study evaluating recovery in over 500 exacerbations (12)) could be a valuable outcome measure.

In this paper, patients completed both London COPD cohort diary cards and EXACT questionnaires prospectively to allow us to examine EXACT changes during unreported exacerbations which were not treated with increased systemic therapy. EXACT scores recorded on the day of exacerbation onset were the same for both reported and unreported events. However, while no significant difference was seen in total symptomatic burden or exacerbation length as judged by EXACT scores between either type of exacerbation, the pattern of recovery observed was different, and maximum EXACT scores recorded during the exacerbation were significantly higher in treated compared to untreated, unreported events. Furthermore, the lack of statistical significance in the total net EXACT recovery score may be due to insufficient sample size. These results demonstrate for the first time that the EXACT is responsive to both reported, HCU exacerbations, and unreported exacerbations where patients do not report symptomatic deterioration to primary care physicians or members of a research team. Identification of unreported exacerbations may be a particular advantage in pharmaceutical interventional trials which historically have experienced unexpectedly low rates of HCU exacerbations (18, 19).

The assessment of exacerbation frequency during clinical trials was an initial aim in the development of the EXACT (14, 20). To facilitate the identification of unreported exacerbations, the instrument pre-specifies a threshold for these symptom-defined events

based on a persistent increase in EXACT score over 2-3 days. In this study, we investigated the relationship between exacerbations identified using the HCU definition, the London Cohort diary card, and the EXACT. We found the strength of the relationship to be modest. It should be noted that patients in the London COPD cohort are instructed to report increased respiratory symptoms as recorded in their diary to ensure prompt assessment and therapy as required, and were not instructed to report based upon EXACT responses. Some studies have attempted to use EXACT scores to enhance reporting of exacerbations by remotely monitoring EXACT scores in real-time and using worsening scores to generate an alert regarding a possible exacerbation (21), however this was not the case in our study.

Both the London COPD cohort diary cards and the EXACT are responsive to a worsening of respiratory symptoms. However the EXACT requires the increase in symptoms to meet a strict numerical threshold to fulfil criteria for symptom-defined events using the EXACT, thus potentially increasing the likelihood of undercounting relative to London COPD cohort diary card defined exacerbations. Furthermore, the seminal event for the calculation of concordance of EXACT symptom-defined events is more typically the HCU exacerbation, with the date of treatment administration as the day of onset, unlike in this paper where we have used cohort diary cards to define the onset of events and then examined the corresponding EXACT scores of both HCU and London COPD cohort diary card defined exacerbations.

Patients in the London COPD Cohort are specifically trained to rapidly recognise and report the increased respiratory symptoms that characterise COPD exacerbations. This may also have impacted on the relationship between symptom-defined events using the EXACT and HCU exacerbations seen in the clinic. Since our patients present early in the course of their

exacerbation and receive prompt systemic treatment, this may alter the evolution of symptoms for HCU exacerbations compared to when presentation is markedly delayed. In such circumstances, if patients do not commence therapy until late in their exacerbation, their symptoms may be of a higher intensity, and thus be more likely to cross the threshold for symptom-defined events using the EXACT. Nonetheless, despite these caveats it remains a concern that only approximately one third of HCU exacerbations within this study fulfilled the criteria for an EXACT event. The strength of the relationship between EXACT events and HCU exacerbations in our study is consistent with preliminary data from the FORWARD trial, which used the traditional physician diagnosis of exacerbations as a co-primary outcome, and the EXACT to enhance exacerbation detection, and also found marked inconsistencies between EXACT events and HCU exacerbations (21, 22).

We examined the relationship between EXACT scores and HCU exacerbations further by exploring the role of baseline COPD disease severity. At baseline, EXACT scores accurately reflected disease severity as judged by lung function impairment and London COPD cohort diary card exacerbation frequency. At exacerbation, patients exhibited smaller rises in EXACT score as baseline disease severity increased, suggesting that patients with more severe stable disease are more likely to report and receive additional systemic therapy at exacerbations associated with smaller increases in symptom intensity than patients with milder baseline disease. This result confirms that people seek care and are treated for exacerbations for a variety of reasons, including varied tolerance to symptomatic change. More severe patients may be more sensitive to change in symptoms, more frightened by smaller changes, or be better trained and therefore report their changes earlier. The London cohort is carefully trained to detect change and seek treatment early, and these results support the success of this program. These results also suggest that the EXACT thresholds for

symptom-defined events are conservative, and are not overestimating the frequency of symptom-defined events that are unreported. It remains important to count HCU events as HCU events, particularly since they remain prominent in major guidelines for the diagnosis of an exacerbation (23). However, all unreported and untreated symptom-defined events also need to be accurately detected with a diary since these events are both common (6, 9, 10) and important, contributing to impaired health status (6, 9).

The EXACT has previously been used in conjunction with a personal digital assistant (14, 24) or smartphone (25). A potential limitation of our study is that the EXACT was administered in paper rather than electronic format. However, we have previously confirmed that PROs can be reliably completed at exacerbation and during recovery in paper format (26). Furthermore, since the content of the EXACT is identical in both formats, this is unlikely to significantly alter the results obtained. The use of a paper version of the tool also ensures that the results of the study are applicable to the widest range of COPD patients, since patients were not excluded because they were not technically capable of using an electronic instrument.

We have demonstrated that the EXACT is an effective tool to evaluate exacerbation severity in outpatient settings when the event was captured by physician review (HCU) or by London COPD cohort diary cards. Future studies should also assess the efficacy of the instrument in hospitalised patients and can use the EXACT to assess both the maximum symptomatic intensity of exacerbations and the total symptomatic burden of events.

In conclusion, the EXACT is an effective method of evaluating exacerbation severity. EXACT scores reflect severity as determined by lung function, exacerbation length and

systemic inflammation. The tool is responsive to both treated and untreated exacerbations and can be effectively used in conjunction with daily symptom diary cards to provide novel outcome measures in clinical trials of acute exacerbation therapies. However, uncertainty remains regarding the effectiveness of the instrument to independently and accurately detect the onset and frequency of exacerbations, a particular concern in the study of preventative therapies for COPD exacerbations.

Acknowledgements

The authors would like to thank Nancy Klein Leidy, Lindsey Murray, and colleagues at UBC for the use of the EXACT in this study.

Funding

The London COPD Cohort is funded by the MRC Patient Cohort Research Initiative.

Table 1. Stable state clinical characteristics of the 58 patients at the time of recruitment to the cohort.

	Mean±SD
Age (years)	70.2±8.2
FEV_1 (l)	1.22±0.56
FEV_1 (% predicted)	48.6±18.1
FEV_1/ FVC (%)	46.6±14.2
Smoking pack years	54.0±42.1
SpO_2 (%)	94.6±2.0
BMI (kg/m2)	26.8±5.7
	Median (IQR)
London COPD cohort diary card Exacerbation Frequency (per patient per year)	2.88 (1.92-4.43)
	n=
Male, n (%)	36 (62.1)
Current Smokers, n (%)	11 (19.0)
Comorbidity present, n (%)	47 (81.0)
Congestive heart failure, n (%)	6 (10.3)
Ischemic heart disease, n (%)	13 (22.4)
Hypertension, n (%)	32 (55.2)
Diabetes Mellitus, n (%)	4 (6.9)
Patients receiving maintenance inhaled corticosteroids, n (%)	52 (89.6)

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Figure legends

Figure 1. Mean EXACT scores at baseline (□), exacerbation onset (▒), and the maximum (■) EXACT scores during the 2 weeks following exacerbation onset. Vertical lines represent standard errors.

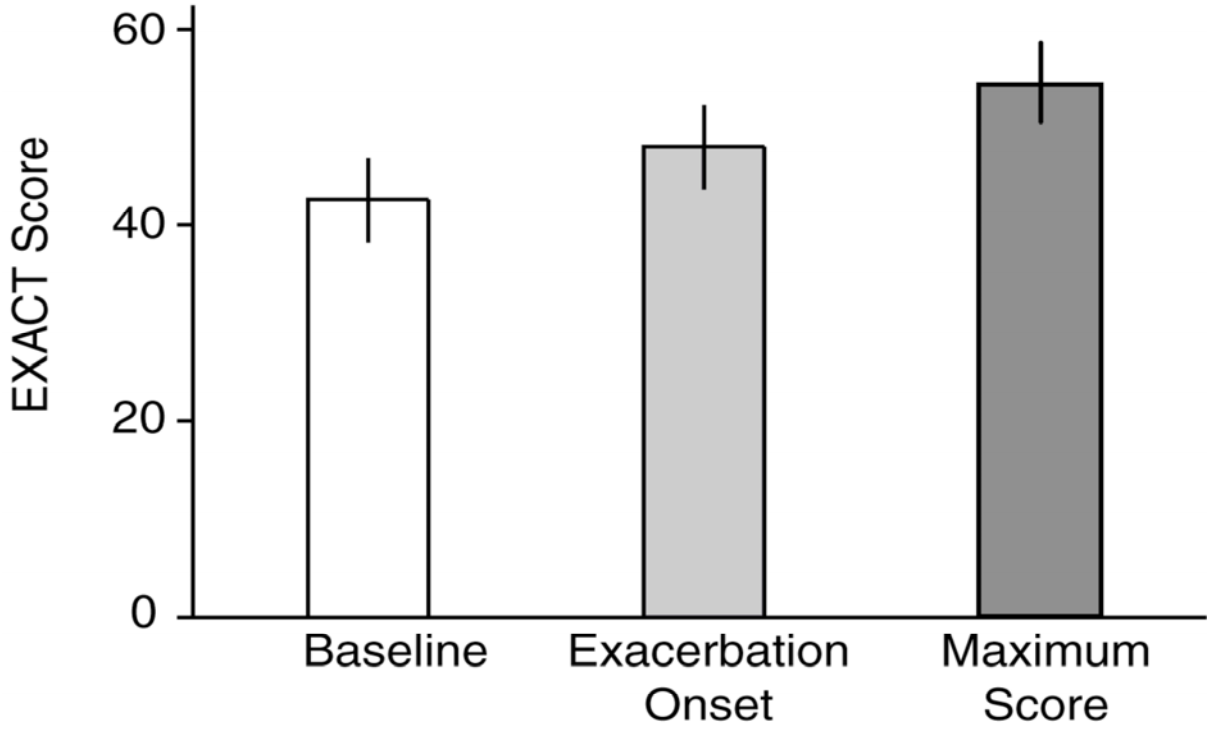

Figure 2. Relationship between log_{10}CRP and change in EXACT scores at exacerbation (rho=0.30; p=0.041).

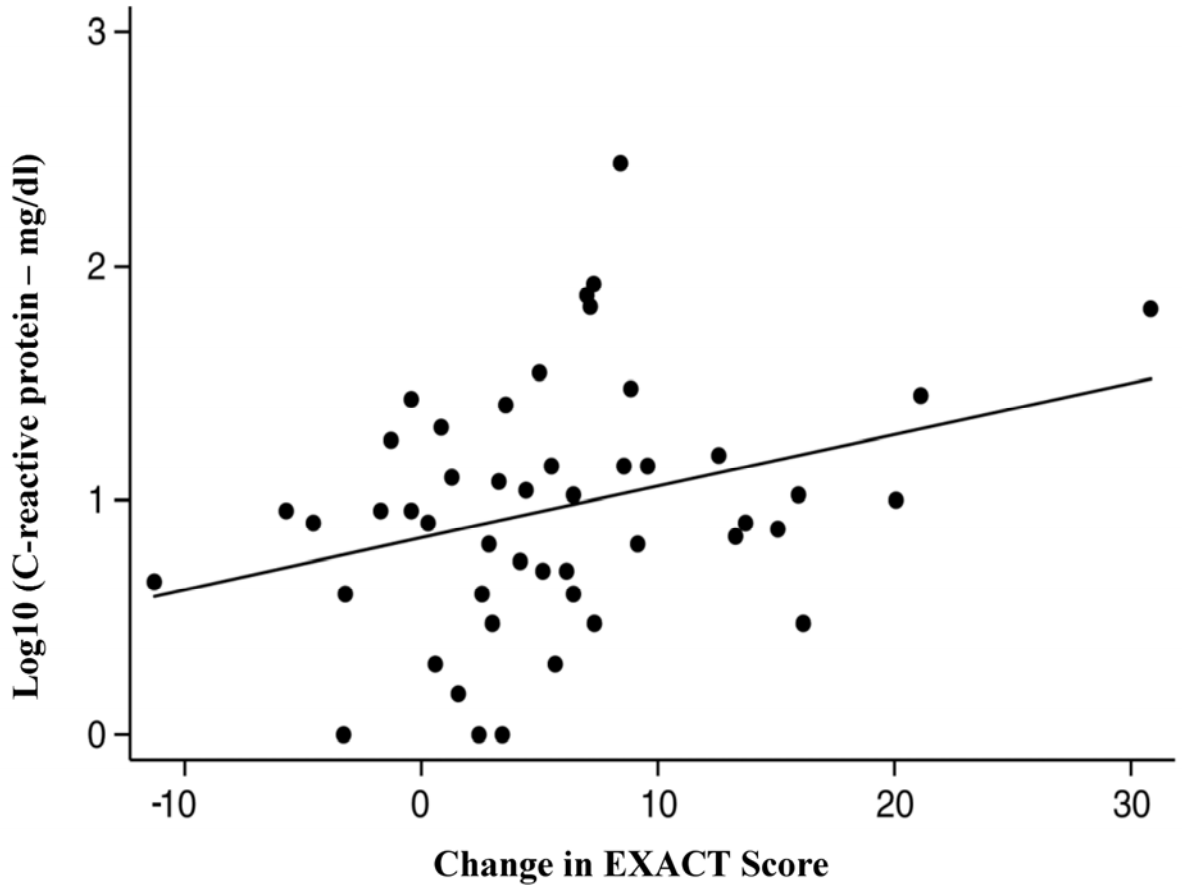

Figure 3. Time course plots of recovery of EXACT score, London COPD cohort diary card symptom counts and peak expiratory flow rate (PEFR) generated using daily mean values of all 128 exacerbations are presented in Figure 3(a), (b) and (c) respectively. Vertical bars represent standard errors. Horizontal lines indicate mean baseline scores.

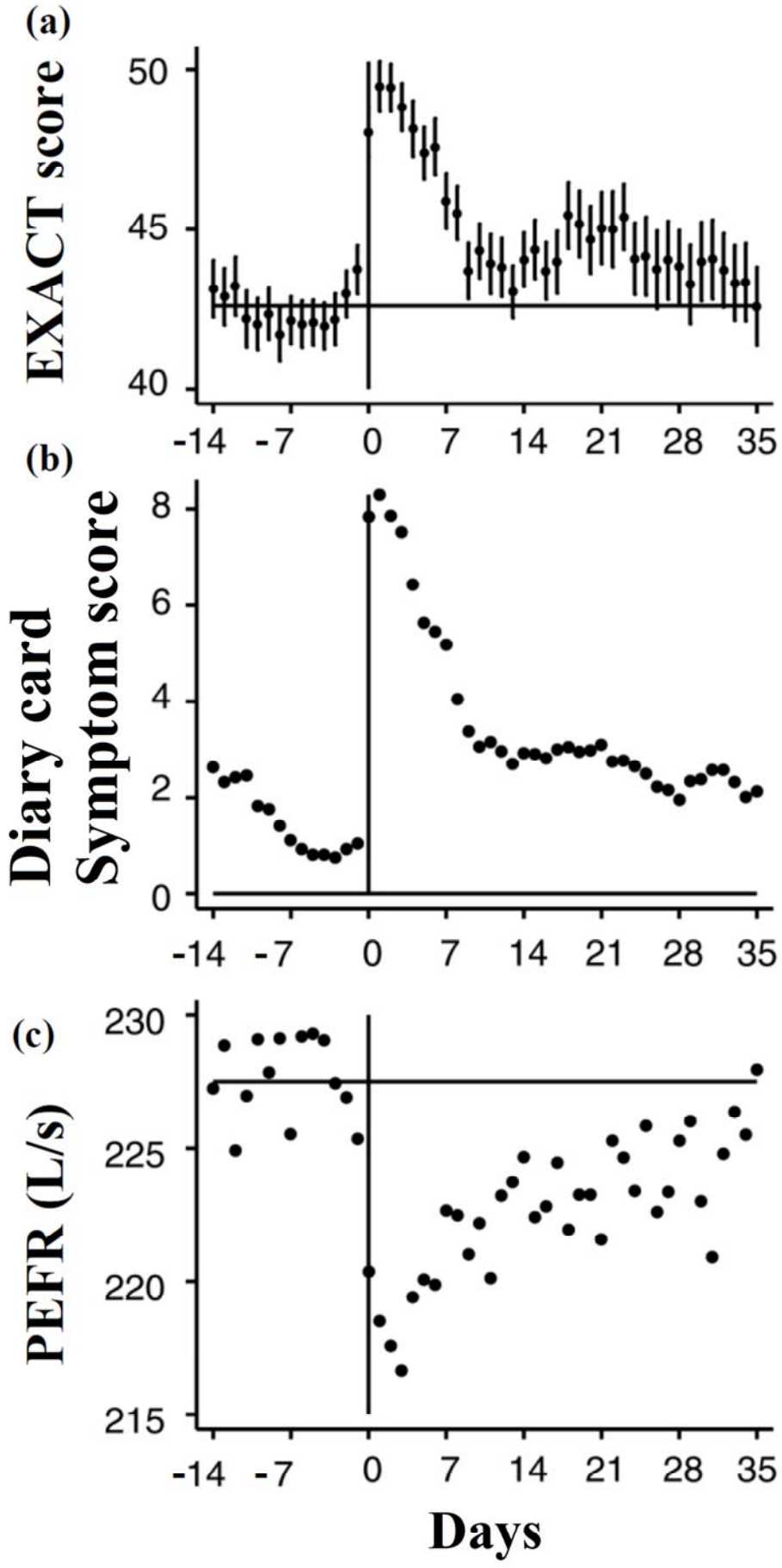
(a)
EXACT score
50
45
40
-14
-7
0
7
14
21
28
35
(b)
Diary card
Symptom score
8
6
4
2
0
(c)
PEFR (L/s)
230
225
220
215
Days

Figure 4. (a) Maximum EXACT scores in COPD patients treated with (▒) and without (■) increased systemic therapy at exacerbation. Vertical lines represent standard errors. (b) Time course of EXACT scores during treated (●) and untreated (○) exacerbations. Vertical lines represent standard errors.

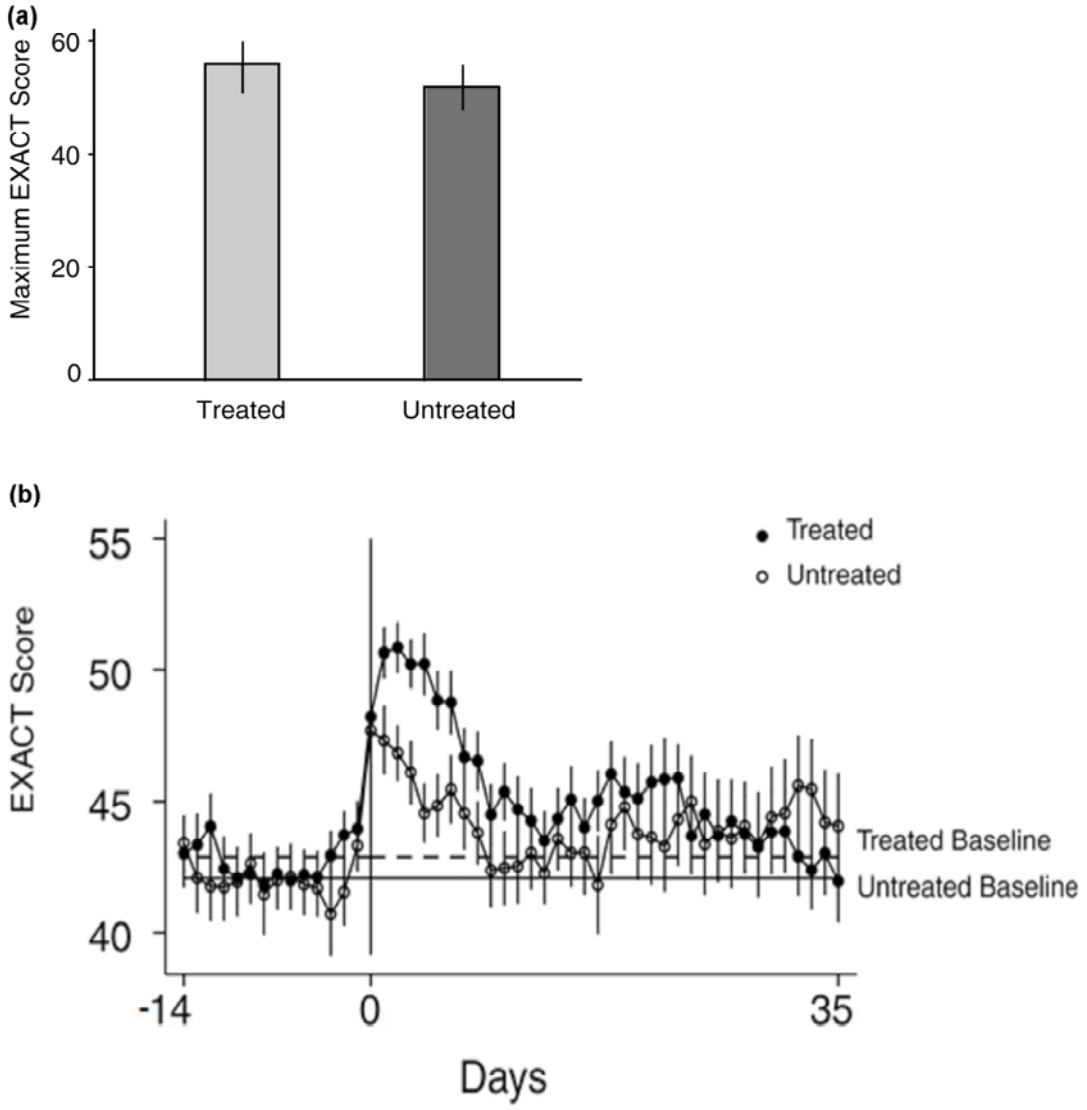

Figure 5. Relationship between baseline EXACT score and maximum rise in EXACT score at exacerbation. Black filled dots (●) represent HCU exacerbations. White unfilled dots (○) represent London COPD cohort diary card defined exacerbations which were not treated with additional systemic therapy.