Predicting exacerbations in patients with chronic obstructive pulmonary disease

by

Thomas Kronborg Larsen

Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable disease characterized by persistent respiratory symptoms and airflow limitation. It is usually due to airway and/or alveolar abnormalities that are often caused by significant exposure to noxious particles or gases. COPD is a major economic burden, and the third leading cause of death globally. The burden of the disease is mainly due to exacerbations, which are defined as acute worsenings of respiratory symptoms that result in additional therapy. COPD exacerbations have a negative impact on health status, rate of hospitalization, readmission and disease progression. A key goal for treatment of COPD exacerbations is therefore to minimize the negative impact of the current exacerbation and to prevent subsequent events. Several studies have attempted to predict exacerbations prior to onset in order to facilitate an early and preventive treatment. The development of predictive models with clinically relevant classification rates has yet to be achieved.

The aim of this thesis was to improve models for predicting exacerbations in patients with COPD. The thesis was based on four studies presented in four individual papers. Study I and IV directly addresses the aim of the thesis, whereas study II and III were method papers leading up to study IV. Study I investigated whether patient and population exacerbation incidence contained predictive information of upcoming exacerbations. This study was based on home measurements of physiological parameters in a large cohort of patients with COPD, but it was limited by the patients submitting measurements only once a week. To determine whether the predictive models could be improved with a higher frequency of measurements, a smaller group of patients that measured at least three times a week was investigated in studies II-IV. A challenge when dealing with a smaller cohort is over-fitting, which is why study II presented double cross-validation with feature selection as a method to prevent over-fitting and ensure generalizable test results. Study III provided a sensitivity analysis of nine different classification algorithms, based on the method presented in study II, and also determined which classification algorithms were best suited for the task of predicting COPD exacerbations. Study IV combines the work of studies I-III and investigated whether a two-layer probabilistic model could improve prediction of COPD exacerbations compared to conventional models.

In conclusion, population exacerbation incidence held predictive information of upcoming exacerbations for patients in telehomecare. Double cross-validation with feature selection was considered a more robust validation method for predicting COPD exacerbations in a small imbalanced data set. The sensitivity analysis revealed that prediction models are highly sensitive to the choice of classification algorithm, and that the linear discriminant classifier, logistic regression, and random forest algorithms had the highest classification rates. Finally, a two-layer probabilistic model can significantly improve the prediction of COPD exacerbations, compared to conventional models, and also provide clinically relevant classification rates.
To fulfill the requirements for the PhD degree, Thomas Kronborg Larsen has submitted the thesis: Predicting exacerbations in patients with chronic obstructive pulmonary disease, to the Faculty Council of Medicine at Aalborg University.

The Faculty Council has appointed the following adjudication committee to evaluate the thesis and the associated lecture:

Associate Professor Christian Fischer Pedersen
Aarhus University
Denmark

Associate Professor Raúl San José Estépar
Harvard Medical School
USA

Chairman:
Associate Professor Lasse Riis Østergaard
Aalborg University
Denmark

Moderator:
Associate Professor Louise Pape-Haugaard
Aalborg University
Denmark

The PhD lecture is public and will take place on:

**Monday 09 March 2020 at 13:00**
Aalborg University – Room 4-111
Niels Jernes Vej 14
9220 Aalborg East

**Program for PhD lecture on**

**Monday 09 March 2020**

by

**Thomas Kronborg Larsen**

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Chairman: Associate Professor Lasse Riis Østergaard
Moderator: Associate Professor Louise Pape-Haugaard

13.00 Opening by the Moderator

13.05 PhD lecture by Thomas Kronborg Larsen

13.50 Break

14.00 Questions and comments from the Committee
Questions and comments from the audience at the Moderator’s discretion

16.00 Conclusion of the session by the Moderator

After the session a reception will be arranged