Predictive value of physiological values and symptom scores for exacerbations: a cohort study of frequent exacerbators with bronchiectasis and COPD

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Abstract

Background: COPD and bronchiectasis are common and exacerbations contribute to their morbidity and mortality. Predictive factors for frequency of future exacerbations include previous exacerbation frequency and airway colonisation. Earlier treatment of exacerbations is likely to reduce severity.

Objective: To determine whether changes in physiological variables or symptom scores can predict exacerbations of chronic airway disease in participants colonised with Pseudomonas aeruginosa or Haemophilus influenzae

Methods: We performed a longitudinal observational cohort study of 30 participants with bronchiectasis and/or COPD, at least 2 exacerbations per year and colonisation with Pseudomonas aeruginosa or Haemophilus influenzae. Daily symptom and physiological data were collected comprising pulse rate, blood pressure, oxygen saturation, peak flow rate, step count, weight and temperature. Exacerbations (defined as the onset of new antibiotics for respiratory symptoms) were collected, and predictive values for abnormal values in the ten days prior to an exacerbation were calculated.

Results: 30 participants were recruited collecting a total of 39,534 physiological and 25,334 symptom data points across 5,358 participant-days including 78 exacerbations. Peak flow rate and weight were significantly different at the point of exacerbation but no significant trends around exacerbation were noted and no clinically beneficial predictive value was found in overall or individually adjusted models. Symptom scores trended to worsening for 10 days either side of an exacerbation, but of insufficient magnitude for prediction with AUROC values of 0.4-0.6.

Conclusions: This study demonstrated a lack of utility for either physiological or visual analogue scale symptom predictors in early detection of exacerbations in participants with frequent exacerbation and airway colonisation. This suggests that the self-management education provided as standard of care is superior to either of these other approaches.

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TITLE
Predictive value of physiological values and symptom scores for exacerbations: a cohort study of frequent exacerbators with bronchiectasis and COPD

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Abstract

Introduction

COPD and bronchiectasis are common and exacerbations contribute to their morbidity and mortality. Predictive factors for frequency of future exacerbations include previous exacerbation frequency and airway colonisation. Earlier treatment of exacerbations is likely to reduce severity.

Objective

This study tested the hypothesis that, in a population of frequent exacerbators with bronchiectasis and/or COPD with airway colonisation, changes in symptom scores or physiological variables within 10 days prior to an exacerbation would allow prediction of the event.

Materials and methods

We performed a six-month longitudinal observational cohort study of 30 participants with bronchiectasis and/or COPD, at least 2 exacerbations per year and colonisation with *Pseudomonas aeruginosa* or *Haemophilus influenzae*. Daily symptom and physiological data were collected comprising pulse rate, blood pressure, oxygen saturation, peak flow rate, step count, weight, and temperature. Exacerbations (defined as the onset of new antibiotic use for respiratory symptoms) were collected, and predictive values for abnormal values in the ten days prior to an exacerbation were calculated.

Results

30 participants were recruited collecting a total of 39,534 physiological and 25,334 symptom data points across 5,358 participant-days including 78 exacerbations across 27 participants with the remaining three participants not exacerbating within the six-month observation period. Peak flow rate, oxygen saturation and weight were significantly different at the point of exacerbation but no significant trends around exacerbation were noted and no clinically beneficial predictive value was found in overall or individually adjusted models. Symptom scores trended to worsening for 10 days either side of an exacerbation, but of insufficient magnitude for prediction with AUROC values of 0.4-0.6.

Conclusion

Within this small cohort with bronchiectasis and/or COPD and airway colonisation, physiological and symptom variables did not show sufficient predictive value for exacerbations to be of clinical utility. The self-management education provided as standard of care may be superior to either of these approaches but benefit in another or larger cohort cannot be excluded.

Introduction

COPD and bronchiectasis are common causes of morbidity and mortality across the world[1, 2]. Much of this morbidity and mortality is associated with exacerbations - acute deteriorations of the disease[3, 4]. Exacerbations often require additional treatment, up to and including hospitalisation, and are a risk factor for progressive disease[5, 6]. Certain factors are known to be associated with increased risk of future exacerbations including recurrent previous exacerbation[7, 8] and airway colonisation with organisms such as *Pseudomonas aeruginosa*[9, 10].

It is thought that earlier treatment of exacerbations is associated with improved outcomes including time to recovery and reduced risk of a severe exacerbation [11], but overtreatment risks side effects from the treating medications e.g. corticosteroids and/or antibiotics. Accurate prediction of exacerbations is therefore required. Predictive factors may be physiological e.g. heart rate, oxygen saturations, or symptomatic e.g. degree of breathlessness or fatigue. Monitoring of physiological variables has shown value in predicting mortality in hospital and prehospital care (e.g. National Early Warning Score (NEWS) [12, 13]) including mortality in COPD patients [14] however the same has not been consistently demonstrated for other metrics such as exacerbations of disease and previous studies focussing on lung function monitoring have not demonstrated predictive benefit [15, 16]. Multiple predictors of exacerbation risk exist [17–20], such as the CAT score for COPD and the FACED score for bronchiectasis, but these do not help predict individual exacerbations. In order to predict exacerbations in either physiological or symptom modalities, monitoring must be remote and performed in the home environment.

We conducted a longitudinal observational study examining the capability of physiological and symptom variables to predict exacerbations of airway disease in participants with chronic bronchitis with frequent exacerbation and airway colonisation with *Pseudomonas aeruginosa* or *Haemophilus influenzae.* We hypothesized that changes in symptom scores or physiological variables within 10 days prior to an exacerbation would allow prediction of the event.

Materials and methods

Study design and setting

We conducted a six-month blinded observational cohort study, recruiting 30 adult participants from secondary care with a diagnosis of COPD, bronchiectasis or both. Participants were recruited from a secondary care clinic during 2014, and the study ran from September 2014 for six months.

Participants

Participants were required to have had a least two exacerbations in the last twelve months, at least one of which was within the last six months. Participants were required to be colonised by *Pseudomonas aeruginosa* or *Haemophilus influenzae*, demonstrated by at least two cultures at exacerbation in the last twelve months without culture of the other organism. Participants were able to give informed consent, comply with study procedures and produced at least five mL of sputum most days. A full study protocol has been previously published [21] and participant flow is shown in the Figure S9.

Variables

At enrolment, participants provided clinical history, spirometry and symptom questionnaires including the St Georges Respiratory Questionnaire (SGRQ). A home visit was conducted when participants were provided with home physiological monitoring equipment [21], specifically digital peak flow meter, pulse oximeter, physical activity (step) tracker, infrared thermometer, automatic sphygmomanometer and weighing scales (see supplement table S3 for models), which were linked by Bluetooth to an iPad which also collected 10-point visual analogue scale symptom scores for appetite, breathing, cough, energy, and wellness. This data was transmitted daily to a secure cloud-based database, and the study team were blinded to the data until all participants had completed the study, except for a single unblinded technical observer who ensured data was being received from

each participant. Participants were asked to record whether they had started a course of antibiotics at home (defining a moderate exacerbation as per guidelines) or whether they were in hospital for this (defining a severe exacerbation)[22].

Outcomes

The outcome under investigation is the accuracy of abnormal values of the physiological and symptom variables listed above to predict a moderate exacerbation of airway disease as defined by patient reported initiation of antibiotics for a worsening in respiratory symptomatology. Independent variables are therefore symptom scores (appetite, breathing, cough, energy, and wellness) and physiological values (heart rate, blood pressure, peripheral oxygen saturation, temperature, weight, daily step count).

Study size

To establish an association between predictive markers and the occurrence of exacerbations, the study was designed around the identification of a presymptomatic period. Based on clinical expertise and literature review, we have determined that a 10-day window before the onset of an exacerbation is a critical timeframe in which deviations in predictive markers can be most reliably attributed to a forthcoming exacerbation. This period selection aligns with the natural history of exacerbations as detailed in prior studies. Given the adoption of a 10-day cycle as a unit of observation, we anticipated a minimum of 12 such units per participant across an expected follow-up duration of four months. This frequency follows from the inclusion criterion requiring participants to have had at least two exacerbations in the previous year, paralleling the exacerbation frequency described by Seemungal et al [23].

For the study to hold clinical relevance, we aimed to achieve a positive predictive value (PPV) of 60% and a negative predictive value (NPV) of 90%. This was based on the study teams experience rather than published data. On the assumption that each participant would experience at least one exacerbation during the study period and using a significance threshold of 5% with 90% statistical power to discern the prescribed PPV and NPV, the initial calculation suggested the need for 120 time units of observation.

However, to address the statistical challenge posed by the non-independence of repeated measurements from individual participants—each contributing multiple observation periods—an intra-class correlation coefficient (ICC) of 0.18 was employed to adjust for within-participant correlation. The resulting design effect, reflecting this lack of independence, was calculated to be approximately 3. This design effect was used to multiply the basic sample size estimate, leading to a final requirement of 360 observational time periods. Consequently, a total cohort of 30 participants would satisfy this criterion, meeting the robust statistical power necessary for the intended analyses.

The study team estimated a maximum feasible window of 10 days prior to an exacerbation when derangement of a predictive value may be attributable to a subsequent exacerbation. Using time periods of 10 days, it was estimated that there would be at least 12 time periods per participant (assuming a minimum of 4-months of follow-up). Minimally clinically acceptable predictive values were estimated at a positive predictive value of 60% and negative predictive value of 90%. It was assumed that participants would experience an average of at least one exacerbation during the study period, based on recruitment criteria of at least two exacerbations in the previous 12 months, which is consistent with findings reported by Seemungal et al. Using a 5% significance level and 90% power to detect the above selected predictive values, 120 time periods would be required. This was adjusted for lack of independence, given multiple time-periods came from each participant and assuming intra-class correlation of 0.18, a design effect of approximately 3 was calculated. 360 time

periods were therefore required equating to a total of 30 participants for the study.

Statistical methods

Data Analysis was conducted using SPSS version 28 (IBM), alongside visualisation in Tableau Desktop (Tableau Software) and data management in Excel 365 (Microsoft). Descriptive statistics were utilised to characterise the study data, employing mean ± standard deviation to express normally distributed variables and median with interquartile range (IQR) for variables not normally distributed. The determination of normality was guided by kurtosis and skewness indices, with thresholds set at absolute values less than 1 for normal distribution.

Comparative analyses between groups were executed using the Student's t-test for normally distributed data and the Mann-Whitney U test for data that deviated from normal distribution. The onset of an exacerbation was defined as the day on which a participant initiated an antibiotic treatment course; any subsequent antibiotic courses beginning within 10 days of the initial course's end were considered part of the ongoing exacerbation and not as discrete events.

The monitoring tool, a modified National Early Warning Score (mNEWS), was calculated with the exclusion of respiratory rate, as it could not be accurately measured remotely with the equipment provided to participants. Data were assessed longitudinally to establish individualised normal ranges for each participant by calculating variable standard deviations from the participant's average, while omitting any data from a 20-day span encompassing each exacerbation (10 days before and 10 days after).

An abnormal value occurring within the 10-day presymptomatic window preceding an exacerbation was classified as a true positive. Conversely, abnormal values within 10 days following an exacerbation were designated as "late" positives. Abnormal values outside of these windows were flagged as false positives. For the negative results, days featuring no abnormal values were declared true negatives unless they fell within a 10-day period preceding an exacerbation, in such cases, they were categorised as false negatives. We defined "episode sensitivity" for each variable as the detection of at least one abnormal result outside of the participant's normal range within the pre-exacerbation period.

Ethics

Ethical approval was given by the NHS South Central Research Ethics Committee 14/SC/0298 and all participants gave written, informed consent. Participants were allowed to keep study equipment at the completion of the study but there was no financial compensation. Anonymised data can be made available for suitable studies on written request.

Results

		Study population
N		30
Age		68.3 (61.3-73.6)
Female gender		17 (56.7%)
Smoking status	Never	12 (40%)
	Ex	17 (56.7%)
	Current	1 (3.3%)

Pack year history	15.5 (0-30)
Antibiotic Courses per participant in the past 12 months	4 (3-5)
BMI	26.3 (±5.6)
Bronchiectasis	17 (56.7%)
COPD	4 (13.3%)
Bronchiectasis and COPD	9 (30.0%)
Ischaemic heart disease	4 (13.3%)
Heart failure	4 (13.3%)
Type 2 diabetes	2 (6.7%)
FEV1 (% predicted)	66.1% (±28.4)
FVC (% predicted)	85% (±23.4)
FEV1/FVC ratio	62.6% (±16.0)
Sputum culture Pseudomonas	20 (66.7%)

Table 1: Study population baseline data. n (%), median (IQR) or mean (±SD). All participants with COPD were GOLD D.

30 participants were recruited with study population baseline data shown in Table 1. A CONSORT diagram of study recruitment is shown in the supplement, figure S9. A total of 39,534 physiological and 25,334 symptom data points were collected across 5,358 participant-days. A total of 78 exacerbations were reported during the six-month study period, by 27 of 30 participants with the median exacerbation count being 3 (IQR 1-3.75) and the remaining three participants not exacerbating during the study period. Four participants suffered a total of six hospital admissions for respiratory symptoms were recorded during the study, giving an overall annualised rate of 0.2 per year compared to 0.6 per year (17 emergency hospital attendances of 7 participants) in the year prior to admission. Participant level physiological and symptom data showed high inter-individual differences around the point of exacerbation as shown in figure S5-6.

Physiological data,	**All data (n=30)**	**Exacerbation period d0 ±10d (n=27)**	**Normal range excluding exacerbation period (n=27)**	**p-value**
Weight (Kg)	72.7±13.9	74.5±14.2	72.2±14.2	<0.001
Step count (/day)	3065 (1242-7088)	3296 (1285-6428)	2975 (1183-7469)	0.479
Peak Flow	233 (149-320)	209 (133-289)	243 (159-327)	<0.001

(L/min)				
O2 Saturation (%)	95.4(92.0-97.2)	95.2 (92.0-97.0)	95.5 (92.5-97.3)	<0.001
Systolic BP (mmHg)	130±22	130±24	130±22	0.902
Diastolic BP (mmHg)	77±12	77±13	77±12	0.884
Pulse rate (/min)	78.4±13.2	78.8±14.1	78.2±11.9	0.052
Temperature (ºC)	36.7(36.5-37.0)	36.7 (36.5-37.0)	36.6 (36.5-37.0)	0.008
mNEWS score	1.4±1.6	1.5±1.7	1.3±1.6	<0.001

Table 2: Average results for physiological data throughout the study using mean ± SD or median (IQR), p-value from t-test of at exacerbation vs excluding exacerbation for normally distributed data or Mann-Whitney U test for non-normally distributed data. Exacerbation data based on 27 participants as 3 participants did not exacerbate.

Physiological data (Table 2) were compared using individualised Z-scores to adjust for inter-participant differences in exacerbation frequency. Values from exacerbation and 10 days either side were compared with non-exacerbation days outside of this window. Peak flow rates and O2 saturations were significantly lower during the exacerbation window while weight and mNEWS significantly higher (p<0.001). Mean values of temperature, pulse rate, PEFR and systolic BP around exacerbation are shown in figure 1.

Symptom scores	All data (n=30)	Exacerbation period d0 ±10d (n=27)	Normal range excluding exacerbation period (n=27)	p-value
Wellness score	6.1±1.8	5.7 ± 18	6.4±1.8	<0.001
Cough score	6.1±1.8	5.6 ± 1.7	6.4±1.8	<0.001
Breathing score	6.0±2.0	5.5 ± 2.0	6.2±1.9	<0.001
Appetite score	6.2±2.0	5.8 ± 2.0	6.4±2.0	<0.001
Energy score	5.8±2.1	5.2 ± 2.0	6.0±2.1	<0.001
Total symptom score	30.1±9.2	27.7 ± 8.9	31.4±9.1	<0.001

Table 3: Average results for all symptom data throughout the study and excluding exacerbations using mean ± SD, p-value from t-test of at exacerbation vs excluding exacerbation

Average appetite, breathing, cough, energy and wellness symptom scores in the first week of data collection were correlated with overall SGRQ giving correlation coefficients of -0.694, -0.761, -0.718, -0.798 and -0.805 respectively (all p<0.001) showing good correlation between patient reported symptom scores and a validated quality of life questionnaire. Symptom scores were also compared using individualised Z-scores to adjust for inter-participant differences in exacerbation frequency. Values from exacerbation and 10 days either side were compared with non-exacerbation days outside of this window. All symptom scores including the total symptom score were significantly lower at and around exacerbation compared to outside this range as shown in table 3 (P<0.001 for each).

The trend of symptom scores around the point of exacerbation are shown in Figure 2, showing a gradual worsening in mean symptom score each day leading to the point of exacerbation, with gradual recovery following this, however the magnitude of the decline is small with each score decreasing by a mean of less than one point and by a similar magnitude.

Trends of total symptom scores through the study were examined, and while the average total

symptom score showed a slight improvement over time, this was not true for those with sputum *Pseudomonas aeruginosa* who started with poorer symptom scores and showed a trend towards worsening over time as shown in Figure 3.

Predictive values

Individual control limits of variable widths were calculated as above. Table 4 shows predictive values at 2 standard deviations which gave a balance between positive predictive value and sensitivity. A range of control interval widths were calculated, and positive predictive values (PPV) for physiological variables were highest at 27.9% (at 3.3SDs) while PPV for symptom variables peaked at 62.4% (at 4SDs) which predicted 17.6% and 26.1% of episodes respectively (Figures S7 and S8). Individual level data demonstrating the range of predictive values at control widths of 2 standard deviations for each participant are shown in supplemental Table S1. Comparison between results for participants with COPD and Bronchiectasis is shown in supplemental table S2, showing slightly higher PPV and episode sensitivity for participants with COPD but still less than 50%.

	PPV	NPV	Sensitivity	Specificity	Accuracy	Episode Sensitivity
Weight	27.23%	82.76%	7.26%	95.82%	80.14%	24.36%
Steps	13.51%	82.51%	3.46%	95.36%	79.45%	19.23%
Peak flow rate	26.18%	83.06%	6.90%	95.91%	80.46%	28.21%
O2 saturation	24.63%	83.17%	6.80%	95.68%	80.39%	33.33%
Systolic BP	21.39%	82.74%	5.82%	95.48%	79.83%	35.90%
Pulse rate	20.00%	82.94%	5.44%	95.48%	79.99%	37.18%
Temperature	24.41%	82.99%	6.99%	95.45%	80.07%	42.31%
Wellness score	36.88%	83.98%	12.99%	95.35%	81.11%	34.62%
Cough score	36.81%	84.28%	16.06%	94.22%	80.69%	42.31%
Breathing score	37.19%	84.51%	18.07%	93.61%	80.52%	43.59%
Appetite score	40.29%	84.27%	14.99%	95.35%	81.44%	47.44%
Energy score	38.44%	84.44%	17.14%	94.25%	80.89%	46.15%
Total symptom score	38.46%	84.28%	15.39%	94.85%	81.11%	43.59%

Table 4: Predictive values of abnormal results for physiological and symptom results with individualised control limits of 2 standard deviations.

Physiological and symptom variables were analysed using receiver operating characteristic (ROC) analysis (figure S3), and no area under the curve (AUC) value was outside a range of 0.4-0.6 indicating no significant predictive value. This was repeated with Z-scores (figures S1-S2) to normalise for individual variation and all AUC values were within 0.45-0.55 again showing no significant predictive value (figure S4). ROC analysis was also conducted for COPD and bronchiectasis alone, and for pseudomonas and haemophilus colonisation alone and in each analysis

no curve exceeded an AUC of 0.4-0.6 with the exception of peak flow in participants with Haemophilus which had an AUC of 0.374.

Discussion

Our study has revealed the limited predictive value of physiological markers and symptom scores in this population with airway disease and chronic colonisation. The variability of physiological data and the subtlety of symptom changes challenge the reliance on these measures alone for predicting imminent exacerbations. Symptom scores on a population level indicated some deterioration around the time of exacerbation but were insufficient as standalone individual level predictors. Our approach to personalise reference ranges, accounting for intraparticipant variability, has been proven valuable but still fell short in enhancing predictive accuracy.

Despite these limitations, the role of these indicators cannot be entirely discounted. Physiological variables and symptom scores remain crucial components of a comprehensive disease monitoring plan for many respiratory diseases. The differentiation between physiological changes and symptom deterioration are important; while physiological parameters may not predict exacerbations with high accuracy, they provide valuable information on a patient's baseline health status, which can be crucial when responding to symptoms that suggest an exacerbation and therefore guide clinical decision-making, particularly when considered alongside an individual's typical symptomatology and exacerbation patterns. This approach was used in the PROMETE study for example, that showed monitoring physiological values with respiratory physician reviews reduced hospital and ED attendances over 7 months with more exacerbations being managed at home [24].

Moreover, the aggregated symptom score highlighted in our study, while not overtly predictive, could have potential applications when considering temporal trends over more extended periods, as some data suggest that telemonitoring is more beneficial over a longer term than in our study [25].While acute predictive value is limited, monitoring this score could be useful for assessing overall disease management and quality of life across broader timeframes, which may be of interest in longitudinal studies. Systematic reviews of previous studies of the effectiveness of remote monitoring of airway disease have focused on COPD and have shown mixed results[26, 27]. Of particular interest, physiological deterioration over time was noted in our study in those colonised by *Pseudomonas aeruginosa* and this is consistent with previously reported data, suggesting a particularly high-risk group of patients[28].

Our study also reflects the multifaceted nature of exacerbations in chronic airway diseases, which likely result from a combination of factors, ranging from environmental triggers to individual patient behaviours. Furthermore, the findings underscore the essential role of education and self-management. The decrease in admission rates during the study, compared to the year prior, may indicate that equipping patients with self-management plans may help avert the most severe manifestations of exacerbations, thereby reducing hospital visits.

While our study has provided valuable insights into the management of chronic airway disease, the inherent limitations must be acknowledged. The relatively small cohort size and the specific inclusion of patients with known chronic airway colonisation restrict the generalisability of the findings. The observational period did not extend across a full year, resulting in a potential underrepresentation of seasonal variations, though it crucially encompassed the winter months when exacerbations are generally more prevalent and severe. The exclusion of respiratory rate—a potentially significant physiological marker—from our data collection may have omitted a critical variable with predictive capability. Additionally, while the symptom scores employed in the study were less complex and showed good correlation with established measures such as the St. George's Respiratory Questionnaire (SGRQ), there remains the possibility that more nuanced symptom evaluation tools could yield stronger predictive correlations. Another notable aspect of the study was participant access to their own longitudinal data, which introduces the potential for reporting bias. However, the anticipated direction of such bias would more commonly lead to an overestimation of symptoms, resulting in false-positive identifications of exacerbations — a phenomenon not observed

in our data. This suggests that while participant awareness of their data could be a confounding factor, its impact on the study's outcomes may be minimal. Despite these limitations, the study's strengths also warrant mention. By methodically tracking daily symptomatic and physiological changes within a clearly defined patient group, the study provides nuanced insight into the patterns preceding exacerbations. Moreover, the inclusion of the winter months offers pertinent data from a period of high clinical relevance due to the increased exacerbation risk.
Further studies examining respiratory rate, other symptom assessment or continuous monitoring may be of benefit, but a strongly predictive single factor seems unlikely and alternative approaches to monitoring airway disease such as combining multiple sources of predictive data in the home setting are more likely to be useful.

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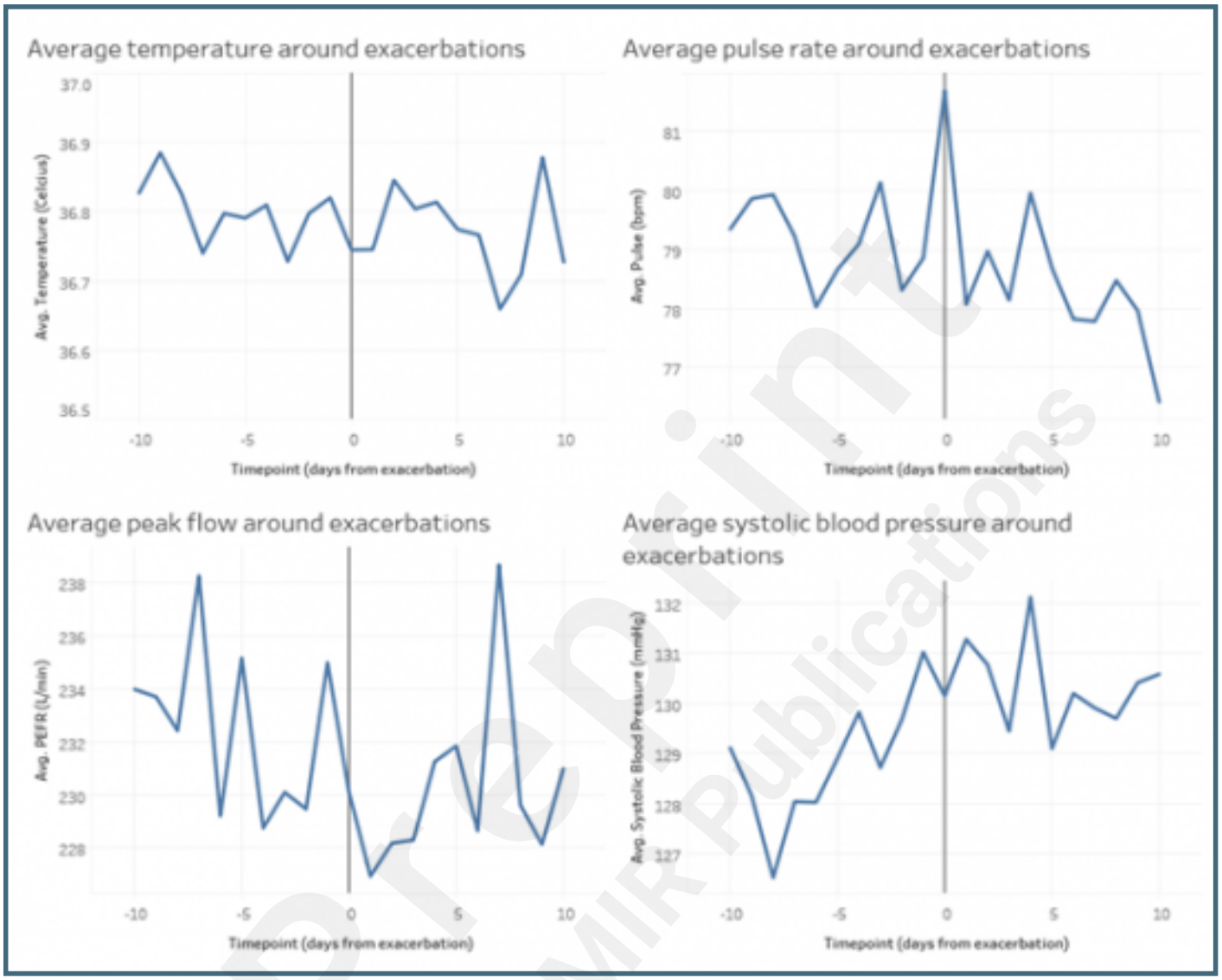
Supplementary Files

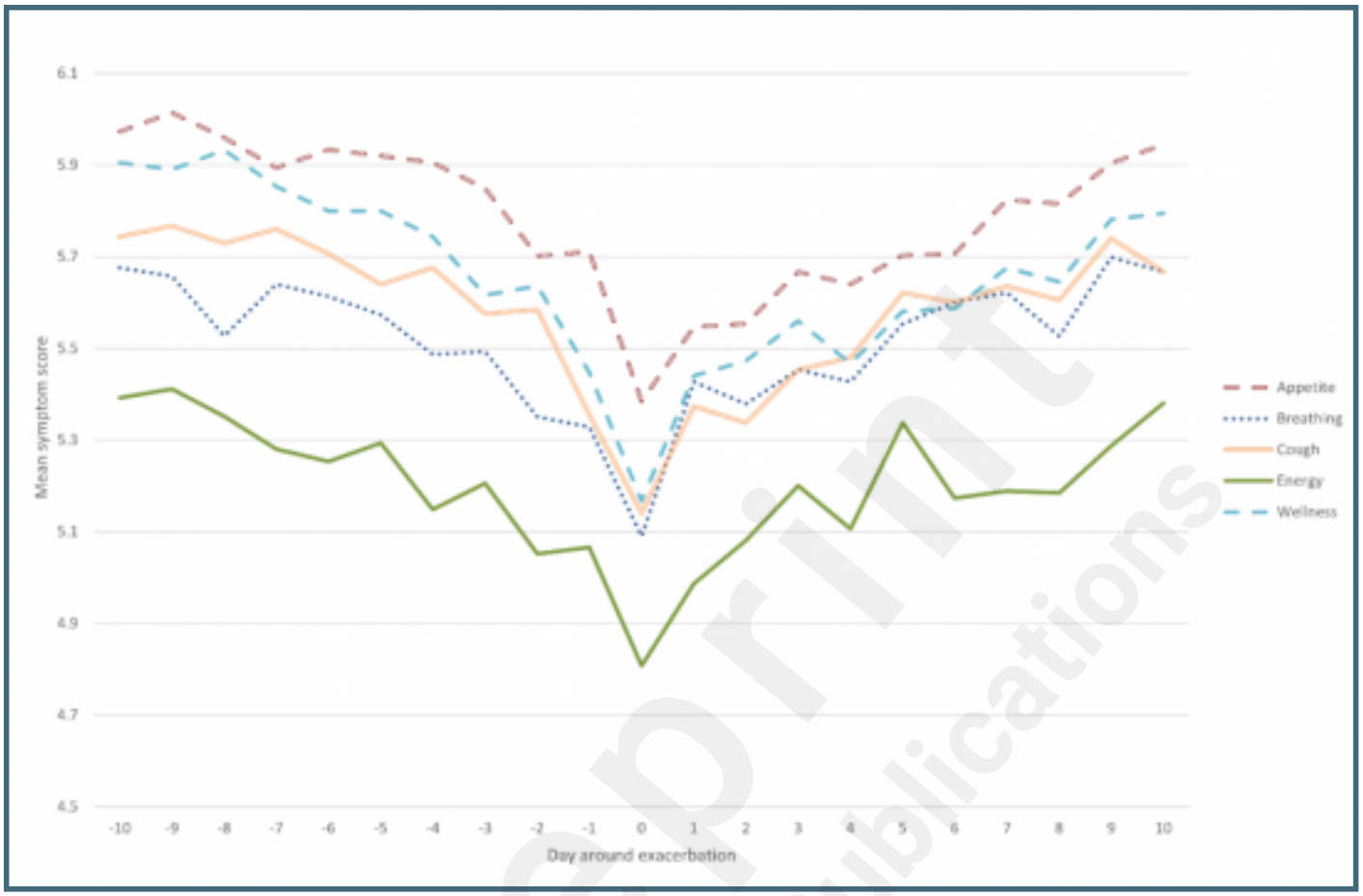
Untitled.
URL: http://asset.jmir.pub/assets/de1877b6beb1eb6a7a33400e927d2558.docx

Figures

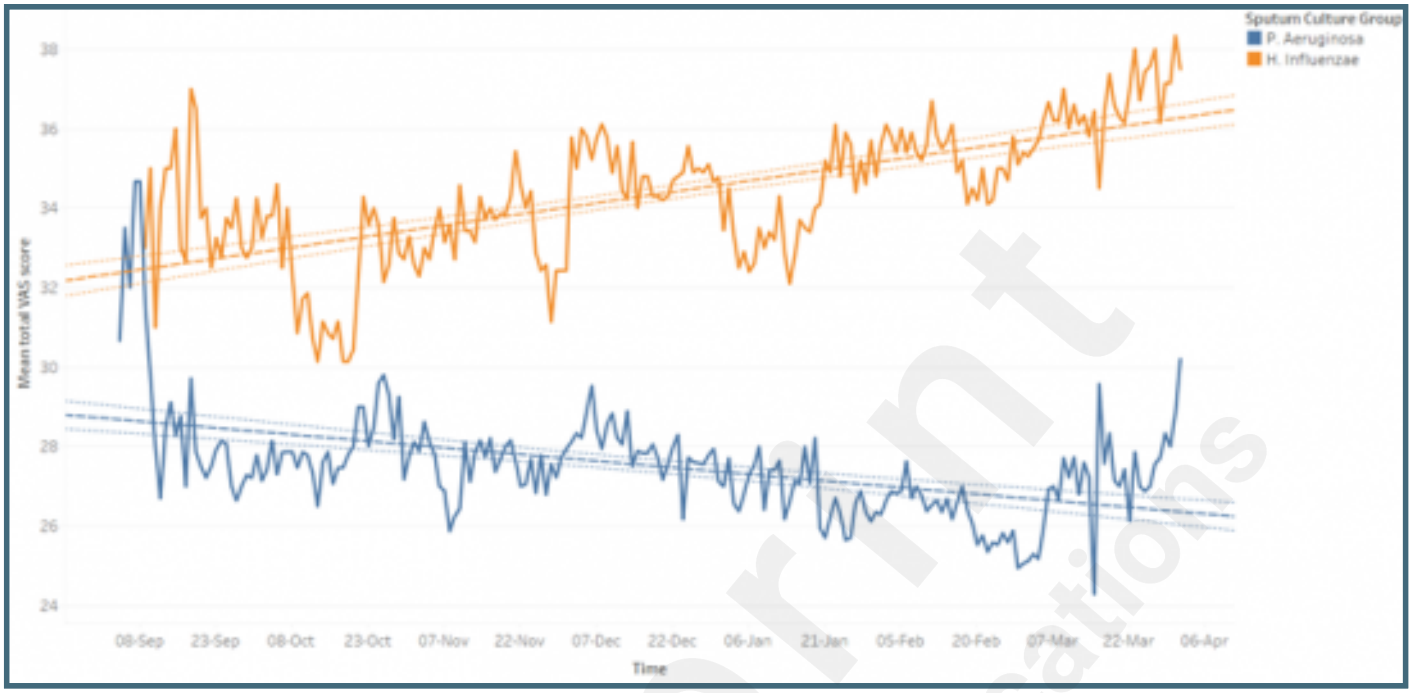
Average temperature, pulse rate, PEFR and systolic BP 10 days either side of the start of an exacerbation for all 78 exacerbations.



Mean symptom scores around the point of exacerbation (day 0) for all exacerbations.



Change in mean total symptom score by sputum culture, demonstrating worsening symptoms over time in the Pseudomonas aeruginosa group (lower line, n=20) and improving symptoms in the Haemophilus influenzae group (upper line, n=10).



Multimedia Appendixes

Supplementary data.
URL: http://asset.jmir.pub/assets/df4886b7efdb6a8d6820edc7cb63b2c7.docx