Prediction Indicators for Acute Exacerbations of Chronic Obstructive Pulmonary Disease By Combining Non-linear analyses and Machine Learning

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***Abstract*—Acute exacerbations are important episodes in the course of chronic obstructive pulmonary disease (COPD) which is associated with a significant increase in mortality, hospitalization and impaired quality of life. An important treatment for COPD is home telehealth-monitoring intervention. Physiological signals monitored continuously with home ventilators would help us address disease condition in time. However, the absence of useful early predictors and poor accuracy and sensitivity of algorithms limit the effectiveness of home telemonitoring interventions. In order to find prediction indicators and improve the accuracy from physiological signals, we developed a prediction method to search for indicators connected with acute exacerbations. In this study, we analyzed one-month physiological data (airflow and oxygen saturation signals) of 22 patients with COPD before acute exacerbations happened. In the analysis we employed non-linear analyses and machine learning. We applied Multiscale entropy analysis (MSE) and Detrend fluctuation analysis (DFA) to extract features from airflow. Random forest (RF), linear discriminant analysis (LDA) and support vector machine (SVM) were used to classify the stable state and acute exacerbations of disease. The results showed that LDA had the best average precision of 62% and SVM had the best average recall of 56%. Additionally, according to the analysis of RF, the most predictive features are mean of airflow, results of DFA and MSE in scale 4. RF shows a highest accuracy of 75% in three methods, when LDA illustrates a highest specificity of 42.9%. This study will provide insights in developing COPD home-monitoring system which can prognose the onset of acute exacerbations, thus reducing the need of hospital admissions and improving the life quality of COPD patients.**

Keywords—chronic obstructive pulmonary disease, acute exacerbations, physiological signals, home telehealth, non-linear analysis, machine learning

I. INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a serious, debilitating condition that has become a major public health concern and by 2020 is projected to rank fifth in global burden of disease and third in global mortality [1-3]. From a pathophysiologic perspective, COPD is characterized by chronic airflow limitation and a range of pathological [4]. The symptoms include wheeze, breathlessness, chest tightness and cough and are associated with fixed airflow limitation. COPD exacerbations are associated with accelerated worsening of lung function, increased disease burden and mortality, thus they are important in identifying and treating these patients [5].Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are important episodes in the course of the

disease associated with a significant increase in mortality, hospitalization and health-care use and impaired quality of life. The current definition of AECOPD in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Guidelines is as follow: An exacerbation is defined as an acute event characterized by a worsening of the patient's respiratory symptoms from the stable state and beyond day-to-day variation, leading to a change in medical treatment and/or hospitalization [6].Key symptoms indicating an exacerbation include increased dyspnea; sputum purulence; sputum volume; cough, wheeze, or fatigue; chest tightness; reduced exercise tolerance; fluid retention; or acute confusion [7].

A recent cross-country study has shown that the greatest proportion of healthcare use is in primary care [8]. The largest component of total costs is attributable to admissions because of AECOPD [9]. Therefore, management of AECOPD becomes a crucial problem to be solved. An important treatment for COPD is home telehealth-monitoring intervention. The data collected through the telehealth system would enable clinicians to provide a more patient-centered service by identifying whether patients required additional supportive home visits to address any fluctuations in their condition. In addition, recent advancement in data mining and machine learning methods offer the opportunity to combine prior knowledge of the clinical context with telemonitoring data sets to reveal predictive patterns [10].

At present, people use the continuous measurement of human physiological parameters of the data obtained by the majority of its average, and occasionally use the variance, the maximum or minimum. Some of the important statistical parameters (such as dynamic complexity) that are hidden in continuous measurement data are yet to be explored. Fernández-Granero et al. [11]were able to detect AECOPDs an average of 4.8 days before onset with 80.5% accuracy using a questionnaire analyzed by a probabilistic neural network, but this approach is not part of the standard care pathway and adds an incremental step. Mohktar and Antoniades [12] found that CART algorithm could classify home telehealth measurement data into either a ‘low risk’ or ‘high risk’ category with a 71.8% accuracy. Hardinge et al. [13] displayed that 40% of exacerbations had alert signal during the three days prior to the event. However, some major reported factors limit the effectiveness of home telemonitoring interventions. Such as the absence of useful early predictors, poor patient compliance and the poor accuracy and sensitivity algorithms for predicting AECOPD.

Based on the background, if we could provide early and accurate detection of AECOPD within telehealth monitoring, novel predictors and mathematical algorithms, it is able to offer an opportunity for early intervention to alleviate symptoms and reduce care costs. This way could prevent hospital admissions, reduce health resource utilization and improve the quality of life of patients with COPD.

II. METHODS

A. Patients

This is a prospective cohort study, with ethics approval from the appropriate committees. We selected 22 patients with COPD from 300 patients in Beijing Chaoyang Hospital for our study. Flow of patients throughout this research can be appreciated in the flowchart. All patients were enrolled in the use of non-invasive ventilator (RESmart GII BPAP Y-25T, BMC Medical Co., Ltd., Beijing, China), and the mode set to S / T mode. These patients wore ventilator continuously for more than 4 hours a day for continuous monitoring of ventilator especially during the sleeping time. Inclusion criteria were: 1) Going to hospital because of AECOPD at least once within these years; 2) using non-invasive ventilator almost every day before hospitalization; 3) no of the complications were founded. Exclusion criteria were: 1) significant comorbidities (e.g., cancer, cardiac failure); 2) Pregnant women and children.

The demographic characteristics of patients are shown in Table 1. We could analyze three variables from non-invasive ventilator: airflow, pressure and saturation of pulse oxygen (SpO2). These variables were continuously monitored by home ventilator and transmitted to a data platform. Then the data of these patients were referred to their primary care physicians. We counted the ventilator usage rate of these patients one month before going to hospital.

B. Data processing

All continuous monitoring data were anonymous, identified only by study identity number. Prior to doing analysis, the data were grouped by day and divided into several segments according to using time. Since the data quality may affect the prediction performance, we should think about processing of missing values and outlier detection. These missing values were deleted if their length less than 200 data points (Fig.1). As for the outlier detection, first some statistical parameters were calculated: the median (50th percentile), and the lower (25th percentile) and upper (75th percentile) quartiles. Secondly, lower and upper thresholds were calculated as the 25th percentile minus 1.5 times the interquartile range, and the 75th percentile plus the 1.5 times the interquartile range, respectively. Any data values outside these limits were considered as outliers and deleted [14].

Fig.1 shows procedure of missing values. These pictures display: one day data of a patient (including missing data), deleting missing value, 500 data points, 100 data points, missing data breakpoints and deleting missing values.

TABLE I. DEMOGRAPHIC CHARACTERISTICS OF THE STUDY GROUP

Variable	***N (%)***
Age (years)	76.14±11.60
Male (%)	81.81% (18)
Height (cm)	167.27±7.92
Weight (kg)	60.09±15.49

Variable	*N (%)*
Before hospitalization (%)	
One week	86%
One month	90%

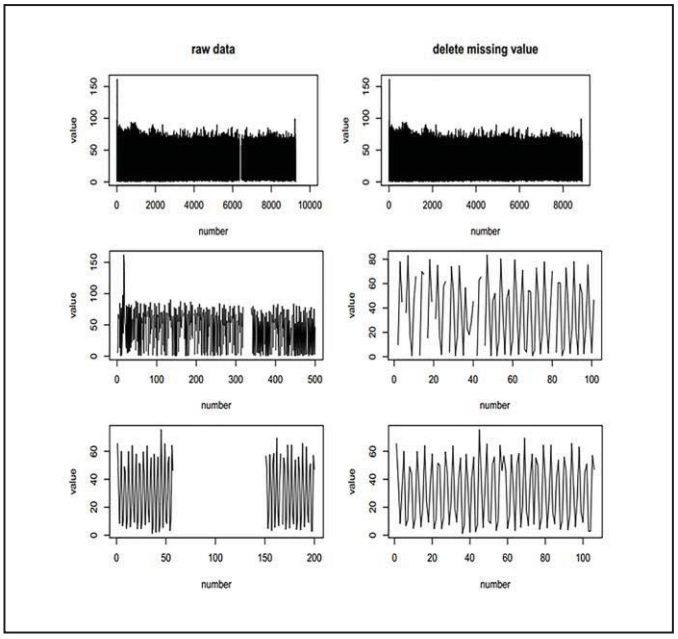

Fig. 1. Procedure of missing values. 1) one day data of a patient (including missing data), 2) deleting missing value, 3) 500 data points, 4) 100 data points, 5) missing data breakpoints, 6) deleting missing value

C. Non-liner analysis

- Multiscale entropy

Multiscale entropy (MSE) analysis introduced by Costa and Goldberger et al. was used to quantify complexity from physiological time series [15-17]. The basic idea of MSE analysis is to produce a new time series based on nonoverlapping segments of equal length (τ) and then to calculate corresponding entropy for each coarse-grained time series. This procedure could be divided into two steps as follow: According to a coarse-graining procedure, a set of time series could be constructed and it represented the system dynamics on different time scales. Given a monovarietal discrete signal of length N, we determined the scale factor τ and the coarse-grained time series. Then we calculate sample entropy (SampEn) for each coarse-grained time series.

- Detrend fluctuation analysis

The original Detrend fluctuation analysis (DFA) was introduced by Peng et al. [18] to investigate long-range correlation in non-stationary time series. The scaling exponent of DFA is an important unitless asymptotic value that quantifies the degree of long-range correlations. In addition, it can analyze the diverge of the profile and linear regression with the increasing time window. Briefly, we calculate the root mean square fluctuation of the detrended time series. Next, we applied a modified root mean square analysis of a random walk to quantify the relationship between fluctuation and the observation window size. DFA scaling exponents in range (0.5,1) indicate the time series are long-term correlated. If scaling exponents are greater than 1.0 indicate a non-stationary local average of the data. When the scaling exponents are less than 0.5 corresponds to long-term anti-correlations [19].

In order to study complexity of physiological signals, we applied these two non-linear methods to analysis airflow signals.

D. Machine Learning

- Random forest

Random Forest is a supervised machine learning algorithm for classification and regression tasks. The original algorithm for random forest was produced by Tin Kam Ho [20] and extended by Leo Breiman and Adele Cutler in 2001 [21]. Random forest is an ensemble of decision trees and the outputting class is the mode of the classes of individual trees. This algorithm combined with bootstrap aggregating method and random subspace method to construct the collection of decision trees with controlled variance. For full details of the algorithm see [21].

- Linear Discriminant analysis

The original method of linear discriminant analysis (LDA) was proposed by Ronald Fisher [22]. This method attempts to find a linear combination of the features of two types of objects to characterize or distinguish them [23]. The advantages of this algorithm are reducing overfitting and computational costs. We applied this method to predict disease status of patients with COPD, especially for distinguishing the stable state and acute exacerbations state.

- Support vector machine

Support vector machine is a supervised learning model for classification and regression analysis [24]. In SVM algorithm, we plot each data item as a point in n dimensional space. And these values are the coordinate values of these data points [25]. Then we find some lines or hyperplane to divide the data into different classification groups. This line or hyperplane allows the distance between the closet points in the two sets to be the farthest. Then, SVM model could distinguish test data into different groups based on the position.

To evaluate the estimator performance, we used five-fold cross validation. We randomly divided the original sample into five equally sized subsamples. Using the data from four subsamples to train this model, and the remaining subsample is applied to test the model. This process is repeated five times, changing subsamples in equal size. The average can be calculated to produce a single estimation.

TABLE II. MSE RESULTS OF THREE DAYS IN SCALE ONE TO TEN

Scale values	*Day 1*	*Day 2*	*Day 3*
1	0.94	1.094	0.952
2	0.302	0.422	0.503
3	0.141	0.194	0.226
4	0.287	0.289	0.377
5	0.525	0.477	0.548
6	0.058	0.075	0.086
7	0.417	0.38	0.439
8	0.46	0.301	0.408
9	0.121	0.145	0.166
10	0.305	0.29	0.398

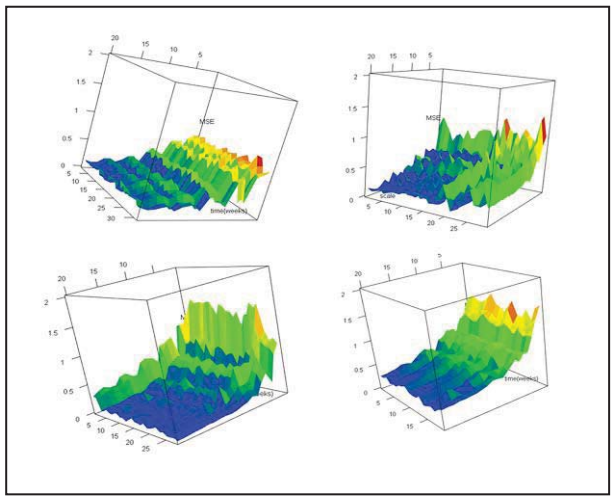

Fig. 2. Three-dimensional picture for four patients during thirty days before happening of acute exacerbations. 0-30 represented the number of days before hospitalization, 0-2 represented the value of entropy, and 0-20 represented the scale parameter of MSE.

III. RESULTS

In order to explore the complexity of airflow for different disease status, we calculated entropy values of airflow in different scales for thirty days. Table 2 showed the results for three days of a patient and scale parameters were 1 to 10. The entropy values changed in different scales of MSE.

Fig.2 demonstrated the three-dimensional picture for four patients thirty patients before happening of acute exacerbations. Each line characterized the entropy of the flow data for each day at different scales. 0-30 represented the number of days before hospitalization, 0-2 represented the value of entropy, and 0-20 represented the scale parameter of MSE. We can see that there was a significant increase in entropy (the red area in the figure) about five days before hospitalization. Although the data pattern distributions were different, the flow entropy values showed significant fluctuations and increases (red and orange areas in the figure) at five to seven days before hospitalization.

TABLE III. PRECISION AND RECALL ON TRAIN AND TEST SET IN MICRO- AND MACRO-AVERAGING.

Data set	**Results**	**Machine learning methods**		
		RF	***SVM***	***LDA***
Training	Macro-average			
	Precision	0.7464	1.0	0.8756
	Recall	0.6133	1.0	0.7307
	Micro-average			
	Precision	0.7928	1.0	0.86
	Recall	0.7928	1.0	0.86
Testing	Macro-average			
	Precision	0.6248	0.5310	0.6032
	Recall	0.5458	0.5120	0.5606
	Micro-average			
	Precision	0.7451	0.7408	0.7373
	Recall	0.7451	0.7408	0.7373

a. RF: random forest; SVM: support vector machine; LDA: Linear Discriminant analysis

In LDA, RF and SVM daily records were used directly as input. Records that fell within 7 days before AE onset were assigned as group 1 and the remaining records were assigned as group 0. Group 0 contained 416 records and group 1 contained 133 records. Stratified 5-fold cross validation was applied and the averages of precision and recall were calculated.

The result of all three analyses demonstrated some features of the dataset (Table 3). The macro-averages showed a discrepancy between training set and test set, suggesting that the model was not generalizing the dataset well and the trained classifiers would not be able to classify unseen data. This could be because the variance within group was very high or the dataset was not sufficiently large.

Considering the testing result, LDA had the best average precision of 62% and SVM had the best average recall of 56%. The high values in micro-averages implied that there was an imbalance of precision and recall between the two groups, which can be observed in the confusion matrices. The number of group 0 records was high enough that although most of the group 1 were misclassified the recall would still be higher than 0.7.

On the other hand, it can also be observed that RF fitted the training set perfectly but the performance on test set was the worst. It further demonstrated the high variation between training set and test set.

Feature importance calculated by RF indicated that mean and DFA ranked among the top three most important features, while MSE in scale 4 being on the second rank. The top three features surpassed the remaining by about 1% to 3% (Table 4 and Fig.3).

TABLE IV. THE IMPORTANCE OF ALL FEATURES.

Features	*Importance (%)*
1	0.0324
2	0.0463
3	0.0423
4	0.0635
5	0.0464
6	0.0431
7	0.0452
8	0.0469
9	0.0437
10	0.0424
Mean	0.0714
SD	0.0449
DFA	0.0591

[b.] mean, standard deviation (SD) and multiscale entropy (MSE) of airflow in scale 1 to 10.

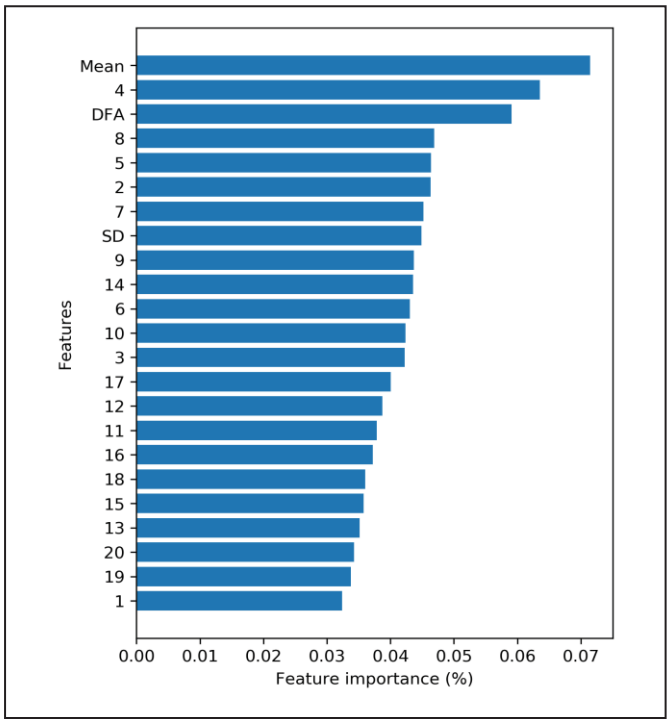

Fig. 3. Features importance by random forests methods. These features include mean, standard deviation (SD) and multiscale entropy (MSE) of airflow in scale 1 to 20.

The classification results of the three machine learning methods were shown in Table 5. LDA demonstrated an accuracy of 74.5%, sensitivity of 77.6% and specificity of 42.9%. As for SVM, it classified the status with 73.7% accuracy, 78.3% sensitivity and 42.0% specificity. While RF had almost the same accuracy as LDA and lowest specificity.

TABLE V. THE ACCURACY, SENSITIVITY AND SPECIFICITY OF THREE METHODS

Machine learning methods	*Accuracy*	*Sensitivity*	*Specificity*
LDA	74.5%	77.6%	42.9%
SVM	73.7%	78.3%	42.0%
RM	75.0%	76.4%	40.9%

RF: random forest; SVM: support vector machine; LDA: Linear Discriminant analysis

IV. DISCUSSION

In this study, we tried to find the most important prediction indicators of exacerbation events by combining non-linear analyses and machine learning methods. All the data of COPD patients were collected by home telehealth non-invasive ventilators. we applied MSE and DFA to analyze and extract features from these signals. RF, LDA and SVM were used to classify the stable state and acute exacerbations of disease.

Acute exacerbations of COPD are important episodes in the course of the disease associated with a significant increase in mortality, hospitalization and health-care use and impaired quality of life [10, 26-28]. Thus, early detection and prompt treatment of AECOPD might have important public health implications. It could reduce the risk of hospitalization and consequently the burden of the disease [29, 30].

According to the analysis of RF, the most predictive features were the mean of airflow, results of DFA and MSE in scale 4. Table 4 and Fig.3 show the importance of all features in descending order. Additionally, LDA had the best average precision of 62% and SVM had the best average recall of 56% for the test results (Table 3). RF showed a highest accuracy of 75% in three methods, when LDA illustrated a highest specificity of 42.9% (Table 5). The incompleteness of the measurement data may affect the classification results. Furthermore, the amount of the two groups also influence the results. The group 0 contained 416 records and group 1 contained 133 records so the variance within group is very high.

For the future work, we will try to figure out the amount variance in different groups. It could be better if we discuss with hospital to add more patients in our study. To improve the accuracy and specificity, we will add more features for machine learning methods analysis. SpO2 and pressure are also important physiological signals and they should be considered to analyze. As for the machine learning methods, we could apply more appropriate methods to build acute exacerbations prediction model for patients with COPD. This study will provide insights in developing COPD home-monitoring system which can prognose the onset of acute exacerbations, thus reducing the need of hospital admissions and improving the life quality of COPD patients.

CONFLICT OF INTEREST

The authors report no conflicts of interest in this work.

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