STUDY REPORT SYNOPSIS

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| **Development of AECOPD identification tool (DETECT study) A diagnostic test to develop an AECOPD identification tool through characteristic variables extracted from diagnosed AECOPD patients** | |
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| Milestones: | |  |  | | --- | --- | | Final protocol | 2020-07-30 | | First subject enrolled | 2020-04-22 | | Last subject last visit | 2021-01-18 | | Clinical data lock date | 2021-04-13 | | Final TFL | 2021-07-30 | | Final SAR | 2021-08-30 | | Final CSR | 2021-09-13 | |
| Phase of development: | Non-interventional study |
| Sponsor: | AstraZeneca |
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| This study was performed in compliance with Good Clinical Practice (GCP) and Good Pharmacoepidemiology Practice (GPP), including the archiving of essential documents. | |
| This submission/document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca (AZ) and opportunity to object. | |

**Background/rationale:** Acute exacerbations of COPD (AECOPD) are very important to the management of COPD because they negatively impact health status, rates of hospitalization and readmission, and disease progression [4]. However, due to lack of an objective and standard quantitative identification tools or items, misdiagnosis and miss diagnosis are common in current clinical practice especially in primary clinical settings. To accommodate the facts, an identification tool with majorly symptoms evaluation and simple test results would be developed in this study to fulfil the need of physicians at primary care.

**Objectives:** Primary Objective: To develop an identification tool on purpose of differentiating AECOPD from patients with respiratory symptoms in the community hospitals of China.

Secondary Objective: To investigate clinical characteristics of disease severity of AECOPD patients.

Exploratory Objective: To develop an AECOPD and the disease severity identification tool use for self-management of COPD patients.

**Study design:** This was an observational, multi-center and cross-sectional study.

**Data source:** 1. Case Report Form (CRF). 2. Medical records. 3. Patient-Reported Outcome (PRO) questionnaires.

**Study population:** There were to be 3 types of patients eligible for this study, including 90 Non-COPD Patients with high risk factors, 90 Moderate to severe COPD Patients, 120 AECOPD patients (60 mild/moderate and 60 severe). All subjects were to be diagnosed by clinical experts from tertiary hospitals.

**Inclusion criteria**:

1. ≥ 40 years old of age.
2. Patients see doctors due to suffering respiratory disease below:

Disease type 1- diagnosed moderate and severe stable COPD

* Patients with a diagnosis of COPD and documented record with predicted ratio of FEV1 to forced vital capacity (FVC) < 0.70 before the study visit
* COPD with moderate to severe airflow obstruction (FEV1<0.8 predicted)

Disease type 2- AECOPD

* Patients with a diagnosis of COPD and documented record with predicted ratio of FEV1 to forced vital capacity (FVC)<0.70 before the study visit
* Patients consult the clinic or the emergency department because of acute worsening with an AECOPD

Disease type 3

* Non-COPD patients with chronic respiratory symptoms such as cough, sputum and wheeze, dyspnea etc. (≥2 high risk factors \*)

\* Risk factors including Symptoms, exposure, health history, recent history of respiratory event.

**Exclusion criteria**:

1. Patients with severe cardiovascular disease;
2. Patients with lung cancer, esophageal cancer or mediastinal tumors;
3. Patients who participated in any drug clinical trials within 4 weeks before enrollment;
4. Patients with severe infection;
5. Patients suffering from mental illness and poor compliance;
6. Patients inappropriate for inclusion decided by investigator.

**Statistical methods:**

Analysis of this study was mostly descriptive. Numerical data were presented as number of subjects, mean, standard deviation, median, min and max. Categorical data were presented as frequency and percentage of patients. Both types of data will be summarized in each disease condition category (Non-COPD, COPD, AECOPD) and overall.

A multivariate logistic regression model used primarily to construct the identification tool of AECOPD. Within this model, the occurrence of exacerbation was the dependent variable and the disease characteristics, patients characteristics and other risk factors were the independent variables.

Three different training models were built and bootstrap method was used for the internal validation of the equation. During model training, a stepwise procedure was used to select the variables with significance levels smaller than 0.15 to enter the model and 0.20 to stay in the model. Important variables can be forced to stay in the model. Model apparent performances include the Akaike information criterion (AIC), Bayesian information criterion (BIC), R squared, and area under the ROC curve (AUC). A smaller AIC or BIC score was preferable to a more significant score in the model selection process, whereas a higher R squared or AUC was more desirable for model selection.

Above procedure was repeated until the identification tool achieves 0.70 for both sensitivity and specificity. A similar procedure to the analysis of primary objective was employed to construct an index or tool for the severity of AECOPD.

**Results**: Totally 7 tertiary hospitals with top experts in respiratory area were involved as the study sites. The study finally enrolled 299 patients. 246 (82.3%) patients were included in FAS. Among 246 patients in FAS, 74 were moderate to severe COPD patients (47 moderate, and 27 severe), 100 were AECOPD patients (48 mild and moderate, and 52 severe), and 72 were Non-COPD patients with high risk factors.

1. Primary endpoints

Three different models had been built for identifying the patients with AECOPD. After the integrated consideration of adjusted performance results, sensitivity and specificity, Model 2 was considered the best model which the accuracy was 0.801 (0.744, 0.846), the sensitivity was 0.840 (0.754, 0.901), the specificity was 0.774 (0.707, 0.845), and the optimal cut-off value was 0.374 .Model 2 included independent variables Age, Sex, Chest Tightness（CAT）, GOLD Classification, Most Recent Exacerbation in the Past 12 Months, No. of Exacerbations Resulted in Hospitalisation, Phlegm Colour（Core Symptom -Present）, and Respiratory Rate. We calculated predicted risk of developing AECOPD by the regression equation of model 2. A subject will be categorized as test positive (suspected AECOPD) when predicted risk ≥ 0.374, whereas classified as test negative when predicted risk <0.374.

2. Secondary Objective & Exploratory Objective

Three different models had been built for identifying the patients with severe AECOPD. After the integrated consideration of adjusted performance results, sensitivity and specificity, Model 3 considered the best model which the accuracy was 0.820 (0.750, 0.890), the sensitivity was 0.904 (0.825, 0.980), and the specificity was 0.729 (0.602, 0.856), and the optimal cut-off value was 0.405. Model 3 included independent variables Age, Sex, Most Recent Exacerbation in the past 12 months, Limited When Doing Home Activities (CAT), No. of Exacerbations Resulted in Hospitalisation, Onset Time of Symptom (Core Symptom - Present).We calculated predicted risk of developing severe AECOPD by the regression equation of model 3. A subject will be categorized as test positive (suspected severe AECOPD) when predicted risk ≥ 0.405, whereas classified as test negative when predicted risk <0.405.

**Conclusion**:

In conclusion, we have established the diagnostic model that can identify patients with acute exacerbations and severe acute exacerbations, which has great internal validation and performed well in discrimination. The model may be of value to clinicians and patients to make an early identification of AECOPD when the diagnosis is uncertain and make salutary prevention management in clinical practice. However, further research is still required to external validate the use of the model especially in primary clinical settings.

**Confidentiality statement:**

This document contains trade secrets and privileged or confidential information that may not be disclosed without written permission of the sponsor.