Deep Learning Model for Early Subsequent COPD Exacerbation Prediction

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Abstract: Chronic Obstructive Pulmonary Disease (COPD) patients have a burden of frequent exacerbations during daily life. Automatic solutions for early COPD exacerbation prediction could promote COPD healthcare and reduce hospital readmissions. Previous works didn't consider symptoms change patterns which might not be effective for timely and personalized therapy. When using a pulse oximeter for COPD diagnosis, arterial oxygen saturation (SPO2) levels are targeted, depending on whether a patient is stable, hospitalized, or being recovered from exacerbation states. However, the timely management of COPD is a problem, due to the manual monitoring of individual measurements. This research investigates whether the Long Short-Term Memory (LSTM) model can predict early COPD subsequent exacerbation by prompting therapy depending on COPD symptoms patterns and SPO2 burden levels. Time-stamped Electronic Health Record (EHR) from COPD patients' data time series were examined, over subsequent days, with the aim to evaluate a short-time window which a monitoring system for an accurate and early prediction of subsequent exacerbations could be based on. Therefore, the LSTM model was evaluated by varying a window of one to six prior time-steps, to forecast a subsequent day. The window of 1 day showed a good performance of a training accuracy of 87%, a testing accuracy of 85% and an area under the curve (AUC) of 0.83, by employing the training and testing model on only 54 patients.

Keywords: Early prediction, Subsequent COPD exacerbation, Data-time series, LSTM, Monitoring system.

1. Introduction

COPD is a progressive chronic lung disease that presents persistent respiratory symptoms and may exhibit exacerbation during the disease course time. The symptoms of COPD exacerbation include increased dyspnea (shortness of breath), cough, and production of sputum (mucus) that go beyond day-to-day baseline symptoms variations and require a change in medication or hospital visits (COPD Foundation, 2020). Once exacerbation occurs, subsequent exacerbations are likely to follow, that may be due to persistent symptoms. COPD is a highly prevalent chronic disease worldwide and acute exacerbations are associated with disease progression, frequent exacerbations, hospital readmission and death.

Monitoring COPD symptoms patterns for early prediction of exacerbation events is very essential as early therapy of exacerbations could alleviate symptoms burden and shorten worsening symptoms duration by improving patients' health.

On one hand, patients symptoms patterns should be considered for timely and personalized therapy. Monitoring COPD symptom patterns for patients' healthcare would be impossible without a combination of EHR and a remote monitoring system for patients. There should be a maintained EHR that contains individual variables and symptoms for the prediction of adverse events such as exacerbation. Patients will recognize their symptoms and report their vital signs consistently each time there is a change in any worsening symptom. According to the GOLD 2020 update (Yawn et al., 2021), there should be a way to monitor COPD individual symptoms over time by relating the patient's previous status to his/her current status, in order to assess symptoms baseline change. This could guide a timely and personalized therapy that matches COPD patient impairment and change, by evaluating the severity, range, type, duration and frequency related to the patients' symptoms (Swaminathan et al., 2017).

While symptoms baseline change over time should be tracked for capturing symptoms severity change over time, evaluating symptoms by an overall score of symptoms questionnaire can hide symptoms patterns, for example, when are evaluated at the initial therapy or emergency (Global Initiative for Chronic Obstructive Lung Disease, 2020). Moreover, symptoms assessment by a questionnaire at the individual level can have discordance with the Modified Medical

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Research Council (mMRC) or breathlessness scale (Huang et al., 2015), and moving from one breathlessness scale level to another level requires a large functional change, therefore, it might not reflect symptoms patterns over time (Yawn et al., 2021).

On the other hand, prediction of early subsequent exacerbation is required before a greater deterioration of the patient's condition occurs. Normally substantial recovery from Acute Exacerbation of COPD (AECOPD) onset occurs in the following 7 days (Wageck et al., 2019) and a 7-day prodromal period precedes COPD exacerbation (Shah et al., 2017). "With the aim to determine a short-time window which the model proposed for automatic and early COPD prediction could be based on, the performance of the LSTM model was evaluated on data time series within the interval from 1 day to 6 days or within prior timesteps, looking for the right prior timestep in which the model prediction of the following day could attain a good accuracy." SPO2 and HR (Heart Rate) have been shown to undergo several changes before the exacerbation event. Therefore, to consider vital signs fluctuations that may occur in prodromal or recovery process period, 7 days were considered to evaluate LSTM model. 7-day prodromal periods are periods ahead of the exacerbation events and may contain changes in patients' measurement around the exacerbation event. Since the aim of this paper is to predict early subsequent exacerbation events, the time interval varying between 1 and 6 days was considered for the LSTM timesteps.

In the present study, the LSTM model was evaluated on data time series containing worsening symptoms, measured as the presence or absence of shortness of breath, cough, etc., in comparison with the baseline chronic symptoms, so as to capture symptom patterns. The pulse oximeter-acquired vital signs, such as SPO2, were also included, as they have been shown to vary before the exacerbation event and to predict the exacerbation event (Buekers et al., 2019)

When a pulse oximeter is used for COPD diagnosis, respiratory symptoms are evaluated and monitored manually without matching the time of variation with the severity of symptom (The International Primary Care Respiratory Group, 2010). Moreover, there may be a challenge for doctors, to correlate patients' symptoms with SPO2 measurements over time and assess the occurrence of exacerbation. This might be due to how frequently these symptoms are changing but when being in a stable state, even patients in the advanced stages of the disease may be adapted to low oxygen or SPO2. Therefore, there is a challenge to know when a specific SPO2 could lead to an exacerbation event (Swaminathan et al., 2017). Moreover, there are some pre-set SPO2 to target depending on whether a patient is in a stable or exacerbated state or is recovering from an exacerbated state (The International Primary Care Respiratory Group, 2010). This research proposes a model that could help to avoid manual, tiring, and inefficient monitoring of patients by pairing an automated monitoring system with an EHR that maintains COPD time series data about the patients' reported symptoms. It is important to note that the present study focuses only on the design of the model and on the existing monitored data.

According to symptoms patterns used in conjunction with individual SPO2 levels, the model could prompt exacerbation events automatically over time, by showing current symptoms patterns and SPO2 levels. This can help clinicians to decide on individual SPO2, for example, by applying SPO2 that should be targeted once a patient is in exacerbation and symptoms are keeping or not deteriorating (The International Primary Care Respiratory Group, 2010). An online tool could be designed, based on a pre-trained predictive model, to issue, at any time step, an alert over EHR for automatic and timely monitoring of patients or a specific patient.

The remaining part of this paper is organized as follows: Section 2 presents the literature review on the prediction of frequent COPD exacerbations. Section 3 explains the methods and data used in this work and the model setting. Section 4 provides and discusses the implementation results. Finally, the conclusion and recommendations for future work are made in Section 5.

2. Literature Review

Previous studies attempted early prediction of COPD exacerbations by examining COPD symptoms patterns or not. This research presents

a deep learning model for COPD that could prompt patients' health change automatically, for a comprehensive assessment of individual SPO2 levels and worsening symptoms patterns.

Polsky and Moraveji (2021) examined manually, within 7 days, patients' vital signs such as heart rate and breathing rate (BR), that had been taken on a remote monitoring system to evaluate period with vital signs baseline deviation and found that recurrent BR modification is able to treat COPD exacerbation early and promptly. However, the model was not designed for automatic and timely monitoring of COPD patients. Claxton et al. (2021), designed an automatic cough sound events detector-based algorithm for COPD exacerbation early identification by using patients' characteristics and patient-reported variables such as age, new cough, and fever. The accuracy attained was 82.6% for 82 evaluated patients. Although the developed model was reported instantaneous, it cannot prompt early diagnosis of an exacerbation before its occurrence. COPD clusters over time and can occur at any time during the disease course time. Therefore, there is still a need for an automated system for a timely subsequent exacerbation prediction (Hurst et al., 2009). Similarly, in (Fernández-Granero et al., 2018), by using respiratory sounds that were recorded daily, the authors trained and validated symptom-based exacerbations by applying a decision tree forest classifier for the early detection of COPD patients' severity and exacerbation. The designed model predicted correctly 32 out of 41 exacerbations, that is equivalent to the accuracy of 78%, with a margin of 4.4 days before onset. In (Fernández-Granero et al., 2015), for early COPD exacerbation prediction over a computerized system, the authors recorded respiratory sound and extracted features which were optimized using Principal Component Analysis (PCA) to be input into the Support Vector Machine (SVM) classifier. An accuracy of 75.8% was achieved by disclosing exacerbations about ± 1.9 days earlier compared to the medical attention.

In (Swaminathan et al., 2017), the authors applied different classifiers to patients' symptoms patterns and vital signs, for exacerbation prediction of COPD patients. Logistic Regression (LR) and Gradient-Boosted Decision Trees (GB) outperformed other models by showing an accuracy of 89.1% and of 88.1%, respectively. For early exacerbation prediction, the GB classifier results were compared to the determined consensus decisions and achieved 97%, by determining if an exacerbation had happened. However, the days before exacerbation were not specified and the designed model varied greatly depending on many variables that could make difficult a clinical decision. By integrating Internet-of-Things (IoT)-based platform for COPD data collection, Wu et al. (2021) applied various machine learning and deep learning models on COPD data that were evaluated with a symptoms assessment questionnaire and by including environmental data to trace the health conditions of patients with COPD. For the early detection of AECOPD within the next 7 days, the proposed AECOPD predictive model achieved an accuracy of 92.1%, sensitivity of 94%, and specificity of 90.4%. Esteban et al. (2015), applied Random Forests Algorithm to data from patients with frequent hospital admissions such as heart rate, temperature, oxygen saturation, respiratory rate, steps walked, and a questionnaire form about symptoms, obtaining an Area Under the Curve (AUC) of the Receiver Operating Characteristic curve (ROC) of 0.87, when predicting the occurrence of exacerbation before the next three days. In (Fernández-Granero et al., 2014), during a six-month telemonitoring of 16 patients, the authors designed a Probabilistic Neural Network (PNN) classifier that enabled the automatic prediction of exacerbations for early COPD prediction with a margin of 4.8 ± 1.8 days (average ± SD). The accuracy for the detection was 80.5% of which 78.8% were reported exacerbations and 87.5% were unreported episodes.

COPD exacerbations are not random events but cluster over time, and some studies such as (Claxton et al., 2021; Polsky & Moraveji, 2021), detected exacerbation without predicting early subsequent COPD, whereas, other studies investigated recurrent exacerbations over a long-time period such as eight or more weeks (Aaron, 2009) to predict future events and hospital readmission (Kerkhof et al., 2015; Liu et al., 2015; Min et al., 2019; Quintana et al., 2022; Wu et al., 2020), by considering the overall score of the symptom questionnaire or by using symptoms in defining onset and recovery of symptoms-based COPD exacerbations (Shah et al., 2017). The present study aims to rely on immediate and timely measurable vital signs and symptoms, in order to provide a model that can predict early subsequent COPD within a short-

time scale, up to a daily rate time interval. For giving details on such model designs for hospital readmission and frequent exacerbations, the models from (Kerkhof et al., 2015; Min et al., 2019) were described and the prediction accuracy of studies from (Liu et al., 2015; Quintana et al., 2022; Wu et al., 2020) was shown, respectively: the Area Under the Curve (AUC) of the Receiver Operating Characteristic curve (ROC) of 0.703; the re-exacerbation index of re-exacerbation with a C-statistic of 0.750 (P<0.001), the AUC for the logistic model of 0.845 and the c- index for the Cox model of 0.707. Kerkhof et al. (2015), investigated predictive risk factors to provide a model that can predict frequent exacerbations within a single year. The Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) is defined for a cut-point of (≥2) exacerbations in one year, for the risk of frequent future events. Univariable and multivariable logistic regressions were applied to chosen variables without considering patients 'symptoms, and the validation was done by comparing the developed model with the Dyspnea, Obstruction, Smoking, Exacerbation (DOSE) index and GOLD categories A–D, using the mMRC and Forced Expiratory Volume in 1 second (FEV1) to assign patients categories (Global Initiative for Chronic Obstructive Lung Disease, 2017). The predictive accuracy of the achieved model was approximately (*C* statistic 0.751), when predicting two or more COPD exacerbations in the following year, with two subpopulations of 9,393 and of 3,713 patients, respectively. Min et al. (2019) evaluated various machine learning and deep-learning models on 111,992 patients to predict the risk of hospital readmission, by achieving an accuracy of an AUC of approximately 0.65. Other COPD readmission models can be seen in the review from (Press et al., 2020). Nunavath et al. (2018) used feed-forward neural networks (FFNN) for classification and LSTM for early prediction of COPD exacerbation and subsequent triage. By varying LSTM prior time-steps from 1 up to 5, to evaluate which timestep could reach an accurate model prediction at a subsequent day, authors found the day-ahead prediction to be much more accurate with a computed accuracy of 84.12%. The model was trained and evaluated on 94 tele-monitored patients by using daily measurements of the result of symptom assessment questionnaire, heart rate and SPO2 baselines.

As it could be seen from the above-mentioned studies, excluding the work in (Swaminathan et al., 2017), these studies didn't include individual symptoms patterns, and the work in (Swaminathan et al., 2017) used about 31 features for individual COPD prediction. This might not prompt a specific COPD treatment, as the interpretation and relationship of multiple features could be challenging. Other works used symptoms patterns in defining COPD based exacerbations time point for their model design (Shah et al., 2017). Although various authors worked on COPD recurrent exacerbation prediction by applying different predictive models, no other study so far has designed the LSTM model for early subsequent prediction of COPD exacerbation, in association with SPO2 and symptom patterns over time intervals, for a prompt and effective therapy.

For a subsequent prediction of COPD exacerbation, various predictive models utilized various variables as described in the literature review of this study. However, the performance attained by previously designed models, is generally lower than the accuracy needed to avoid false alarms. There is still a need for early COPD subsequent prediction models, as long as the latter could provide a good model accuracy and or prompt COPD treatment based on assessed variables. Unlike the aforementioned studies, the present research applied the LSTM model to only 54 patients' data time series, achieving an accuracy of 85% and an AUC of 0.83 when determining the diagnosis of COPD, by using a pulse oximetry protocol needed to evaluate SPO2 levels in relation to the patients' symptom patterns (The International Primary Care Respiratory Group, 2010). Interesting papers using deep learning techniques are introduced by Athilakshmi et al. (2023) and Dumitrescu et al. (2019).

2.1 LSTM Architecture

The present article aims to predict COPD subsequent exacerbation before its occurrence. The LSTM model is chosen for this research (refer to the architecture components of LSTM in Figure 1) (Van Houdt et al., 2020). LSTM extends a Recurrent Neural Network by creating both short-term and long-term memory components to efficiently study and learn sequential data (Balas et al., 2019).

The Python library, Keras, has been used for the deep learning model development. Since it is a binary classification problem, after initializing the sequential model, the hidden layers and the output

layer with one unit and sigmoid activation function were added for the proposed LSTM network.

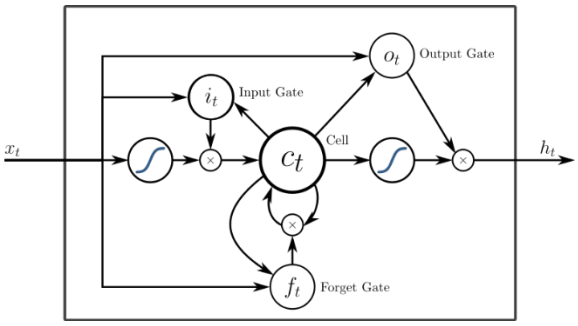

Figure 1. LSTM architecture (Sun et al., 2018)

The equations of an LSTM with a forget gate (Varsamopoulos et al., 2018) are the following:

$$f_t = \sigma_g\left(W_f x_t + U_f h_{t-1} + b_f\right) \quad (1)$$

$$i_t = \sigma_g\left(W_i x_t + U_i h_{t-1} + b_i\right) \quad (2)$$

$$o_t = \sigma_g\left(W_o x_t + U_o h_{t-1} + b_o\right) \quad (3)$$

$$\tilde{c}_t = \sigma_c\left(W_c x_t + U_c h_{t-1} + b_c\right) \quad (4)$$

$$c_t = f_t \odot c_{t-1} + i_t \odot \tilde{c}_t \quad (5)$$

$$h_t = o_t \odot \sigma_h\left(c_t\right) \quad (6)$$

where $c_0 = 0$ and $h_0 = 0$ are the initial values, the operator $\odot$ denotes the Hadamard product and the subscript t presents the time step.

Explanation of the notation used in LSTM equations is provided below:

$x_t \in \mathbb{R}^d$: input vector to the LSTM unit;

$f_t \in (0,1)^h$: activation vector of the forget gate;

$i_t \in (0,1)^h$: activation vector of the input/update gate;

$o_t \in (0,1)^h$: activation vector of the output gate;

$h_t \in (-1,1)^h$: hidden state vector, also known as output vector of the LSTM unit;

$\tilde{c}_t \in (-1,1)^h$: cell input activation vector;

$c_t \in \mathbb{R}^h$: cell state vector;

$W \in \mathbb{R}^{h \times d}$, $U \in \mathbb{R}^{h \times h}$ and $b \in \mathbb{R}^h$: weight matrices and bias vector parameters which need to be learnt during training, d and h *are the number of input features and hidden units, respectively.*

σ_g: Sigmoid function

σ_c and σ_h: hyperbolic tangent functions

3. Methodology

3.1 Patients Data and Data Pre-processing

The labeled dataset that contains measurements of COPD exacerbations for COPD patients' data time series with one-day sampling rate was used. The data were collected during the insight study and were received from Peter Lucas, one of the authors of the papers (Boer et al., 2018; Liu, et al., 2019; van der Heijden et al., 2013) in which the same dataset was used for designing an automated tool to support self-management of COPD exacerbations, Bayesian networks in learning from clinical time series data with irregularity and an autonomous mobile system for the management of COPD, respectively. A written informed consent was signed by all of the participants. The Medical Ethical Committee CMO of the region Arnhem and Nijmegen (Netherlands) approved the research (approval number 2011/242). From the original dataset, the following features were derived: pulse oximeter acquired SPO2, dyspnea, sputum color, sputum volume, wheezing, and cough worsening symptoms. The symptoms were provided in the form such as breathlessness is present or absent, compared to the baseline of chronic symptoms. For a patient, the symptoms reported at a given instance show a set of current state (severity and trends), when measuring an exacerbation event. Data were preprocessed by techniques of filling in missing data, data normalization, and data sequencing.

Firstly, the dataset was loaded, and categorical variables were label-encoded. Afterward, SPO2 was normalized using Min/Max scaling technique, the dataset was transformed into subsequences using a user-defined series_to_supervised function.

The final dataset contained 3151 daily measurements of vital signs and corresponding symptoms of 54 patients. The present data were divided into subsequences from 1 to 6 steps, to classify exacerbation recurrence early or at a short-time scale. The aim was to find with what prior time-steps, the model would forecast the exacerbation event on the following day, accurately based on a window that varies in the

above-mentioned sub-sequences interval (the number of prior observations that the model will use as input to make an accurate prediction of a subsequent exacerbation). It was hypothesized that a monitoring system could be based on the pre-trained model with a window interval, that presented an accurate and early prediction. Therefore, the supervised learning problem was framed as predicting the next-day exacerbation, given the exacerbation measurements and patient conditions at the prior time-steps (1 up to 6 timesteps). The patients' variables for the subsequent day, to be predicted, are then removed.

Moreover, to predict COPD subsequent exacerbation, at any day or time step, each formed subsequence was taken into consideration, whose timesteps were counted either from exacerbation event or not. Shaped data (samples, time-steps, features) were prepared for the present neural network according to the timestep considered, without overlapping patients' data time series. Here, variable length sequences pose no problem to the model training as subsequences for each patient were counted by considering a time window and the day to predict, separately from other patients.

3.2 Model Parameters Setting

Secondly, the LSTM model was defined and fitted. The LSTM model with parameters was defined as follows: 50 neurons in each of the four hidden layers and 1 neuron in the output layer, for predicting exacerbation events. The input shape will be 1 to 6 timestep(s), with 6 features. Binary cross entropy loss function and efficient Adam optimizer algorithm were used as an extension to stochastic gradient descent. The model was trained for 20 epochs with a batch size of 32. Finally, both training and testing losses were observed during the running process, setting aside 25% of the data set for model evaluation purposes.

4. Results and Discussion

At the end of the run, both training and testing plots for only the model, with a window that achieved a good score (window=1), were drawn. See below, Figures 2, 3 and 4 with plots on training and validation loss and accuracy, with their respective AUC ROC curves.

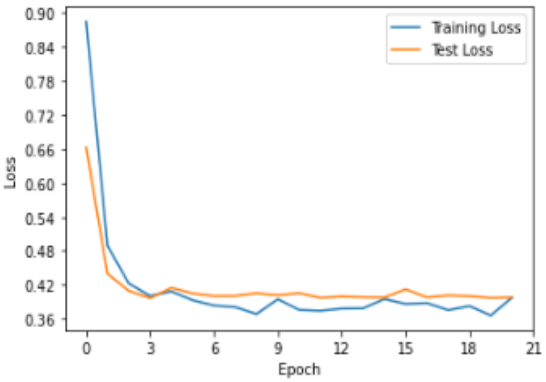

Figure 2. Plot for the loss function

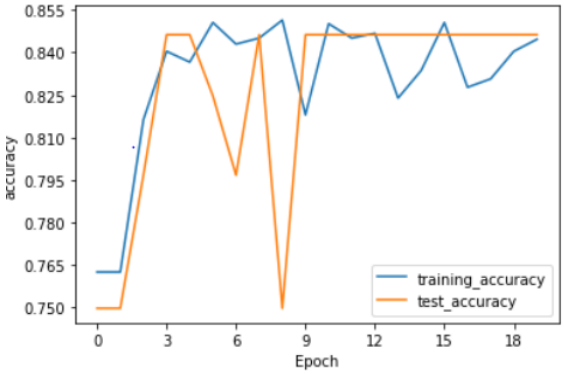

Figure 3. Plot for model accuracy

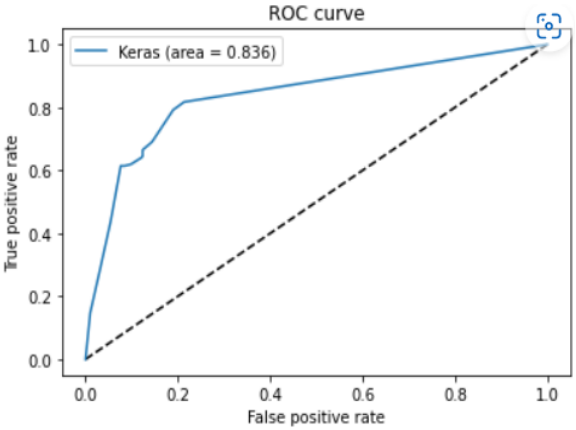

Figure 4. Plot for testing ROC

For each run, a binary cross-entropy computed score is noted, to be compared at the end of the implementation. See Figure 5 and 6 for the comparison of obtained scores, each from 1 to 6 days inputs. From the following figures, it could be easily seen that a time window of 1 day produced a better score in comparison with the time windows of the other days.

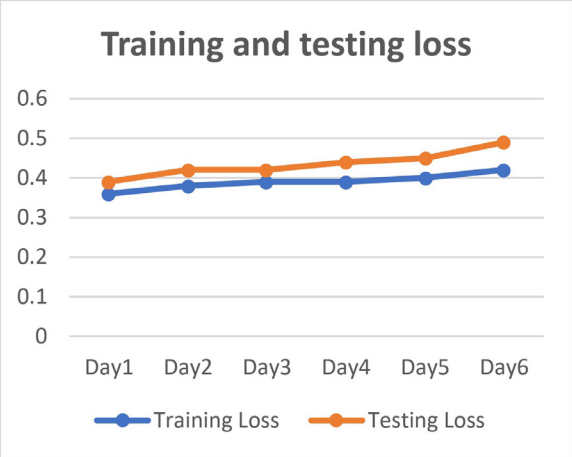

Figure 5. Training and testing loss

With a time window of 1 day on the dataset, the model training attained a testing accuracy of 85% and a testing AUC of 0.83.

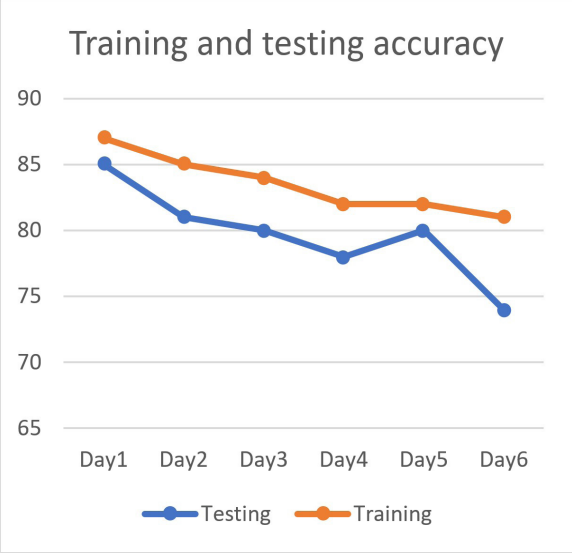

Figure 6. Training and testing accuracy

Table 1. Performance metrics computed values

	Loss		Accuracy	
Days	**Testing**	**Training**	**Testing**	**Training**
Day 1	0.39	0.37	85	87
Day 2	0.42	0.38	81	85
Day 3	0.42	0.39	80	84
Day 4	0.44	0.39	78	82
Day 5	0.45	0.4	80	82
Day 6	0.49	0.42	74	81

5.Conclusion and Recommendation

During this study, a predictive LSTM model was evaluated to see if it could predict an early next-day exacerbation event based on varying prior time-steps, within a time interval of 6 days. The plot shows that one day ahead produced good scores, thus could be used to forecast early, subsequent exacerbation for a specific patient. Moreover, an online algorithm could be designed over EHR, using a pre-trained model to issue an early alert, at any time step, based on one day. Such a model could serve as a warning system for patients who are likely to experience a subsequent short-time exacerbation, contrary to previously developed models of long-scale exacerbation events. The model prediction obtained a performance of a training accuracy of 87%, a testing accuracy of 85%, and an AUC of 0.83 for only 54 patients, which is a promising performance to enhance a manual monitoring system.

However, both for any future work and before using the model in clinical practice, it is recommended to train the network on more data.

This could improve the model accuracy, but also the “heart rate” parameter should be considered for a more complete clinical reliance, specifically when the pulse oximetry protocol for COPD diagnosis is used.

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