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Comparison of peak expiratory Flow(PEF) and COPD assessment test (CAT) to assess COPD exacerbation requiring hospitalization: A prospective observational study

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Abstract

Background: Acute exacerbation of chronic obstructive pulmonary disease (COPD) resulting in hospitalization is significantly associated with the increased morbidity and mortality, but there is a lack of an effective method to assess it. This study aimed to compare the ability of peak expiratory flow (PEF) and COPD assessment test (CAT) to assess COPD exacerbations requiring hospitalization. Methods : A cohort of 110 patients with moderate to severe COPD was studied over a period of 12 months, and their daily morning PEFs and CAT scores were recorded throughout the study. Results : After 12 months of follow-up, 72 patients experienced 156 COPD exacerbations, 74 (47%) that resulted in hospitalization and 82 (53%) that did not result in hospitalization. Change in CAT score from baseline to exacerbation was significantly related to change in PEF and Spearman's rho =0.375 (95% CI, 0.227 to 0.506; $p < .001$). Change in PEF and CAT score from baseline to hospitalized exacerbation was significantly larger than that from baseline to non-hospitalized exacerbation ($p < .05$). Multivariable analysis indicated that ΔPEF (OR 1.11, 95% CI 1.06–1.16, $p < .001$) and ΔCAT (OR 1.64 95% CI 1.18–2.27, $p = .003$) were independently associated with risk of hospitalized exacerbation. ROC analysis indicated that the optimal cutoff value of ΔPEF for identifying hospitalized exacerbation was 49 L/min (27% from baseline), with a sensitivity and specificity of 82.7% and 76.7% (area under the curve [AUC] = 0.872 (95% CI 0.80–0.944, $p < .05$). The optimal cutoff value of ΔCAT score for identifying hospitalized exacerbation was 10.5 (63% from baseline), with a sensitivity and specificity of 67.3% and 77.4% [AUC]=0.763 (95% CI 0.67–0.857, $p < .05$). The AUC of ΔPEF and ΔCAT combined for the identification of hospitalized exacerbation was 0.900 (95% CI 0.841–0.959, $p < .05$), which was larger than that of ΔCAT or ΔPEF. Conclusions: ΔPEF and ΔCAT were independently associated with risk of hospitalized exacerbation. Compared with CAT, PEF was superior to identify hospitalized exacerbation. Identification via PEF and CAT combined is more effective than using PEF or CAT alone. These results help to assess the severity of COPD exacerbation and provide valuable information for clinical decision-making.

Keywords

PEF, CAT, AECOPD, hospitalized exacerbation, assess

Background

Chronic obstructive pulmonary disease (COPD) is a major global health concern because of the high morbidity and high mortality, heavy social and economic burden.[1,2] It is characterized by persistent respiratory symptoms and

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airflow limitation, and it is a complex heterogeneous disease.[3] Severe exacerbations of COPD resulting in hospitalization are key events in the course of disease, and they are significantly associated with accelerated decline in lung function, reduced quality of life, and increased risk of death.[4–7] However, according to the (GOLD) Guidelines,[3] the assessment of exacerbation severity based on the therapy is retrospective, and it is subjectively determined by the clinician. Therefore, it is necessary to develop an effective method for identifying and assessing it in clinical practice.

Peak expiratory flow (PEF) and COPD assessment test (CAT) are commonly used tools to assess the lung function and health status in COPD patients. Previous studies have suggested that PEF is an inexpensive and easy method that can be used safely instead of spirometry.[8–12] Moreover, PEF is reportedly significantly reduced at COPD exacerbation, and this reduction is associated with increased respiratory symptoms.[13] The CAT is a questionnaire containing 8 questions, and it can be used to quantitatively evaluate the impact of COPD on the health and daily life of patients. It is simple and easy to administer and it correlates well with St George's Respiratory Questionnaire (SGRQ).[14] In a previous study, CAT score increased at exacerbation and it reflected the severity of COPD exacerbation.[15] The present study was conducted to compare the ability of peak expiratory flow (PEF) and COPD assessment test (CAT) for the assessment of COPD exacerbation resulting in hospitalization.

Methods

Study design and population

This study was conducted over 12 months on 110 of 126 patients recruited from Ningbo Ninth Hospital in China between December 2018 and May 2019. Patients were at least 40 years old, had clinical COPD diagnosed in accordance with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Guidelines,[3] and were in a stable stage of disease with no history of exacerbations in the past 8 weeks at the time of study enrollment. Patients with any other significant respiratory diseases were excluded. Patients' basic data were obtained at recruitment, including age, sex, height, weight, spirometry results, blood gas analysis, comorbidities, smoking history, sputum production history, and baseline PEFs and CAT scores. The ethics committees of the hospital approved the study, and all the patients provided written informed consent after understanding the content of the study.

All patients were required to be proficient at using the Mini-Wright peak flow meter (Keka, Shanghai, China) and recorded daily morning post-medication PEFs and any increase in respiratory symptoms on diary cards. Patients were seen in clinic monthly and if necessary guided them how to complete the diary cards. In addition, patients were asked to contact the clinical team telephonically if their respiratory symptoms deteriorated. The clinical team continued to focus on their PEFs and CAT scores until COPD exacerbations or symptoms resolved spontaneously, as well as the performance of exacerbations recovery to stable period. After the exacerbations relieved, the above monitoring continued until the end of the study. In accordance with a previous study,[13] exacerbation was defined as an increase in any two major respiratory symptoms (sputum purulence, sputum volume, and dyspnea) or an increase in one major and one minor respiratory symptoms (sore throat, cold, cough, and wheeze) for at least two consecutive days. The first of the two consecutive days was considered the day of onset of the exacerbation. The duration of exacerbation recovery was defined as the number of days from the first day of exacerbation to the first day of 5 consecutive days in which symptoms had returned to usual baseline levels.[16]

Statistical analysis

Statistical analyses were performed using SPSS software (version 23.0). Normally distributed quantitative data were presented as mean and standard deviation and skewed data as medians and interquartile range. Qualitative data were presented as percentages. Quantitative variables were compared using the Mann–Whitney U test or Student t-test. Categorical data were compared using Pearson's chi-square test or Fisher's exact test. Pearson correlation tests were used to analyze the relationship between the PEF and CAT. Multivariable logistic regression was used to analyze the relationship between the ΔPEF and ΔCAT score and risk of hospitalized exacerbation. The performance of CAT, PEF, and combined CAT and PEF for the identification of hospitalized exacerbation was analyzed and compared using the area under the receiver operating characteristic (AUROC) curve. $p < .05$ was considered statistically significant. Changes in PEF and CAT on the day of onset of the exacerbation were compared with the baseline period (mean of 5 consecutive days within stable stage of COPD).

Results

Patient characteristics

A total of 126 patients were included; 6 did not complete the PEFs and CAT scores, 7 patients failed to meet inclusion criteria, and 3 patients did not consent to the study. Therefore, 110 patients from Han nationality were included in the analyses (Figure1). Their baseline characteristics are reported in Table 1 alongside 72 patients who experienced exacerbations. The mean age was 73.3 ± 8.8 years, 81 (85.3%) were male, and mean FEV1%predicted was 34.2 ± 12.2 %. The BMI, smoking pack-years, GOLD stage, and history of chronic sputum production are all presented in Table 1.

Correlation between PEF and CAT score at baseline and exacerbation

At baseline, there was a statistically significant but weak relationship between CAT and PEF, Spearman's rho = –0.191 (95% CI, −0.3418 to -0.02985; p = .0171), At exacerbation, CAT score was significantly related to the PEF, Spearman's rho=−0.343 (95% CI, −0.478 to -0.192; p = .001). Change in CAT score from baseline to exacerbation was significantly associated with change in PEF, Spearman's rho =0.375 (95% CI, 0.227 to 0.506; p < .001). (Figure 2).

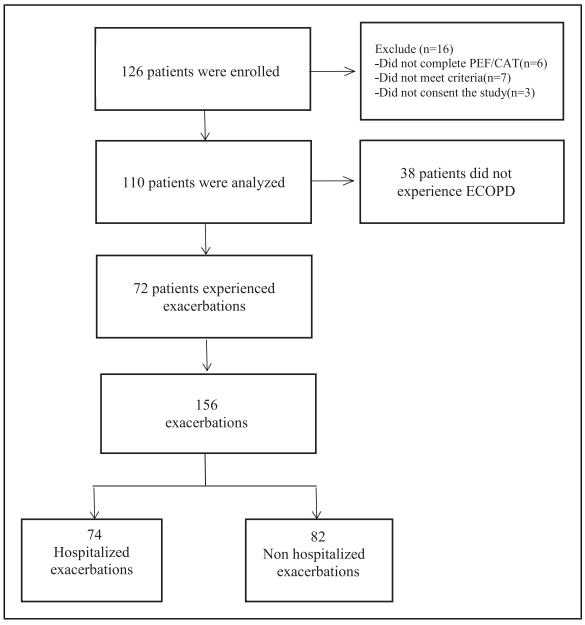

Figure 1. Patients and exacerbations included in the study.

Change in PEF and CAT score from baseline to exacerbation

72/110 patients experienced one or more exacerbations, 13 exacerbations were missed because of eight patients did not contact us in time. Therefore, 156 exacerbations were finally recorded and analyzed. The median duration of exacerbation recovery was 10 days (IQR, 8–15; n = 156). Hospitalized exacerbations had longer recovery times (median 14 days, IQR, 10–19) compared with those of non-hospitalized exacerbations (median 8 days, IQR, 7–10; p < .001). At hospitalized exacerbations, PEF decreased from a baseline value of 181.6 ± 53.7 L/min to 120.2 ± 36.7 L/min (p < .05), and CAT score rose from a baseline value of 19.4 ± 4.6 to 30.4 ± 3.6 (p < .05). At non-hospitalized exacerbations, PEF decreased from a baseline value of 190.5 ± 46.8 L/min to 145.0 ± 35.9 L/min (p < .05), and CAT score rose from a baseline value of 13.5 ± 2.5 to 21.8 ± 2.9 (p < .001) (Figure 3). Mean changes in PEF and CAT score from baseline to hospitalized exacerbation were significantly larger than those from baseline to non-hospitalized exacerbation (p < .05) (Figure 4).

The assessing ability of ΔPEF and ΔCAT score for hospitalized exacerbation

By multivariable analysis, ΔPEF (OR 1.11, 95% CI 1.06–1.16, p < .001) and ΔCAT (OR 1.64 95% CI 1.18–2.27, p = .003) were independently associated with risk of

Table 1. Baseline characteristics of patients included in the analyses.

	All patients (n=110)	Exacerbation (n=72)	p value
Age, years (SD.)	73.3 ± 8.8	73.1 ± 8.1	0.88
Gender (males), n%	81 (85.3)	63(87.5)	0.62
BMI, kg/m^2 (SD.)	21.3 ± 4.1	21.2 ± 4.2	0.83
Smoking pack-years (IQR)	30.0 (15.0–50.0)	30.0 (15.0–50.0)	0.69
FEV1, %predicted (SD.)	34.2 ± 12.2	31.9 ± 10.7	0.21
FVC, %predicted (IQR)	50.8 (39.5–61.0)	48.1 (38.3–59.0)	0.51
FEV1/FVC (IQR)	50.0 (44.6–60.0)	48.7 (43.3–56.1)	0.26
PaO2, kPa (IQR)	10.5 (8.7–11.4)	10.4 (8.7–11.4)	0.86
PaCO2, kPa (IQR)	5.8 (5.2–6.9)	6.0 (5.3–7.2)	0.41
History of chronic sputum production, n%	61 (64.2)	43 (59.7)	0.71
History of cardiovascular disease, n%	30 (31.6)	27 (37.5)	0.42
GOLD stage, n%			0.53
I	0 (0)	0 (0)	
II	20 (18)	6 (8.3)	
III	55 (50)	36 (50.0)	
IV	35 (32)	30 (41.7)	

Definition of abbreviations: BMI: body mass index; PaO2: oxygen partial pressure measured by arterial blood gas analysis; PaCO2: carbon dioxide partial pressure measured by arterial blood gas analysis; GOLD: Global Initiative for Chronic Obstructive Lung Disease.

hospitalized exacerbations (Figure 5). ΔPEF and ΔCAT were independent risk factors of hospitalized exacerbations.

Moreover, the quantitatively identifying ability of ΔPEF and ΔCAT for hospitalized exacerbation are shown in Figure 6. ROC analysis indicated that the optimal cutoff value of ΔPEF for identifying hospitalized exacerbation was 49 L/min (27% from baseline), with a sensitivity and specificity of 82.7% and 76.7%. The ROC area under the curve (AUC) was 0.872 (95% CI 0.80–0.944, $p < .05$). The optimal cutoff value of ΔCAT score for identifying hospitalized exacerbation was 10.5 (63% from baseline), with a sensitivity and specificity of 67.3% and 77.4%. The ROC AUC was 0.763 (95% CI 0.67–0.857, $p < .05$). The AUC of ΔPEF and ΔCAT combined for identifying hospitalized exacerbation was 0.900 (95% CI 0.841–0.959, $p < .05$).

Discussion

The current observational study assessed and compared the ability of ΔPEF and ΔCAT score to identify the COPD exacerbation resulting in hospitalization. In this prospective study, we have some important observations. Change in PEF and CAT score from baseline to hospitalized exacerbation was significantly larger than that from baseline to non-hospitalized exacerbation. Multivariable analysis indicated that ΔPEF and ΔCAT were independently associated

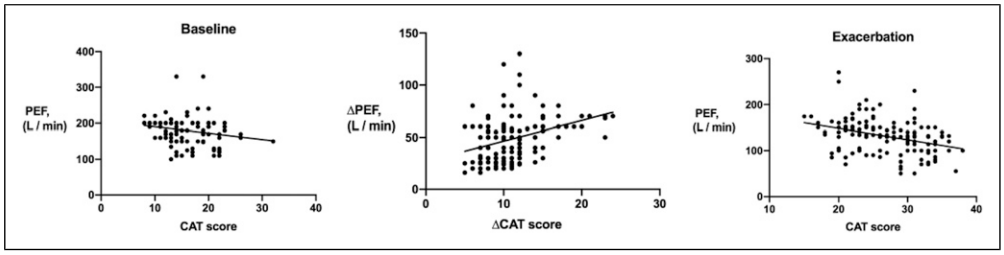

Figure 2. Correlation between PEF and CAT at baseline and exacerbation.

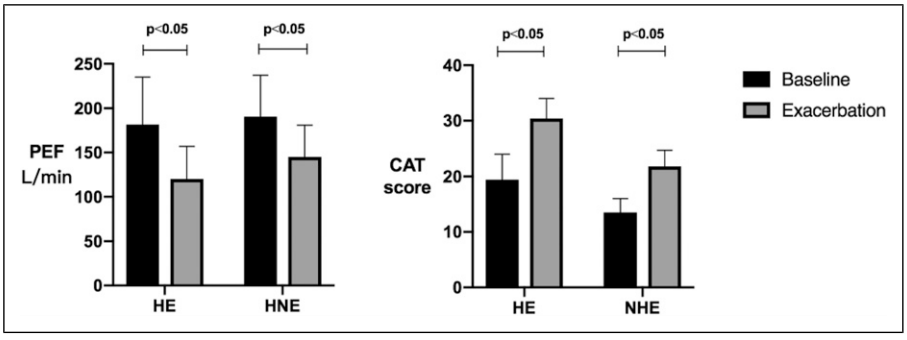

Figure 3. Change in PEF and CAT score from baseline to exacerbation. (HE: hospitalized exacerbation, NHE: non-hospitalized exacerbation).

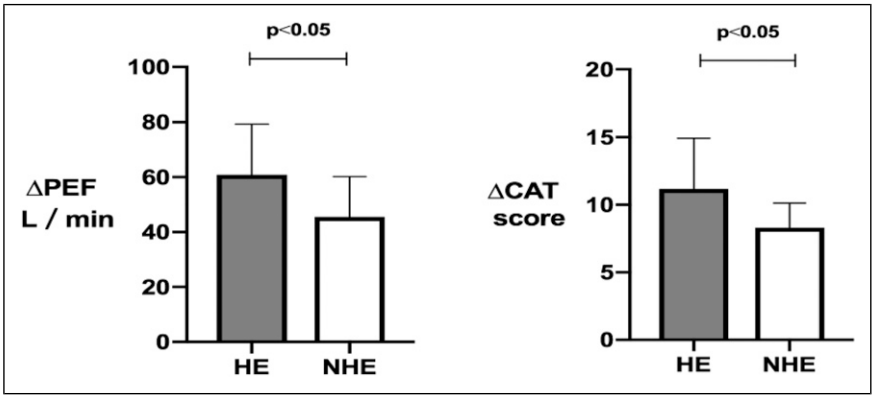

Figure 4. Mean ΔPEF and ΔCAT at hospitalized exacerbation (HE) and non-hospitalized exacerbation (NHE).

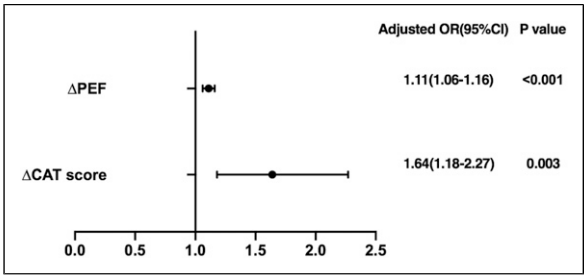

Figure 5. Forest plot of ΔPEF and ΔCAT independently associated with risk of hospitalized exacerbation.

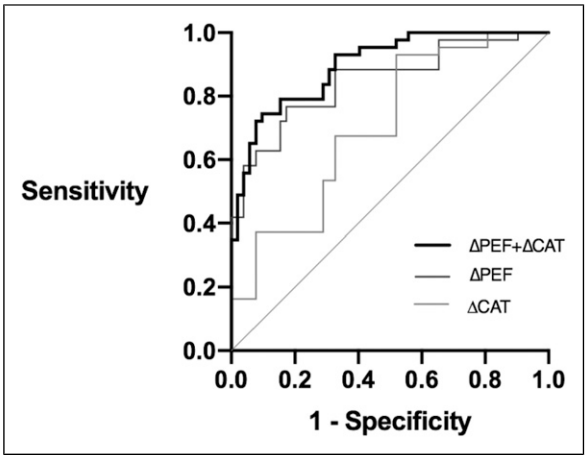

Figure 6. Receiver operative characteristic (ROC) curves and corresponding areas under the curve (AUC) for hospitalized exacerbation. The AUC of ΔPEF + ΔCAT, ΔPEF, and ΔCAT was 0.900(95% CI 0.841–0.959, $p < .05$), 0.872 (95% CI 0.80–0.944, $p < .05$), and 0.763 (95% CI 0.67–0.857, $p < .05$), respectively.

with risk of hospitalized exacerbation. The ROC curves showed the PEF has a higher ability to differentiate hospitalized exacerbation than CAT. Furthermore, PEF and CAT combined has better identifying ability than PEF or CAT alone.

Due to the heterogeneity and complexity of COPD, sometimes assessment of the severity of the exacerbations is inaccurate, which can affect the treatment and prognosis. Due to inadequate assessment of exacerbations, patients often do not report to healthcare professionals for timely treatment.[17] This can delay the administration of optimal treatment and worsen the condition. Thus, an effective tool to help to identify the severity of exacerbation will fulfill an important clinical need.

According to the (GOLD) Guidelines,[3] severity of COPD exacerbations was divided into three categories, mild (treated with short-acting bronchodilators only), moderate (treated with short-acting bronchodilators plus antibiotics and/or oral corticosteroids), and severe (requiring hospitalization or emergency room treatment). Notably, however, this qualitative assessment of exacerbation severity based on therapy and hospitalization is retrospective. The assessment is subjective in nature and there are no quantitative indicators that directly determine the physician's treatment strategy in clinical practice. To date, few studies have achieved quantitative and effective assessment of the severity of COPD exacerbation. To our knowledge, the present study is the first to compare the ability of PEF and CAT for the assessment of hospitalized exacerbation. The PEF and CAT are both portable and economical self-monitoring tools, and they are easy for patients to master and apply, even during exacerbation.

Mackay et al. [15] investigated the usefulness of the CAT for evaluating COPD exacerbation severity by comparing baseline (stable state) scores with scores at exacerbations, and analyzing the relationship between CAT scores and systemic inflammatory markers, lung function changes, and symptom recovery. In that study, CAT scores increased at exacerbation and reflected the severity of exacerbation as determined by exacerbation length and reduction in lung function. In other studies, PEF decreased significantly at COPD exacerbations, in conjunction with increased respiratory symptoms.[13,18,19] These studies only reported trends, however, did not compare the ability of them or provide a specific quantitative index. The current study supplements existing work by comparing the ability of these two indicators and providing optimal cutoff values.

According to the previous literature,[20–22] DECAF (dyspnea, eosinopenia, consolidation, acidemia, atrial fibrillation) score was used to try to assess the severity of acute exacerbation by predicting hospital mortality. It could be scored on admission as a risk stratification tool and accurately predicted risk of death. However, these assessments were based on prognostic performance. Therefore, it was a prediction of prognosis and did not effectively evaluate the severity of exacerbations.

It has previous been reported that the increase in systemic inflammatory markers at exacerbation could be used to assess acute exacerbation.[23] However, obtaining samples for inflammatory markers assessment is usually invasive, and the results cannot be obtained quickly. The sensitivity, specificity, and application value of this method also require further study.[24] In comparison, PEF and CAT score are non-invasive and easy to obtain, which is conductive to patient cooperation and improves the efficiency of evaluation.

In our study, a part of patients had both hospitalized exacerbations and non-hospitalized exacerbations during follow-up. Therefore, in order to avoid confusion, PEF and CAT at baseline were not suitable for establishing a predictive model of hospitalized exacerbations. Based on every exacerbation had its corresponding ΔPEF and ΔCAT score and might reflect the severity of exacerbation, the present study developed a predictive model and compared the ability of ΔPEF and ΔCAT score to assess hospitalized exacerbations. Multivariable analysis indicated that ΔPEF

and ΔCAT could independently predict the risk of hospitalized exacerbations. By comparing the differences of the AUC of these indicators, the AUC of ΔPEF and ΔCAT combined was larger than the AUC of ΔPEF or ΔCAT. Therefore, identification via PEF and CAT combined is much more effective, and we recommend using PEF and CAT combined as a useful indicator to identify COPD exacerbation requiring hospitalization. This is an innovative method attempt to assess the severity of COPD exacerbation, and the results may be useful for guiding appropriate therapy at exacerbation and providing valuable information for clinical decision-making.

There are several limitations in our study. First, the COPD patients chosen exhibited disease severity ranging from moderate to very severe, due to the mild stage COPD patients would likely have fewer exacerbations and therefore not including this group in the study may have led to an increase in the observed exacerbation frequency when compared to a more balanced COPD population. Second, some patients did not contact us in time, resulting in an increase in missed rates. But, because we recorded most of the exacerbations, it might have little impact on the results. Finally, the study population was not so large. In future research, we will perform larger multi-centric studies to validate the results.

Conclusion

This prospective study demonstrated that PEF and CAT could be used for the assessment of COPD exacerbation resulting in hospitalization. ΔPEF and ΔCAT were independent risk factors of hospitalized exacerbations. Compared with the PEF or CAT alone, PEF and CAT combined is more effective for clinical application. The results may facilitate better clinical strategy and more timely effective treatment.

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Authors' contributions

JC contributed to the study concept and design and drafting of the manuscript. JC and LW contributed to data collection, analysis, and interpretation. Both authors approve the final manuscript.

Conflict of interest statement

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of, the manuscript entitled.

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List of abbreviations

COPD: chronic obstructive pulmonary disease; ROC=receiver operating characteristic; PEF: peak expiratory flow; CAT: Chronic Obstructive Pulmonary Disease Assessment Test; ΔPEF=change in PEF relative to baseline; ΔCAT= change in CAT relative to baseline; AUC: area under the curve; BMI: body mass index; PaO2: oxygen partial pressure measured by arterial blood gas analysis; PaCO2: carbon dioxide partial pressure measured by arterial blood gas analysis; GOLD: Global Initiative for Chronic Obstructive Lung Disease.

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References

1. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the global burden of disease study 2010. *Lancet* 2012 Dec 15; 380(9859): 2095–2128.
2. Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the global burden of disease study 2010. *Lancet* 2012 Dec 15; 380(9859): 2163–2196.
3. Vogelmeier CF, Criner GJ, Martinez FJ, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report. GOLD executive summary. *Am J Respir Crit Care Med* 2017 Mar 1; 195(5): 557–582.
4. Antoniu SA and Carone M. Hospitalizations for chronic obstructive pulmonary disease exacerbations and their impact on disease and subsequent morbidity and mortality. *Expert Rev Pharmacoecon Outcomes Res* 2013; 13(2): 187–189.
5. Suissa S, Dell'Aniello S and Ernst P. Long-term natural history of chronic obstructive pulmonary disease: severe exacerbations and mortality. *Thorax* 2012; 67(11): 957–963.
6. Mullerova H, Maselli DJ, Locantore N, et al. Hospitalized exacerbations of COPD. *Chest* 2015; 147(4): 999–1007.
7. Garcia-Aymerich J, Serra Pons I, Mannino DM, et al. Lung function impairment, COPD hospitalisations and subsequent mortality. *Thorax* 2011; 66: 585–590.
8. Kelly JL, Bamsey O, Smith C, et al. Health status assessment in routine clinical practice: the chronic obstructive pulmonary disease assessment test score in outpatients. *Respiration* 2012; 84(3): 193–199.
9. Kokturk N, Turktas H, Kara P, et al. A randomized clinical trial of magnesium sulphate as a vehicle for nebulized

salbutamol in the treatment of moderate to severe asthma attacks. *Pulm Pharmacol Ther* 2005; 18(6): 416–421.
10. Agarwal D and Gupta PP. A comparison of peak expiratory flow measured from forced vital capacity and peak flow meter manoeuvres in healthy volunteers. *Ann Thorac Med* 2007; 2(3): 103–106.
11. Kodgule RR, Singh V, Dhar R, et al. Reference values for peak expiratory flow in Indian adult population using a European union scale peak flow meter. *J Postgrad Med* 2014; 60(2): 123–129.
12. Lahdensuo A, Haahtela T, Herrala J, et al. Randomised comparison of guided self management and traditional treatment of asthma over one year. *BMJ* 1996; 23312(7033): 748–752.
13. Seemungal TA, Donaldson GC, Bhowmik A, et al. Time course and recovery of exacerbations in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000; 161(5): 1608–1613.
14. Jones PW, Harding G, Berry P, et al. Development and first validation of the COPD assessment test. *Eur Respir J* 2009; 34: 648–654.
15. Mackay AJ, Donaldson GC, Patel AR, et al. Usefulness of the chronic obstructive pulmonary disease assessment test to evaluate severity of COPD exacerbations. *Am J Respir Crit Care Med* 2012; 185(11): 1218–1224.
16. Aaron SD, Donaldson GC, Whitmore GA, et al. Time course and pattern of COPD exacerbation onset. *Thorax* 2012; 67(3): 238–243.
17. Seemungal TA, Donaldson GC, Paul EA, et al. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998; 157(5): 1418–1422.
18. Van den Berge M, Hop WC, van der Molen T, et al. Prediction and course of symptoms and lung function around an exacerbation in chronic obstructive pulmonary disease. *Respir Res* 2012; 613: 44.
19. Donaldson GC, Law M, Kowlessar B, et al. Impact of prolonged exacerbation recovery in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2015; 15192(8): 943–950.
20. Steer J, Gibson J and Bourke SC. The DECAF score: predicting hospital mortality in exacerbations of chronic obstructive pulmonary disease. *Thorax* 2012; 67: 970–976.
21. Echevarria C, Steer J, Heslop-Marshall K, et al. Validation of the DECAF score to predict hospital mortality in acute exacerbations of COPD. *Thorax* 2016; 71: 133–140.
22. Echevarria C, Gray J, Hartley T, et al. Home treatment of COPD exacerbation selected by DECAF score: a non-inferiority, randomised controlled trial and economic evaluation. *Thorax* 2018; 73: 713–722.
23. Zhou A, Zhou Z, Zhao Y, et al. The recent advances of phenotypes in acute exacerbations of COPD. *Int J Chron Obstruct Pulmon Dis* 2017; 12(12): 1009–1018.
24. Lacoma A, Prat C, Andreo F, et al. Value of procalcitonin, C-reactive protein, and neopterin in exacerbations of chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2011; 6: 157–169.