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Time course of inflammation resolution in patients with frequent exacerbations of chronic obstructive pulmonary disease

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: When exacerbation of chronic obstructive pulmonary disease (AECOPD) occurs frequently, patients have high levels of airway and systemic inflammation and a poor quality of life. This study compared the nature and course of systemic and airway inflammation during AECOPD between patients who experienced frequent exacerbations and those with non-frequent exacerbations.

Material/Methods: Consecutive hospitalized patients with AECOPD were recruited and divided into 2 groups according to the frequency of AECOPD they had experienced in the previous year. Frequent exacerbators (defined as 2 or more AECOPD in the previous year) and non-frequent exacerbators (defined as zero or 1 AECOPD in the previous year). Inflammatory (interleukin 6, interleukin 8, myeloperoxidase, and C-reactive protein) and clinical (dyspnea, COPD assessment test (CAT), and peak expiratory flow) indices were assessed on the day of admission before starting therapy, day 7 of treatment, the day of planned discharge (day 10–14), and 8 weeks after discharge.

Results: We analyzed data from 135 patients; 78 (57.8%) were non-frequent exacerbators and 57 (42.2%) were frequent exacerbators. In both groups, the inflammatory and clinical indices at day 7, the day of planned discharge (day 10–14), and 8 weeks were significantly improved compared to those at admission. Frequent exacerbators had a smaller reduction in their inflammatory indices and CAT scores between exacerbation onset and all the other time points compared with infrequent exacerbators.

Conclusions: Frequent exacerbators have a reduced response to treatment of AECOPD in terms of inflammatory indices and quality of life.

MeSH Keywords: Quality of Life • Inflammation • Pulmonary Disease, Chronic Obstructive

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Background

Chronic obstructive pulmonary disease (COPD) is characterized by persistent airflow limitation that is usually progressive. It is now recognized that COPD is a heterogeneous disease and that the severity of the airflow obstruction is not the only determinant of the severity of COPD and its impact. An exacerbation of COPD (AECOPD) is an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond day-to-day variations and leads to a change in medication [1]. The frequency of AECOPD is variable among patients. A previous study has shown that patients with "frequent exacerbations" (defined as 2 or more per year) and those with "infrequent exacerbations" (defined as zero or 1 exacerbation per year) tended to remain in the same category of exacerbation frequency for all 3 years of the study, irrespective of disease severity. The authors interpreted this stability of exacerbation frequency as evidence that patients who have frequent exacerbations represent a distinct COPD phenotype, implying the existence of some underlying genetic, biologic, or behavioral mechanism that determines susceptibility or resistance to recurrent exacerbations that is independent of disease severity [2,3]. Patients with a history of frequent exacerbations have a more rapid decline of lung function [4,5], worse quality of life [6], and higher mortality rates [7,8].

Inflammation is a prominent feature of COPD. Patients with frequent exacerbations have increased airway inflammation in their stable state [9]. A study has recently reported that patients with frequent exacerbations have a faster rise in systemic inflammation over time compared with those with infrequent exacerbations [10]. Exacerbations of COPD are generally considered to reflect a flare-up of these underlying inflammatory processes [11,12]. A patient's quality of life decreases during an episode of AECOPD [13]. However, there is limited information on the time course for resolution of the inflammatory response and the resulting improvement of quality of life during severe AECOPD. Our hypothesis was that patients with frequent exacerbations have a reduced response to therapy in terms of inflammation and quality of life, which results in these patients experiencing persistently higher inflammatory markers and a poorer quality of life. If this is the case, then understanding the problem should lead to better treatment for the affected patients. The aim of this study was to investigate the time course of the change in inflammatory mediators and quality of life during hospital treatment for AECOPD in patients who were stratified according to their exacerbation frequency, to see if the frequently affected patients do indeed have a reduced response to treatment.

Material and Methods

Patients

Between 1April 2009 and 30 September 2011, a prospective study was conducted including consecutive patients presenting with AECOPD admitted to the Respiratory Department in Peking University's Third Hospital (Peking, China).

Inclusion criteria were a COPD diagnosis (the post-bronchodilator spirometric values from the patients' records during their stable condition in the 6 months prior to study inclusion were used to diagnose COPD), the presence of exacerbation according to the Global Initiative of Chronic Obstructive Lung Disease definition [14], and admission to the hospital for more than 24 h. For patients admitted more than once during the study period, only the first admission was included in the analysis. Patients with the following conditions were excluded: asthma, bronchiectasis, pneumonia, cancer, sleep apnea syndrome or other forms of active lung disease; and hospitalization for reasons other than AECOPD (including acute coronary syndrome and congestive heart failure). Exclusions also included the need for intubation or admission to ICU; length of stay (LOS) longer than 30 days; long-term oral corticosteroids therapy (more than 3 months treatment with 7.5 mg per day of prednisone or equivalent); and patients who had received systemic corticosteroids for their exacerbation for more than 48 h before presentation.

Written informed consent was obtained from all patients and the Ethics Committee of the Peking University third hospital approved the study protocol.

Study design

According to the frequency of AECOPD in the previous year, patients were divided into 2 groups: frequent exacerbators (defined as 2 or more AECOPD in the previous year) and non-frequent exacerbators (defined as zero or 1 AECOPD in the previous year).

According to the GOLD guidelines [14], patients were treated with nebulized salbutamol, ipratropium bromide, budesonide, and intravenous prednisolone in a dosage of 30 to 40 mg daily. The duration of intravenous therapy was 3 days. On day 3, patients were switched to an oral tapering schedule of prednisolone. Antibiotics were administered if bacterial infection was suspected (patient-reported sputum purulence) and adjusted according to antimicrobial susceptibilities, when available. Initial antibiotic therapy was defined as the antibiotics received on the first day of therapy for AECOPD. It was defined as inappropriate if it was inactive *in vitro* against the isolated organism(s) [15,16].

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Mechanical ventilation was initiated by the treating physician for indications such as respiratory arrest, deterioration in the level of consciousness, and increasing partial pressure of arterial carbon dioxide (PaCO2), despite maximal pharmacological treatment. Non-invasive ventilation was used initially whenever possible and indicated. Decisions regarding admission or transfer to the ICU were made by the treating unit.

After a baseline measurement on their admission day, prior to initial treatment, patients were followed up on day 7 of treatment, the day of planned discharge (day 10–14), and 8 weeks after discharge. At each time point, dyspnea was assessed using the 5-grade Medical Research Council dyspnea scale [16]. The COPD Assessment Test (CAT) was completed on the morning before treatment, based on their symptoms experienced on the day of completion; peak expiratory flow (PEF) was measured with a mini-Wright peak flow meter (Clement Clarke, Harlow, UK) in triplicate in the morning before treatment by the same experienced technician for each subject. The highest of 3 values was recorded.

Clinical data collection

Clinical data collection, including demographic data, spirometric values during their stable condition, comorbid conditions, continuing management, smoking habits, exacerbation frequency in the previous year, and admission symptoms, was conducted. Exacerbation frequency in the previous year was based on the number of exacerbations the patient recalled for the year before recruitment. Previous work has shown a good correlation between the number of exacerbations recorded on diary cards and the number of exacerbations remembered by the patient over the same 1-year period [17]. On the day of admission, the severity of AECOPD was determined according to the symptoms before starting treatment according to the Anthonisen criteria [18]. All treatments provided during hospitalization were recorded.

The adverse clinical outcomes (death from any cause in hospital or within 8 weeks of discharge, need for mechanical ventilation after the second hospital day, or recurrent exacerbations within 8 weeks of discharge) of the patients and their cardiovascular complications in hospital or within 8 weeks of discharge were collected during follow-up [19,20]. A recurrent exacerbation was defined in the present study as a second exacerbation, fulfilling the present criteria, occurring within 8 weeks of the index discharge. Symptoms from the first exacerbation must have recovered to pre-exacerbation levels.

Sampling and experimental methods

Patient sputum and serum samples were collected on the admission day prior to initial treatment, on the 7th day of treatment (day 7), at the day of planned discharge (day 10–14), and when clinically stable (approximately 8 weeks after discharge).

Spontaneous sputum was used; when no spontaneous sputum was available, induced sputum was collected according to a previous study on the equivalence of induced and spontaneous samples for assessment of airway inflammatory markers [21]. Of the sputum samples taken, 97% were spontaneous. Each sample was confirmed to be a valid sputum sample suitable for processing if there were >25 polymorphonuclear leukocytes and <10 squamous cells present on Gram stain on low power (×100) magnification [22]. Sputum samples were processed within 2 h of collection and divided into 2 aliquots. One sample was processed with phosphate-buffered saline (PBS) [23,24], cytospins were prepared, and the cell-free supernatant was collected and stored in aliquots at –80°C pending analyses of soluble mediators. Differential cell counts were counted on May Grünwald Giemsa stained cytospins in a blinded fashion. Quantitative sputum cultures were performed using the second sample according to previously described methods [25]. Bacterial agents were classified as potentially pathogenic microorganisms (PPMs) or non-PPMs. Only PPM growth at thresholds higher than 10^5 colony-forming units for *Streptococcus pneumoniae* and 10^6 colony forming units for other isolates were considered as significant according to the study by Miravitlles et al. [26]. Peripheral venous blood (7 mL) was collected into a Vacutainer tube (BD Diagnostics, NJ) and centrifuged at 2000 × g for 10 min at 4°C. Serum was then separated and stored at –80°C until further analysis.

Serum interleukin (IL)-6, sputum IL-8, and myeloperoxidase (MPO) were quantified using commercial sandwich ELISA kits (R&D Systems, Abingdon, UK). Serum high-sensitivity C-reactive protein (hs-CRP) was measured by a latex agglutination test, performed using an Olympus AU5400 automatic biochemical analyzer. All the samples from each patient were measured in the same assay to reduce inter-assay variability. The limit of detection was 0.7 pg/mL for serum and sputum IL-6, 7.5 pg/mL for sputum IL-8, 0.062 ng/ml for sputum MPO, and 0.1 mg/L for serum hs-CRP.

Statistical analysis

Statistical analysis was performed using SPSS version 11.5.0 (SPSS Inc., Chicago, IL). The data were not normally distributed; therefore, nonparametric statistics were used. Categorical variables are presented as percentages and numerical variables are presented as median (interquartile ranges). Wilcoxon's signed rank test was used for analysis of paired data and the Mann-Whitney U test was used for analysis between 2 groups. Categorical outcome variables were analyzed using chi-square tests. A value of $P<0.05$ was considered significant.

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Results

Patient characteristics

A total of 173 eligible patients were included in the present study. However, 38 patients were withdrawn from the study due to pneumonia (n=6); congestive cardiac failure or left ventricular failure at admission (n=5); pulmonary embolism (n=3); need for intubation at admission (n=14); length of stay (LOS) longer than 30 days (n=5); and having received systemic corticosteroids for their exacerbation for more than 48 h (n=5). Therefore, in the final analysis we included a total of 135 patients. Overall, 78 (57.8%) had 0 or 1 AECOPD in the year before the index hospitalization, and 57 (42.2%) had 2 or more. The characteristics of frequent exacerbators and non-frequent exacerbators are shown in Table 1. Compared with non-frequent exacerbators, the group of frequent exacerbators had: lower forced expiratory volume in 1 second (FEV1)% of predicted; higher CAT value at stable status; more patients with arterial hypertension; more patients using long-term inhaled corticosteroid (ICS) treatment; the mean daily dose of methyl-prednisolone or equivalents was not statistically different (P=0.411); more patients were classified as Anthonisen type I; more patients with cold symptoms at presentation; and more patients with positive PPM results at admission and on the day of discharge.

In the patients that survived after hospitalization (n=124), 38 patients has positive sputum results at admission; in these

Table 1. Characteristics of frequent exacerbators and non-frequent exacerbators.

	Frequent exacerbators (n=57)		Non-frequent exacerbators (n=78)		Statistics	Significance
Male gender (%)	50	(87.7)	69	(88.5)	0.017	0.895
Age (years)	67	(63, 74)	66	(60 ,74)	–0.912	0.362
Smoking habit						
Current smokers	12	(21.1)	17	(21.8)	0.011	0.917
Ex-smokers	40	(70.2)	50	(64.1)	0.547	0.460
Pack-year	30	(20 ,40)	20	(15 ,30)	–0.128	0.068
Cor pulmonale (%)	17	(29.8)	28	(35.9)	0.547	0.46
FEV1 (%pred)	45	(36 ,54)	52	(43 ,55)	–1.979	0.048*
CAT value at stable status	13	(9, 17)	9	(4, 14)	–3.242	0.001*
BMI (kg/m^2)	23.8	(20.4, 26.0)	21.3	(18.8, 25.5)	–1.936	0.053
Comorbidities						
Arterial hypertension	26	(45.6)	15	(19.2)	10.84	0.001*
Ischemic heart disease	11	(19.3)	17	(21.8)	0.125	0.724
Diabetes	10	(17.5)	10	(12.8)	0.582	0.445
Congestive heart failure	11	(19.3)	8	(10.3)	2.226	0.136
Renal disease	6	(10.5)	3	(3.8)	1.41	0.235
Preadmission COPD therapy						
Chronic oxygen therapy	10	(17.5)	22	(28.2)	2.07	0.15
Steroid treatment prior to hospitalization						
Long term ICS treatment#	21	(36.8)	43	(55.1)	4.417	0.036*
Long-term oral corticosteroid use*	4	(7.0)	7	(9.0)	0.008	0.927
Regular use of bronchodilator inhaled bronchodilators+						
Long-term inhaled bronchodilators (formoterol/ salmeterol)	42	(73.7)	63	(80.8)	0.956	0.328

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Table 1 continued. Characteristics of frequent exacerbators and non-frequent exacerbators.

	Frequent exacerbators (n=57)		Non-frequent exacerbators (n=78)		Statistics	Significance
Short-term inhaled bronchodilators (ipratropium bromide)	7	(12.3)	7	(9.0)	0.387	0.534
Exacerbation characteristic						
Anthonisen type I	43	(75.4)	46	(59.0)	3.974	0.046*
Cold symptom at presentation	19	(33.3)	12	(15.4)	5.998	0.014*
Positive PPM result at admission	24	(42.1)	18	(23.1)	5.564	0.018*
Type of isolated pathogen at admission						
H. influenzae	7		6			
P. aeruginosa	7		5			
S. pneumoniae	5		2			
K. peneumoniae	3		2			
M. catarrhalis	1		1			
A. baumanii	2		0			
Candida albicans	1		0			
Stenotrophomonas maltophilia	1		0			
Enterobactercloacae	0		1			
Serratiamarcescens	1		0			
Escherichia coli	0		1			
MRSA	1		0			
Positive PPM result at the day of discharge[##]	14	(24.6)	5	(6.4)	5.216	0.022*
Treatment during hospitalization						
Inappropriate initial antibiotic therapy[++]	13	(22.8)	19	(24.4)	0.044	0.834
Use of systemic corticosteroid during hospitalization	50	(87.7)	68	(87.2)	0.009	0.926
Mean daily dose of methyl-prednisolone or equivalents	4.3	(4.3, 5.6)	5.0	(4.3, 5.6)	–0.822	0.411
Duration of systemic corticosteroid	12	(12, 15)	12	(12, 15)	–0.522	0.602
Use of nebulized budesonide during hospitalization	15	(26.3)	18	(49.4)	0.187	0.665
Daily dose of budesonide	3	(2, 4)	3	(2, 6)	–0.657	0.532
Duration of budesonide	11	(4, 12)	11	(5, 12)	–0.018	0.986

Data are presented as median (interquartile ranges) for numerical variables or as number (%) for categorical variables. FEV1 – forced expiratory volume in 1 sec; COPD – chronic obstructive pulmonary disease; AECOPD – acute exacerbations of COPD; CAT – COPD assessment test; BMI – body mass index; ICS – inhaled corticosteroids; PPM – potentially pathogenic microorganisms. [#] Equivalent to Fluticasone Propionate (FP) ≥500 ug/day for more than 1 year. * Oral corticosteroids on a regular basis (more than three months treatment with 7.5mg per day on prednisone or equivalent). Mann-Whitney U test was used for analysis between 2 groups. [##] Results are based on the 124 patients survived from the hospitalization; [+] 3 months of daily use. [++] inappropriate initial antibiotic therapy as that which was inactive *in vitro* against the isolated organism(s).

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Table 2. The rate of adverse events in frequent exacerbators and non-exacerbators.

Event	Frequent exacerbators (n=57)	Non-frequent exacerbators (n=78)	χ^2	P
Patients with ≥1 adverse event	13	29	3.174	0.075
Death during hospitalization	5	6	0.000	1.000
Death within 8 weeks of discharge	2	6	0.42	0.517
Need for mechanical ventilation after the second hospital day	5	13	1.776	0.183
Recurrent exacerbations within 8 weeks of discharge	8	17	1.314	0.252

Sum total of events may be greater than number of patients with events, as some patients had more than one adverse event. Mann-Whitney U test was used for analysis between 2 groups. Categorical outcome variables were analyzed using chi-square tests.

38 patients, the bacteria were cleared from 19 patients (7/21 in frequent exacerbators *vs.* 12/17 in non-frequent exacerbators, *P*=0.022). The proportion of inappropriate initial antibiotic therapy in the frequent exacerbators was comparable to that in the non-frequent exacerbators (22.8% *vs.* 24.4%, *P*=0.834).

Clinical outcome variables

During the study period, a total of 42 (31.1%) adverse events were observed, the rate of adverse events in the frequent exacerbators and non-frequent exacerbators are shown in Table 2. There were no significant differences between the 2 groups.

Cardiovascular events in frequent exacerbators and non-frequent exacerbators

The rate of cardiovascular events in hospital or within 8 weeks of discharge of frequent exacerbators and non-frequent exacerbators were 17/57 (29.8%), 10/78 (12.8%), respectively (χ^2=5.951, *P*=0.015).

Comparison between frequent exacerbators and non-frequent exacerbators in inflammatory indices at different time points during AECOPD

The comparison between frequent exacerbators and non-frequent exacerbators in sputum inflammatory indices at different time points during AECOPD are shown in Figure 1. There was a significant difference in neutrophil numbers between frequent exacerbators and non-frequent exacerbators at all time points. There was a significant difference in MPO between frequent exacerbators and non-frequent exacerbators at admission, day 7, and the day of planned discharge (day 10–14). In groups, the concentration of sputum inflammatory indices at day 7, the day of planned discharge (day 10–14), and 8 weeks after discharge were significantly lower than that at admission.

Figure 2 shows the comparison between frequent exacerbators and non-frequent exacerbators in serum inflammatory indices at different time points during AECOPD. There was a significant difference in hs-CRP between frequent exacerbators and non-frequent exacerbators at all time-points except at admission. In both groups the concentration of sputum inflammatory indices at day 7, the day of planned discharge (day 10–14), and 8 weeks after discharge were significantly lower than that at admission.

Comparison between frequent exacerbators and non-frequent exacerbators in clinical indices at different time points during AECOPD

The comparison between frequent exacerbators and non-frequent exacerbators in clinical indices at different time points during AECOPD are shown in Figure 3. There was a significant difference between frequent exacerbators and non-frequent exacerbators in PEF at day 7, CAT at the day of planned discharge (day 10–14), and 8 weeks after discharge,. In both groups, the value of clinical indices at day 7, the day of planned discharge (day 10–14), and 8 weeks after discharge were significantly improved compared to that at admission.

Discussion

The aim of this study was to investigate the time course of the inflammatory response in patients treated for AECOPD and to discover whether this response is reduced in patients with a history of frequent exacerbations, compared to patients with infrequent exacerbations. The results show that while all patients experienced an improvement in their inflammatory indices, frequent exacerbators had a smaller reduction in response to treatment compared with infrequent exacerbators. This reduced response to treatment was also shown in the patients' CAT scores. These results are important because they indicate

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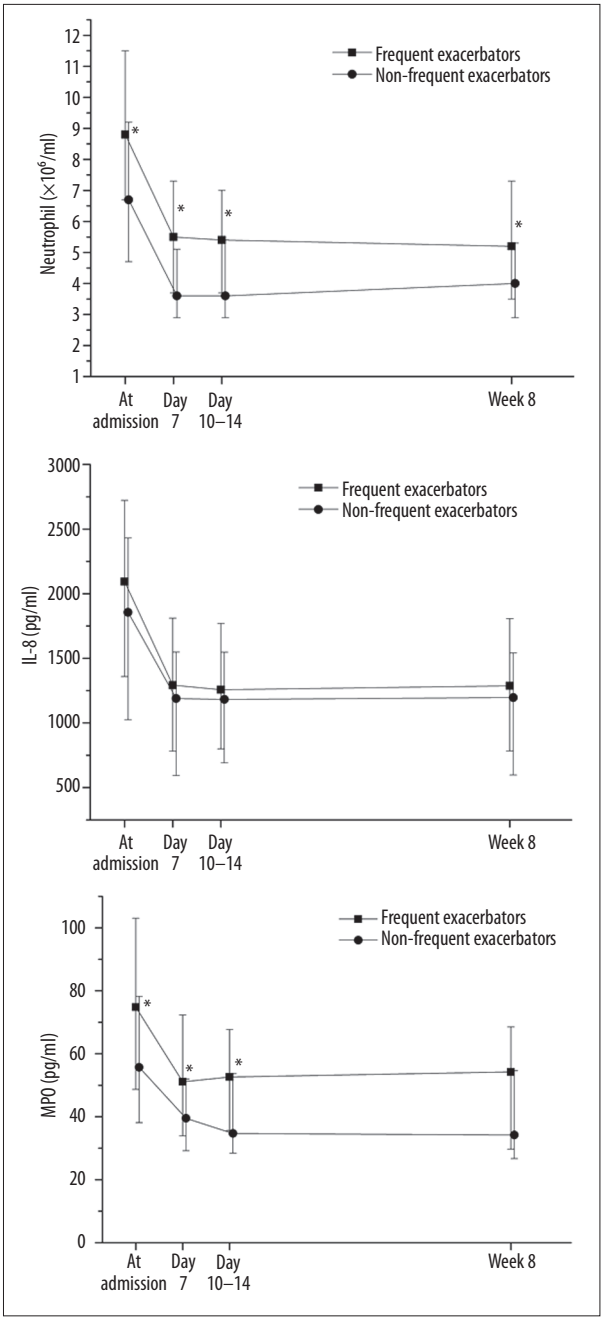

Figure 1. Time course of airway inflammatory indices in the 2 groups. Results are based on the 93 patients from whom samples were acquired at all time points. Data are median values and interquartile ranges. Mann-Whitney U test was used for analysis between 2 groups. Wilcoxon's signed rank test was used for analysis of paired data. IL-8 – interleukin 8; MPO – myeloperoxidase. * P<0.05 *vs.* non-frequent exacerbators. P<0.05 *vs.* at admission in both groups.

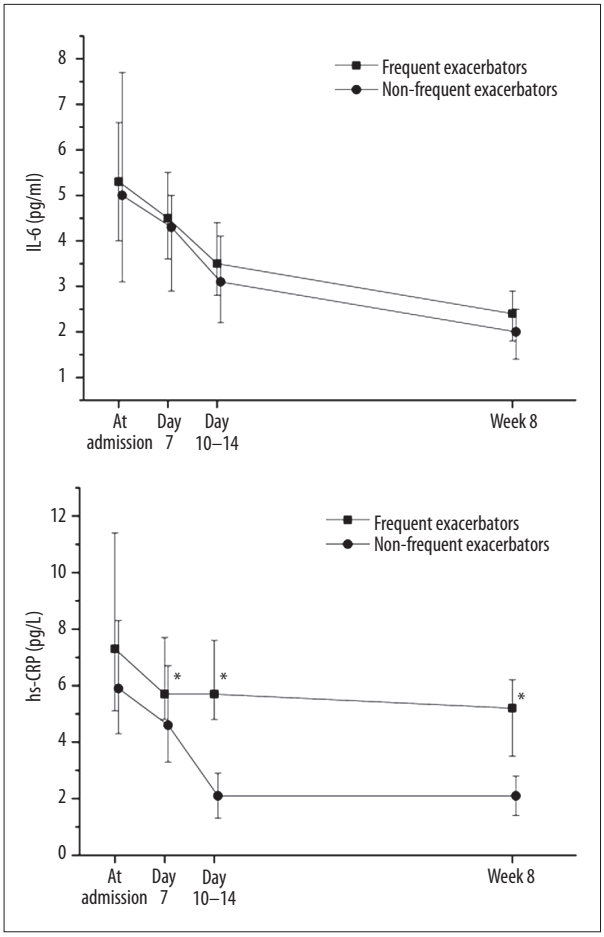

Figure 2. Time course of systemic inflammatory indices in the 2 groups. Results are based on the 93 patients from whom samples were acquired at all time points. Data are median values and interquartile ranges. Mann-Whitney U test was used for analysis between 2 groups. Wilcoxon's signed rank test was used for analysis of paired data. IL-6: – interleukin 6; Hs-CR – high-sensitivity C-reactive protein. * P<0.05 *vs.* non-frequent exacerbators. P<0.05 *vs.* at admission in both groups.

that treatment of these patients should be carefully considered to avoid a fast progression of the disease. The increase in airway and systemic inflammation in stable COPD patients over time is directly linked to disease progression [10]; thus, it can be extrapolated that this delayed recovery in inflammatory markers in frequent exacerbators may be one of the mechanisms underlying a faster decrease in lung function in this group [4,5,27].

In accordance with a previous study on patients with severe COPD exacerbations requiring hospitalization, we reconfirmed that sputum neutrophilia was increased during exacerbations in all subgroups compared with their stable status. Similar results were obtained from the analysis of sputum MPO, a neutrophil degranulation product [28]. In the present study, we also found increased systemic inflammation during AECOPD, which was indicated by increased levels of the serum hs-CRP

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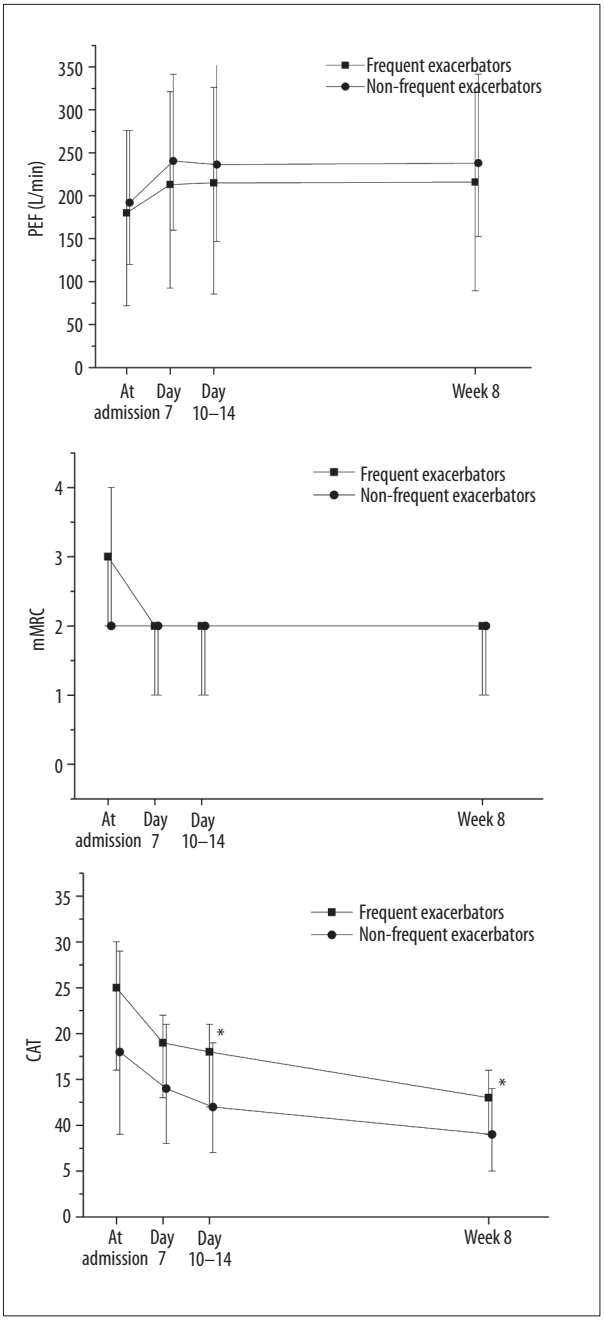

Figure 3. Time course of clinical indices in the 2 groups. Results are based on the 93 patients from whom samples were acquired at all time points. Data are median values and interquartile ranges. Mann-Whitney U test was used for analysis between 2 groups. Wilcoxon's signed rank test was used for analysis of paired data. PEF – peak expiratory flow; mMRC – modified Medical Research Council dyspnea scale; CAT – chronic obstructive pulmonary disease assessment test. * P<0.05 *vs.* non-frequent exacerbators. P<0.05 *vs.* at admission in both groups.

and IL-6 [25,29]. CAT scores increase at exacerbation, indicating a decreased quality of life during AECOPD [13]. Furthermore, both the inflammatory and clinical indices improved significantly during conventional AECOPD treatment, which was consistent with previous studies [30–32].

One study has explored inflammatory changes at COPD exacerbations and found that the frequent exacerbators group had slower resolution of systemic inflammatory markers during an exacerbation [33]. However, the time course of airway inflammatory indices, clinical indices, and quality of life were not compared between the 2 groups in that study.

This research demonstrates, for the first time, that frequent exacerbators have a reduced response in inflammatory indices and quality of life from AECOPD therapy, which results in persistently higher inflammatory markers and CAT score during the recovery period of AECOPD. Previous studies showed that these frequent exacerbators have increased airway inflammation in the stable state [9] and have a faster rise in systemic inflammation over time compared with infrequent exacerbators [10]. A reduced response in quality of life to AECOPD therapy in frequent exacerbators may explain why these patients have worse quality of life when they are in a stable status [6]. There were no significant differences in the time course of improvement in mMRC and CAT value between the frequent and infrequent exacerbators [33].

AECOPD is an important cause of hospitalization and is responsible for 2.4% of all acute medical admissions [34]. Within the first year after admission to hospital with an exacerbation, 63% of patients are readmitted at least once [14]. These repeat admissions were mainly due to recurrent exacerbations; known risk factors for readmission include being a frequent exacerbator and having more severe COPD [8].

One study showed that recurrence of exacerbations is related to persistently higher serum CRP during the recovery phase of the exacerbation [33]. The findings of our study may explain that why frequency of AECOPD in the previous year is an independent risk factor for recurrent exacerbation of COPD [8].

There may be some confounding variables that affect the resolution of inflammatory indices in these 2 groups. First, the rate of bacterial clearance was lower in frequent exacerbators. A previous study showed that failure to eradicate bacteria following acute exacerbations of chronic bronchitis (AECB) was related to smaller decreases in inflammatory markers [35]. Second, although in our study viral etiology could not be assessed, the frequent exacerbators group contained more patients presenting with cold symptoms, which was consistent with previous studies reporting that frequent exacerbators were more likely to acquire colds than were infrequent

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exacerbators [36]. Recent studies show that viruses also play a role in driving the inflammatory process during COPD [37,38]. Third, compared with non-frequent exacerbators, frequent exacerbators had increased cardiovascular morbidity in the peri-exacerbation period; the relationship between systemic inflammation and an increased risk of cardiovascular morbidity and mortality also has been observed in COPD patients [39]. As a descriptive study, our results cannot prove causality. Further study is needed to determine if this increased rate of cardiovascular events in frequent exacerbators is due to persistently higher systemic inflammation or is due to more cardiovascular events in this group. Forth, the frequent exacerbators group contained more patients classified as Anthonisen type 1, indicating that these patients experienced more severe exacerbation. Whether the severity of AECOPD is an affecting factor on the recovery of inflammatory indices and improvement of quality of life during AECOPD needs further study. Fifth, fewer patients in the frequent exacerbators group received long-term ICS treatment. Whether the usual treatment for stable COPD is insufficient and whether this affects the recovery from exacerbation also needs to be studied further. Finally, we cannot completely exclude the influence of anti-inflammatory treatment on the course of inflammatory parameters [40,41], but in our study the therapy was standardized and there were no significant differences in the daily dose and duration of steroid application during hospitalization between the 2 groups.

To compare inflammatory status between frequent exacerbators and non-frequent exacerbators, most studies have been either cross-sectional in nature or have looked at inflammation at a single time-point (mostly when stable) [42,43]. To our knowledge, the present study is novel in that the inflammatory and clinical indices changes in the 2 groups were prospectively followed during the treatment in AECOPD patients admitted to hospital. A distinctive pattern in the time course of recovery of inflammatory cytokines between frequent exacerbators and non-frequent exacerbators provides evidence of a sustained inflammatory reaction during the recovery period of AECOPD in frequent exacerbators, which may preclude full recovery and predispose these patients to recurrence of exacerbations [32]. These findings need to be explored further with interventional studies into therapies such as strengthened anti-inflammatory agents targeted at frequent exacerbators. For example, a recent study has shown that hypoxen antioxidant therapy has beneficial effects in COPD patients through decreasing ROS production [44]. Interventions used in this manner may able to prevent recurrent exacerbations and disease progression.

There are some limitations to this study. First, the inflammatory response during AECOPD is complex and we investigated only a limited panel of biomarkers. We measured sputum neutrophil inflammation because studies on severe AECOPD showed an increase of sputum neutrophil inflammation that was independent of etiology [28]. We measured serum hs-CRP and IL-6 because they have been investigated by the majority of previous studies and are often and easily measured in clinical practice. Second, our study only included hospital-based patients, with the majority having moderate-to-severe COPD; therefore, these results are probably not generally applicable to all populations of COPD patients.

Conclusions

In conclusion, these results show that there is a reduced response to treatment of AECOPD in terms of inflammatory indices and CAT score in patients who have frequent exacerbations. This information should be utilized by clinicians to consider treatment regimens for frequent exacerbators to prevent the rapid progression of COPD.

Competing interests

The authors declared that they have no conflict of interest.

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