Identifying the most effective tool to assess health status of patients with acute exacerbation of chronic obstructive pulmonary disease -a prospective study

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Abstract

Background: There is currently no recognized discharge criteria for patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD). In clinical work, pulmonologists determine whether a patient can be discharged considering the patient self-reported health status and some measurements which are related to the health status of AECOPD patients. Various measurements have been used to evaluate health status in patients with AECOPD, including lung function, fractional exhaled nitric oxide (FENO), blood gas analysis, COPD Assessment Test (CAT) and modified Medical Research Council test (mMRC). However, which one is most closely related to the patient self-reported health status remains unknown.

Methods: Patients with AECOPD were assessed at two visits: on admission and on day 7. The above measurements were tested at each visit. At the second visit, the patients were asked to report the health status according to a five-point Likert scale ranging from 1 to 5, representing 'much better', 'slightly better', 'no change', 'slightly worse' and 'much worse'. Based on patients self-reported outcome, we defined the responders as those patients who reported "much better," or "slightly better", non-responders were those who reported 'no change,' 'slightly worse' or 'much worse'.

Results: 55 patients were recruited into analysis. FENO and CAT could change sensitively based on different health status, except failing to differentiate the patients between those who reported 'slightly better' and 'no changes'. The changes in predicted percentage of forced expiratory volume in 1 s (FEV1%) didn't change significantly between 'no change' group and 'slightly better or much better' group, it could only identify the 'slightly worse' patients. Although mMRC and blood gas analysis (PaO2, PaCO2) changed significantly after treatment, they didn't reflect sensitively the evolution of health status. Among these measurements, the changes in CAT was best correlated with the evolution of health status (Rho=0.81), followed by FENO and FEV1%, the rho was 0.59 and -0.42, respectively.

Conclusion: It's reasonable to monitor CAT and FENO during exacerbation stage, the use of lung function and mMRC to evaluate the evolution of patients' reported health status of patients with AECOPD is limited. Registry number: ChiCTR-ROC-16009087 (http://www.chictr.org.cn/).

Background

Exacerbation is an important life-threatening event for patients with chronic obstructive pulmonary disease (COPD)[1, 2]. It can accelerate deterioration of the disease [3–7], and lead to a heavy economic burden [8]. It's reported that the hospital expenditure accounts for roughly 45%–50% of the total direct cost generated by COPD patients, especially for those with GOLD stage III [9]. Identifying those who reached discharge standard timely could shorten the hospital stay, save cost and reduce the risk of nosocomial infections. However, there is no uniform standard of discharge criteria. In clinical work, pulmonologists judge whether a patient can be discharged considering the patient self-reported health status and some measurements which are related to the health status of AECOPD patients. It was

discovered that there was a significant correlation between the outcome assessed by patients themselves and clinicians[10], however, it's not rigorous to determine whether the patient can be discharged only according to patient's reported health status, it would be more convincing if there is a measurement which could reflect the evolution of health status sensitively. During past decades, various measurements have been used in clinical studies to evaluate the health condition of AECOPD patients, including lung function, blood gas test, COPD Assessment Test (CAT) and modified Medical Research Council test (mMRC) [11–14]. In this study, we are going to investigate which measurement can best reflect the patients' subjective feelings during exacerbation stage, which can provide some suggestions to clinicians to select the tool to monitor the health status of patients with AECOPD.

As we all know, lung function [post-bronchodilator ratio of forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC): $FEV_1/FVC < 0.7$] is regarded as the gold standard for the diagnosis of COPD, and the severity of the disease is always assessed by the post-bronchodilator FEV_1% [15]. In addition, the changes in FEV_1 are always monitored as the main outcome and used to assess response to treatment in stable COPD [16][17]. Meanwhile, $FEV_1 > 12\%$ and > 200 ml are regarded as a significant improvement in health status during exacerbation of COPD [11]. However, it is always very difficult to perform for some patients in the acute exacerbation stage [18, 19]. In addition, it was discovered that lung function during exacerbation do not closely reflect symptom changes, recovery of lung function (peak expiratory flow rate, PEFR) to baseline values was complete in only 75.2% of exacerbations at 35 day, whereas in 7.1% of exacerbations at 91 day PEFR recovery had not occurred. Thus, it has some limitations to use lung function to evaluate the health status in patients with AECOPD.

Apart from lung function, blood gas testing, CAT and mMRC are all regular measurements that provide important information on the health status of the patients [12, 14]. The CAT questionnaire and mMRC are designed to assess the effect of COPD on the patients' daily life. CAT consists of eight items, which include cough, expectoration, dyspnea, chest tightness, confidence, limitation of daily activities, quality of sleep and levels of energy. mMRC is a five-point (0–4) scale based on the severity of dyspnea. In the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2011 document [20], CAT and mMRC were used to classify COPD patients in the stable stage. Some studies proved that the minimum clinical important difference for CAT was 2 units in stable stage [21]. Also, in our previous study, CAT proved to be useful in evaluating the health status of patients both in the stable stage and the exacerbation stage[12, 22]. In addition, CAT was also used to assess the prognosis of patients in acute exacerbation[13, 23–26]. Blood gas testing was also regularly tested in clinical work, it was discovered that there was statistically significant decrease of PaO_2 and an increase of $PaCO_2$ in follow-up period of COPD patients [27].

Fractional exhaled nitric oxide (FENO) measurement has been considered to be a surrogate for airway eosinophilic inflammation [28, 29], which is widely used to predict response to inhaled corticosteroids (ICS) in asthma [30–32]. As we all know, AECOPD shows obvious heterogeneity in airway inflammation: some are neutrophil dominated; others are eosinophil dominated or mixed granulocytic or

paucigranulocytic [33]. It was proved that high eosinophil levels presented a better response to ICS in COPD [34]. As an alternative to eosinophil level, it was demonstrated that FENO was a good measurement for discriminating eosinophilic COPD[35] and used to identify responders and non-responders during exacerbations [11]. However, whether the changes in FENO is related to the evolution of health status in patients with AECOPD needs further investigation. Also, which tool is better correlated to the patients' self-reported health status is still unknown.

Methods

This research was approved by the local Ethics Committee of the Second Xiangya Hospital of Central South University, and all subjects gave written informed consent to participate in the study. The study was registered in the Chinese Clinical Trial Registry (ChiCTR-ROC–16009087; http://www.chictr.org.cn/) on 25th August, 2016, the first patient was recruited on December 1st, 2016.

Study subjects

Patients with clinician-diagnosed AECOPD were recruited from the Second Xiangya Hospital of Central South University in China from September 2016 to December 2017. Patients with a primary diagnosis of AECOPD and aged over 40 years were recruited into the study. Those who had a history of asthma or other respiratory diseases (lung cancer, pulmonary thromboembolism, bronchiectasis, interstitial lung disease), severe heart failure (myocardial infarction, New York Heart Association stage IV) or malignant comorbidities were excluded from the study. The Global Initiative for Asthma (GINA) 2014 document was used to differentiate COPD from asthma and asthma-COPD overlap. In addition, patients with COPD exacerbation who had received systemic corticosteroids prior to hospitalization were also excluded. All diagnoses were established by the clinicians and independently verified by physicians specializing in respiratory medicine. Exacerbation of COPD was defined as increased dyspnea, cough or sputum (quality or quantity) that resulted in the subjects seeking medical care. Smokers were those who smoked tobacco every day and ex-smokers were those who stopped smoking at least 6 months prior to recruitment.

Study design

The demographic data and some basic characteristics were collected on admission. FENO, lung function, blood gas analysis, CAT and mMRC were carried out at two time points: on hospital admission within 24 hours and on day 7, respectively. If the hospital stay was less than 7 days, the second round of measurements was performed at discharge. All measurements were obtained at the same period of day. Treatment during hospitalization was determined by the clinicians based on the GOLD guidelines. In order to reduce the bias, almost all patients received similar treatment without violation of GOLD document, but the type of antibiotic was decided by the clinicians. Treating clinicians were not directly involved in the study and were blinded to the results. Baseline measurements were performed before accepting

treatment in all patients. At the second visit, their health status was divided into five groups based on a five-point Likert scale ranging from 1 to 5, representing ‘much better’, ‘slightly better’, ‘no change’, ‘slightly worse’ and ‘much worse‘, respectively. Responders were defined as having a global rating of change in COPD since last visit of “much better,” or “slightly better”, non-responders were defined as having a global rating of change in COPD since last visit of ‘no change,’ ‘slightly worse’ or ‘much worse’ [10, 36].

Measurements

Measurement of FENO

The FENO measurement was performed using the Nakorun breath analyzer from Wuxi ShangWo Medical Electronics Company, China. The testing process was conducted strictly in accordance with the guidelines recommended by the American Thoracic Society/European Respiratory Society. The exhalation flow rate was controlled at 50 ml/s to measure the FENO level (in ppb).

Lung function tests

Lung function parameters were measured using an electronic spirometer (CHESTGRAPH HI–101) according to American Thoracic Society guidelines by the same professional technician.

Measurement of blood gas analysis

Blood gas parameters were determined using a blood gas analyzer (GEM Premier 3000), with 2 ml of arterial blood taken from the radial artery. Measurements were performed by a respiratory nurse on patients who stopped inhalation of medical oxygen for 30 min.

Measurement of CAT and mMRC

These questionnaires were explained to the patients by clinicians and completed by the patients independently.

Statistical analysis

Clinical characteristics of patients were summarized descriptively. Data were reported as mean ± SD and the level of statistical significance was set at 0.05 (two-sided). Changes in measured variables obtained at hospital admission and on day 7 showing a normal distribution were tested using paired *t*-tests, whereas variables showing non-normal distribution were analyzed by rank test. Spearman’s rank correlation coefficient method or partial correlation was used to analyze the relationship between health status and CAT, lung function, FENO and blood gas analysis (partial pressure of oxygen in arterial blood, PaO_2; partial pressure of carbon dioxide in arterial blood, $PaCO_2$). Group comparisons were tested using analysis of variance (ANOVA) or *t*-test. Receiver operating characteristic (ROC) curve comparison analysis

was used to compare the capacity of those measurements for differentiating patients' self-reported responders. SPSS software version 25.0 and Medcalc were used for statistical analysis.

Results

Patient demographic characteristics

A flow chart of the study was shown in Figure 1. Initially, a total of 123 subjects with a primary diagnosis of AECOPD were screened in the study. Among them, 31 patients were excluded because of pneumonia ($n = 17$), lung cancer ($n = 3$), severe heart failure ($n = 4$) and accepting systemic corticosteroids before admission ($n = 7$). During exacerbation, 37 patients failed to complete the second measurements of lung function or FENO. Among these 37 patients, 18 failed to complete the second lung function because of severe dyspnea, 2 refused to complete the FENO measurement and 13 decided to drop out due to unwillingness to perform the tests again. In addition, four patients were transferred to the intensive care unit. Among all the patients who failed to continue the research, most of them ($n = 32$) were divided into GOLD III or IV stage, the mean FEV_1% being 25.66 ± 7.82. Thus, only 55 patients were recruited to the final analysis. Demographic and clinical data were presented in Table 1. The mean age of the patients was 66.96 ± 10.50 years, with 92.73% males and 7.27% females. Among all the patients, 31 were current smokers and 24 were ex-smokers. Almost all patients received similar treatment (antibiotic + Theophylline + Nebulized inhalation of bronchodilators and corticosteroids) based on the GOLD document but the type of antibiotic was decided by the clinicians. No patients were treated with systemic corticosteroids, either orally or intravenously, the detailed information was shown in table 1.

Changes in main parameters between the two visits

All the main parameters improved significantly. The levels of FENO, $PaCO_2$, CAT and mMRC decreased from 26.07 ± 13.48 to 16.31 ± 9.26 ppb, 47.05 ± 10.63 to 41.56 ± 8.823 mmHg, 26.82 ± 17.33 to 17.47 ± 7.45 and from 3.18 ± 0.72 to 1.65 ± 0.75, respectively; and the levels of FEV_1, FEV_1% and PaO_2 at the second visit all increased significantly when compared with the baseline on admission the changes in them were (0.18±0.16), (8.38±6.73), and (12.95±11.52), respectively. Statistical differences were observed between the two visits for all the above parameters (Table 2).

Changes in main parameters between the two visits with different health status

The majority (81.82%) of AECOPD patients reported improved health status at the second visit. Among them, 65.45% of patients ($n = 36$) reported their health status as much better and 16.37% ($n = 9$) as slightly improved. No subject reported 'much worse' in this study. The absolute changes in FENO value decreased in turn from 'much better' (13.92 ± 10.49 ppb) to 'slightly worse' (6.60 ± 9.37 ppb, $n = 5$); there were statistically significant differences between all groups except the 'no change' group ($n = 5$), which only had a significant difference with the 'much better' group. The change in FEV_1 in the 'much better' group (0.23 ± 0.12 l) was much higher than in the 'slightly worse' group (0.03 ± 0.27lL), and the

improvement in FEV_1% in the 'slightly worse' group (0.74 ± 10.44) was lower than in the other three groups. The change in CAT in the 'much better' group was 13.17 ± 3.35, which had statistical significance compared with the other groups. There was no significant difference for the changes in PaO_2 and mMRC among the groups (Table 3).

Changes in main parameters between the two visits with different treatment response

We analyzed the changes in all parameters between the responders and non-responders. As defined before, responders were those who reported "much better," or "slightly better", non-responders were those reporting "no change," or "worse". Among all the patients, 81.82% were responders and 18.18% were non-responders. The changes in FENO, FEV_1%, FEV_1, CAT and mMRC were statistically significant between the two groups, while PaO_2 and $PaCO_2$ didn't change significantly (Table 4).

Correlation of main parameters on admission with health status

After adjusted age, we analyzed the correlation between those measurements (FEV_1, FEV_1%, FENO, PaO_2, $PaCO_2$, CAT, mMRC) and health status. In terms of the baseline level of the above-mentioned parameters, only the level of FENO level had a slightly negative relationship with health status (rho = 0.352, P = 0.008), which means that patients with a high level of FENO on admission were more likely to have a good treatment response (Table 5).

Correlation of changes in main parameters between the two visits with health status

The changes in FENO had a moderate positive relationship with health status (rho = 0.54, $P < 0.001$); furthermore, a strong positive correlation was observed between the changes in CAT and health status (rho = 0.81, $P < 0.001$). However, the improvement in FEV_1 and FEV_1% showed a slightly negative correlation with health status: rho was 0.32 and 0.42, respectively (Table 6).

Comparison of the capacity of the main parameters to differentiate responders

Based on the patient self-reported health status, we regarded the patients who reported 'much better' and 'slightly better' as responders and those who reported 'no change' 'slightly worse' and 'much worse' as non-responders. We found that changes in CAT have the highest AUC (0.978) to differentiate responders, followed by FENO, the AUC was 0.914. The AUC of FEV_1, FEV_1%, and mMRC were 0.697, 0.748 and 0.691, respectively. The changes in FENO and CAT had better capacity to differentiate those responders than FEV_1, FEV_1% and mMRC, but there is no significant difference between CAT and FENO. (Figure 2).

Discussion

To date, there is no uniform discharge criteria for patients with AECOPD. Clinicians judge whether a patient is suitable for discharge according to the patients' self-reported health status and some measurements including lung function, FENO, blood gas analysis, CAT and mMRC. But which

measurement is most closely related the patients' self-reported health status remains unknown. To our knowledge, this is the first study to compare the use of these measurements in evaluating the patients' health status in exacerbation stage of COPD. This longitudinal study demonstrated that CAT, FENO and FEV_1% had good sensitivity in assessing the evolution of the health status of AECOPD patients, while blood gas analysis and mMRC didn't evolve sensitively with different health status. Among these measurements, CAT was best closely related to the patients' self-reported health status, FENO is better correlated to health status than FEV_1 or FEV_1%.

In this study we found that the level of all the parameters changed significantly (with statistical differences) during the two visits, indicating that they may be good tools to monitor the evolution of health status. However, we did not find any differences of changes in PaO_2 and mMRC within the different groups of AECOPD patients, suggesting that PaO_2 and mMRC are not sensitive to changes in patients' health status. In this study we also compared the level of the parameters between responders and non-responders: no significant changes were observed in PaO_2, $PaCO_2$, which suggested that they were not good tools for evaluation of patients' health status.

As a recent study showed, the treatment success ratio (stable stage) in a clinical trial may depend on the selected parameters(CAT, FEV_1 or Clinical COPD Questionnaire (CCQ)) [37], in that study, the patients were defined as responders if they achieved the minimum clinical important difference (MCID) from baseline of ≥100 mL increase in FEV_1 ≥1 unit increase in Transition Dyspnoea Index (TDI) ≥0.4 unit decrease in CCQ or ≥2 unit decrease in CAT. The proportion of patients who were responders was highest for TDI (n = 2008 (46.4%)), followed by FEV_1 (n = 1680 (38.9%)), CAT (n = 1585 (36.7%)) and CCQ (n = 1173 (27.1%)), which indicated that the treatment success ratio(responders) may also vary in exacerbation stage with different measurements. Actually, there is even no validated MCID of the above measurements in exacerbation stage, in Antus's study [11], the responders were those who had a significant increase (>12% and >200mL) in FEV_1, however, this criterion is not suitable for clinical work, since it's too strict to use it as discharge criterion, for some severe patients, it's impossible to get such huge improvement, in our study, less than one third of patient meet this criterion on day 7. If clinicians take this standard into clinical work, it will increase the mean hospital day, economic cost and nosocomial infection risk dramatically. CAT was also used to evaluate the treatment response of AECOPD patients in clinical trial [10], and FENO was proved to be a predictor for evaluating treatment response in AECOPD patients[11]. In our study, FENO, CAT, mMRC, blood gas analysis and lung function (FEV_1 and FEV_1%) were all found to change significantly between two visits, but CAT was the most sensitive measurement to the changes in health status than other measurements, this may be due to that CAT was also completed by patients themselves and it consists the main symptoms of COPD disease. Blood gas analysis and mMRC were not sensitive to the changes in health status, this is may be related to the fact that COPD is a chronic disease, the patients had long term hypoxia and already tolerated, they may feel good even with low PaO_2[38],mMRC is simple dyspnea scale score from 0 to 4 to evaluate the functional impairment due to dyspnea attributable to respiratory disease, the baseline of mMRC in this

study was 3.18 ± 0.72, the changes in mMRC after treatment was 1.53 ± 0.69, it was reasonable that mMRC didn't change much among the different health status groups.

In this study we also compared the relationship between FENO, CAT and lung function (FEV_1 and FEV_1%) on admission, at the second visit, and changes in these parameters with health status, respectively. We found that the changes in them were more closely related to the patients' self- reported health status than the single levels either on admission or at the second visit, which indicates that dynamic monitoring would be more useful in evaluating the patients' health status.

Moreover, we defined responders and non-responders based on the patients' reported outcome. The comparison analysis showed that changes in CAT and FENO had good predictive value for responders, followed by FEV_1%. The reason why FENO was even more closely related with health status was that the recovery of lung function may lay behind lung function[39]. This indicated that in clinical work the monitoring of FENO could provide some information for health status of the patients in exacerbation stage of COPD.

We acknowledge that this study has some limitations. Firstly, the number of cases was limited, especially for those who reported slightly worse or much worse, since they could not perform or refused to perform the second lung function due to severe dyspnea. Secondly, there is no recognized standard for responders, in this study, we defined them as those who reported much better or slightly better, although this is definitely not a gold standard, in this study, the main purpose is analyze which measurement was most closely related to patients' reported health status, thus, it's reasonable to divide the group in this study. Thirdly, we didn't have the baseline data before exacerbation, or it would be more meaningful to study the evolution of lung function, FENO, blood gas analysis, CAT and mMRC with the changes in health status of COPD patients.

Conclusions

In summary, CAT is most closely related to patients' reported health status, FENO is also a good measurement to perform to monitor the health status during exacerbation stage. However, lung function didn't change so sensitively with the evolution of patients' self-reported health status. In clinical work, the pulmonologist can judge the health status based on the patient reported outcome and CAT or FENO.

Abbreviations

AECOPD: acute exacerbation of chronic obstructive pulmonary disease

ANOVA: analysis of variance

AUC: area under the curve

CAT: COPD Assessment Test

COPD: chronic obstructive pulmonary disease

FENO: fractional exhaled nitric oxide

FEV_1: forced expiratory volume in one second

FVC: forced vital capacity

GINA: Global Initiative for Asthma

GOLD: Global Initiative for Chronic Obstructive Lung Disease

ICS: inhaled corticosteroids

mMRC: modified Medical Research Council test

$PaCO_2$: partial pressure of carbon dioxide in arterial blood

PaO_2: partial pressure of oxygen in arterial blood

CCQ: Clinical COPD Questionnaire

MCID: minimum clinical important difference

TDI: Transition Dyspnea Index

Declarations

Ethics approval and consent to participate

This research was approved by the local Ethics Committee of the Second Xiangya Hospital of Central South University (approval number: zay0410), and all subjects gave written informed consent to participate in the study.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

None of the authors have a conflict of interest that could affect this manuscript.

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Author contributions

Aiyuan Zhou and Ping Chen designed the study. All authors contributed toward recruiting subjects, statistical analysis and drafting the paper, and each of the authors agreed to be accountable for all aspects of the work.

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Figures

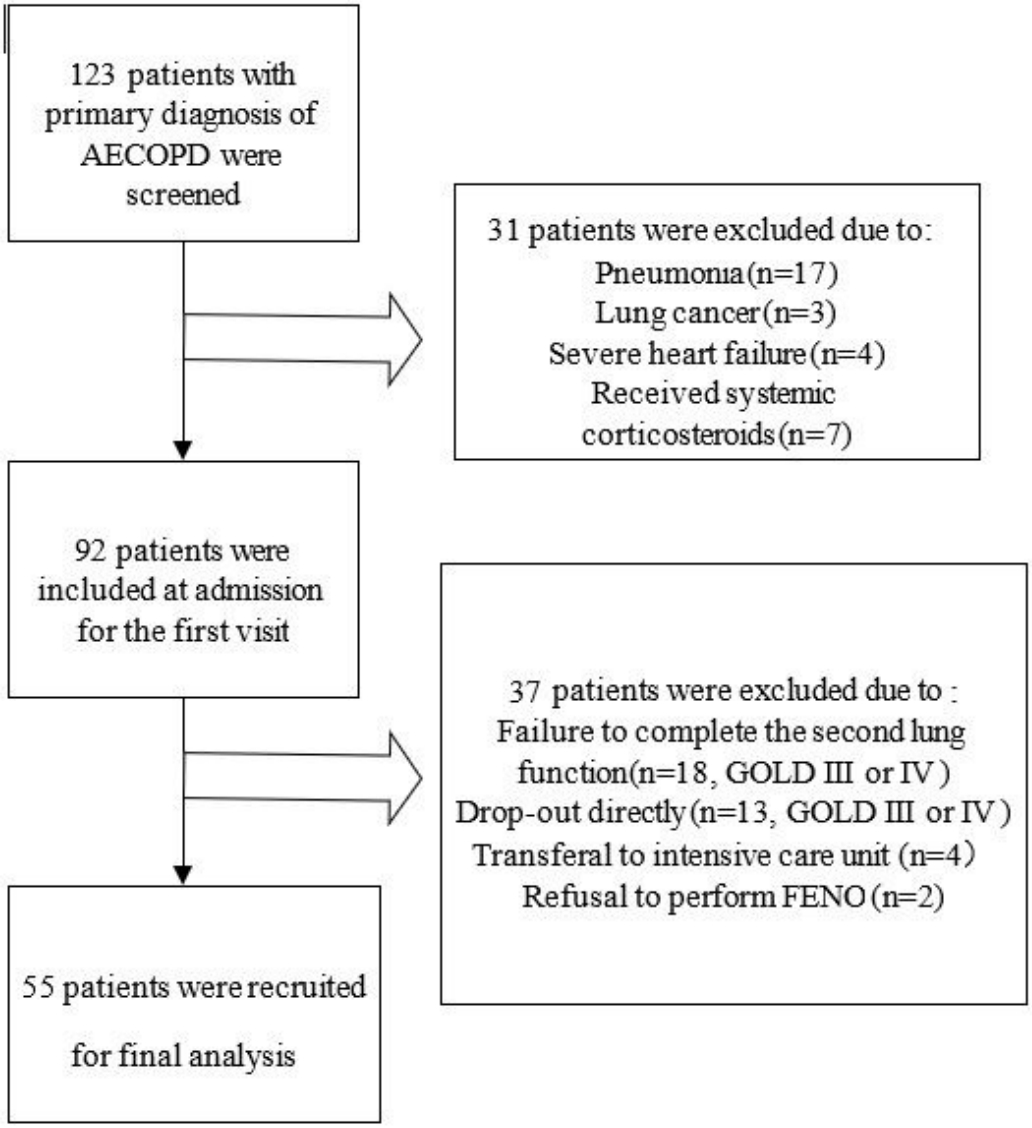

Figure 1

Flow chart of the study to recruit subjects. Legend: Initially, a total of 123 subjects with a primary diagnosis of AECOPD were included in the study. Among them, 31 patients were excluded because of pneumonia (n = 17), lung cancer (n = 3), severe heart failure (n = 4) and accepting systemic corticosteroids before admission (n = 7). During exacerbation, 37 patients failed to complete the second measurements of lung function or FENO successfully. Thus, only 55 patients were recruited to the final analysis.

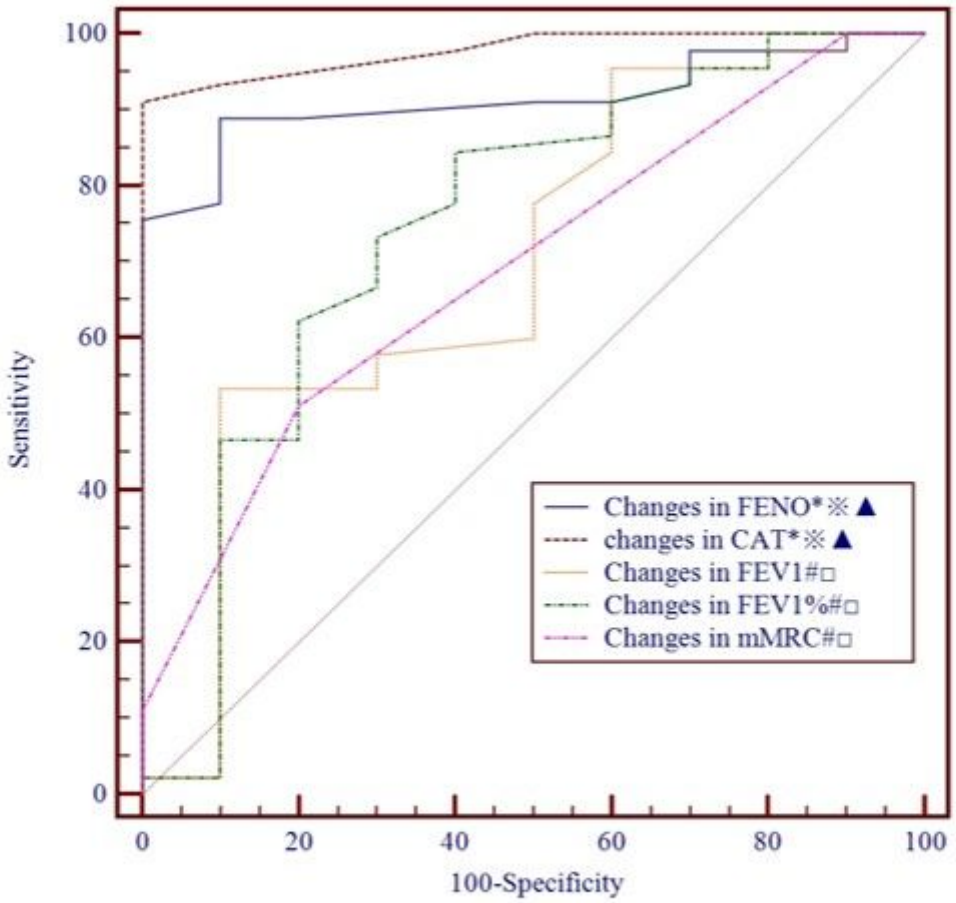

Figure 2

Comparison of the capacity of the main parameters to differentiate non-responders. Legend: The changes in CAT showed the highest AUC of the ROC curve (0.978) to differentiate non-responders, followed by FENO (0.914) and FEV1% (0.748). The AUC of the changes in mMRC was 0.691; * means P < 0.05 vs. 'mMRC', ※ P < 0.05 vs. 'FEV1%', ▲P < 0.05 vs 'FEV1', #P < 0.05 vs. 'CAT', □ means P < 0.05 vs. 'FENO'.