6. Miller M, Cho JY, Pham A, Friedman PJ, Ramsdell J, et al. (2011) Persistent Airway Inflammation and Emphysema Progression on CT Scan in Ex-Smokers Observed for 4 Years. Chest 139: 1380–1387.
7. Barnes PJ, Ito K, Adcock IM (2004) Corticosteroid resistance in chronic obstructive pulmonary disease: inactivation of histone deacetylase. Lancet 363: 731–733.
8. Keatings VM, Jatakanon A, Worsdell YM, Barnes PJ (1997) Effects of inhaled and oral glucocorticoids on inflammatory indices in asthma and COPD. Am J Respir Crit Care Med 155: 542–548.
9. Qiu Y, Zhu J, Bandi V, Atmar RL, Hattotuwa K, et al. (2003) Biopsy neutrophilia, neutrophil chemokine and receptor gene expression in severe exacerbations of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 168: 968–975.
10. Papi A, Bellettato CM, Braccioni F, Romagnoli M, Casolari P, et al. (2006) Infections and airway inflammation in chronic obstructive pulmonary disease severe exacerbations. Am J Respir Crit Care Med 173: 1114–1121.
11. Drost EM, Skwarski KM, Sauleda J, Soler N, Roca J, et al. (2005) Oxidative stress and airway inflammation in severe exacerbations of COPD. Thorax 60: 293–300.
12. Mercer PF, Shute JK, Bhowmik A, Donaldson GC, Wedzicha JA, et al. (2005) MMP-9, TIMP-1 and inflammatory cells in sputum from COPD patients during exacerbation. Respir Res 6: 151.
13. Soler-Cataluna JJ, Martinez-Garcia MA, Roman Sanchez P, Salcedo E, Navarro M, et al. (2005) Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. Thorax 60: 925–931.
14. Donaldson GC, Seemungal TA, Bhowmik A, Wedzicha JA (2002) Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. Thorax 57: 847–852.
15. Tanabe N, Muro S, Hirai T, Oguma T, Terada K, et al. (2011) Impact of exacerbations on emphysema progression in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 183: 1653–1659.
16. Thompson WH, Nielson CP, Carvalho P, Charan NB, Crowley JJ (1996) Controlled trial of oral prednisone in outpatients with acute COPD exacerbation. Am J Respir Crit Care Med 154: 407–412.
17. Niewoehner DE, Erbland ML, Deupree RH, Collins D, Gross NJ, et al. (1999) Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. Department of Veterans Affairs Cooperative Study Group. N Engl J Med 340: 1941–1947.
18. Davies L, Angus RM, Calverley PM (1999) Oral corticosteroids in patients admitted to hospital with exacerbations of chronic obstructive pulmonary disease: a prospective randomised controlled trial. Lancet 354: 456–460.
19. Nakamura H, Nakamura K, Yodoi J (1997) Redox regulation of cellular activation. Annu Rev Immunol 15: 351–369.
20. Tagaya Y, Maeda Y, Mitsui A, Kondo N, Matsui H, et al. (1994) ATL-derived factor (ADF), an IL-2 receptor/Tac inducer homologous to thioredoxin; possible involvement of dithiol-reduction in the IL-2 receptor induction. EMBO J 13: 2244.
21. Yodoi J, Okada M, Tagaya Y, Taniguchi Y, Teshigawara K, et al. (1987) IL-2 receptor gene activation by ATL-derived factor (ADF). Adv Exp Med Biol 213: 139–148.
22. Nakamura H, Herzenberg LA, Bai J, Araya S, Kondo N, et al. (2001) Circulating thioredoxin suppresses lipopolysaccharide-induced neutrophil chemotaxis. Proc Natl Acad Sci U S A 98: 15143–15148.
23. Sato A, Hara T, Nakamura H, Kato N, Hoshino Y, et al. (2006) Thioredoxin-1 suppresses systemic inflammatory responses against cigarette smoking. Antioxid Redox Signal 8: 1891–1896.
24. Son A, Kato N, Horibe T, Matsuo Y, Mochizuki M, et al. (2009) Direct association of thioredoxin-1 (TRX) with macrophage migration inhibitory factor (MIF): regulatory role of TRX on MIF internalization and signaling. Antioxid Redox Signal 11: 2595–2605.
25. Saitoh M, Nishitoh H, Fujii M, Takeda K, Tobiume K, et al. (1998) Mammalian thioredoxin is a direct inhibitor of apoptosis signal-regulating kinase (ASK) 1. EMBO J 17: 2596–2606.
26. Sato A, Hoshino Y, Hara T, Muro S, Nakamura H, et al. (2008) Thioredoxin-1 ameliorates cigarette smoke-induced lung inflammation and emphysema in mice. J Pharmacol Exp Ther 325: 380–388.
27. Tamaki H, Nakamura H, Nishio A, Nakase H, Ueno S, et al. (2006) Human thioredoxin-1 ameliorates experimental murine colitis in association with suppressed macrophage inhibitory factor production. Gastroenterology 131: 1110–1121.
28. Ueda S, Nakamura T, Yamada A, Teratani A, Matsui N, et al. (2006) Recombinant human thioredoxin suppresses lipopolysaccharide-induced bronchoalveolar neutrophil infiltration in rat. Life Sci 79: 1170–1177.
29. Seemungal TA, Harper-Owen R, Bhowmik A, Jeffries DJ, Wedzicha JA (2000) Detection of rhinovirus in induced sputum at exacerbation of chronic obstructive pulmonary disease. Eur Respir J 16: 677–683.
30. Rohde G, Wiethege A, Borg I, Kauth M, Bauer TT, et al. (2003) Respiratory viruses in exacerbations of chronic obstructive pulmonary disease requiring hospitalisation: a case-control study. Thorax 58: 37–42.
31. Robbins CS, Bauer CM, Vujicic N, Gaschler GJ, Lichty BD, et al. (2006) Cigarette smoke impacts immune inflammatory responses to influenza in mice. Am J Respir Crit Care Med 174: 1342–1351.
32. Kang MJ, Lee CG, Lee JY, Dela Cruz CS, Chen ZJ, et al. (2008) Cigarette smoke selectively enhances viral PAMP- and virus-induced pulmonary innate immune and remodeling responses in mice. J Clin Invest 118: 2771–2784.
33. Bauer CM, Zavitz CC, Botelho FM, Lambert KN, Brown EG, et al. (2010) Treating viral exacerbations of chronic obstructive pulmonary disease: insights from a mouse model of cigarette smoke and H1N1 influenza infection. PLoS One 5: e13251.
34. Foster WM, Walters DM, Longphre M, Macri K, Miller LM (2001) Methodology for the measurement of mucociliary function in the mouse by scintigraphy. J Appl Physiol 90: 1111–1117.
35. Hoshino Y, Nakamura T, Sato A, Mishima M, Yodoi J, et al. (2007) Neurotropin demonstrates cytoprotective effects in lung cells through the induction of thioredoxin-1. Am J Respir Cell Mol Biol 37: 438–446.
36. Sato A, Hirai T, Imura A, Kita N, Iwano A, et al. (2007) Morphological mechanism of the development of pulmonary emphysema in klotho mice. Proc Natl Acad Sci U S A 104: 2361–2365.
37. Guerassimov A, Hoshino Y, Takubo Y, Turcotte A, Yamamoto M, et al. (2004) The development of emphysema in cigarette smoke-exposed mice is strain dependent. Am J Respir Crit Care Med 170: 974–980.
38. Ito S, Ingenito EP, Arold SP, Parameswaran H, Tgavalekos NT, et al. (2004) Tissue heterogeneity in the mouse lung: effects of elastase treatment. J Appl Physiol 97: 204–212.
39. Wang X, Nelin LD, Kuhlman JR, Meng X, Welty SE, et al. (2008) The role of MAP kinase phosphatase-1 in the protective mechanism of dexamethasone against endotoxemia. Life Sci 83: 671–680.
40. Turpeinen T, Nieminen R, Moilanen E, Korhonen R (2010) Mitogen-activated protein kinase phosphatase-1 negatively regulates the expression of interleukin-6, interleukin-8, and cyclooxygenase-2 in A549 human lung epithelial cells. J Pharmacol Exp Ther 333: 310–318.
41. Vogt A, McDonald PR, Tamewitz A, Sikorski RP, Wipf P, et al. (2008) A cell-active inhibitor of mitogen-activated protein kinase phosphatases restores paclitaxel-induced apoptosis in dexamethasone-protected cancer cells. Mol Cancer Ther 7: 330–340.
42. Gonzalez-Navajas JM, Fine S, Law J, Datta SK, Nguyen KP, et al. (2010) TLR4 signaling in effector CD4+ T cells regulates TCR activation and experimental colitis in mice. J Clin Invest 120: 570–581.
43. Gomez-Cambronero J, Horn J, Paul CC, Baumann MA (2003) Granulocyte-macrophage colony-stimulating factor is a chemoattractant cytokine for human neutrophils: involvement of the ribosomal p70 S6 kinase signaling pathway. J Immunol 171: 6846–6855.
44. D'Hulst A I, Vermaelen KY, Brusselle GG, Joos GF, Pauwels RA (2005) Time course of cigarette smoke-induced pulmonary inflammation in mice. Eur Respir J 26: 204–213.
45. Nakamura H, Hoshino Y, Okuyama H, Matsuo Y, Yodoi J (2009) Thioredoxin 1 delivery as new therapeutics. Adv Drug Deliv Rev 61: 303–309.
46. Harrison FE, Best JL, Meredith ME, Gamlin CR, Borza DB, et al. (2012) Increased expression of SVCT2 in a new mouse model raises ascorbic acid in tissues and protects against paraquat-induced oxidative damage in lung. PLoS One 7: e35623.
47. Vlahos R, Bozinovski S, Chan SP, Ivanov S, Linden A, et al. (2010) Neutralizing granulocyte/macrophage colony-stimulating factor inhibits cigarette smoke-induced lung inflammation. Am J Respir Crit Care Med 182: 34–40.
48. Salojin KV, Owusu IB, Millerchip KA, Potter M, Platt KA, et al. (2006) Essential role of MAPK phosphatase-1 in the negative control of innate immune responses. J Immunol 176: 1899–1907.
49. Hurst JR, Vestbo J, Anzueto A, Locantore N, Mullerova H, et al. (2010) Susceptibility to exacerbation in chronic obstructive pulmonary disease. N Engl J Med 363: 1128–1138.

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Clinical features and determinants of COPD exacerbation in the Hokkaido COPD cohort study

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Running head: Clinical features of COPD exacerbation

Take home message
Impaired health-related quality of life and weight loss are independent risk factors for COPD exacerbations.

ABSTRACT

Exacerbations are among the major factors that may affect the natural history of chronic obstructive pulmonary disease (COPD). The aim was to investigate the clinical characteristics and determinants of COPD exacerbations in our 5-year observational cohort study that had a very low exacerbation frequency.

A total of 279 patients with COPD participated in the Hokkaido COPD cohort study, and 268 subjects who had clinical data for multiple visits were analyzed. Exacerbation was defined in multiple ways: patient's subjective complaint, symptom definition, requiring prescription change, requiring antibiotic treatment, and requiring hospital admission.

Exacerbation frequency (events/person/year) was 0.78 ± 1.16 (subjective complaint), 0.24 ± 0.47 (symptom definition), 0.20 ± 0.43 (prescription definition), 0.13 ± 0.28 (antibiotic definition), and 0.06 ± 0.19 (admission definition). Exacerbation events did not significantly affect the annual decline in FEV_1. A high St. George's Respiratory Questionnaire total score, especially its Activity score, and a low body mass index were strongly associated with exacerbation-free survival, exacerbation frequency, and development of recurrent exacerbations.

Despite the low exacerbation frequency in our cohort study, impaired health-related quality of life and weight loss were found to be independent risk factors for COPD exacerbations.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by persistent airflow limitation that is usually progressive and is a leading cause of morbidity and mortality worldwide [1]. Exacerbations of COPD are an acute event characterized by a worsening of respiratory symptoms, and they are very important in the clinical course of COPD because they are associated with poor quality of life (QOL), increased mortality, and high socioeconomic costs [1-3]. Recently, Hurst et al. reported that patients who have frequent exacerbations belong to a clinically stable phenotype that is susceptible to further exacerbations [4]. Therefore, it would be critical to determine the clinical characteristics and predictors of exacerbations for better management of COPD patients.

The Hokkaido COPD cohort study is a carefully designed, multi-center, observational cohort, which primarily aims to examine the annual decline in FEV_1 over a period of 5 years based on clinical phenotypes in patients with smoking-related COPD [5, 6]. We have already reported that the rate of annual change in FEV_1 was highly variable among patients with COPD and was not associated with exacerbation frequency [6]. A unique finding of our cohort study was that the exacerbation frequency was much lower than the previous large-scale clinical trials [6]. However, the characteristics and risk of exacerbations in a population with such low exacerbation frequency have not yet been clarified. In this study, the clinical characteristics and determinant of COPD exacerbations were examined in our 5-year observational cohort.

METHODS

Participants

The recruitment of the COPD patients has been described elsewhere [5, 6]. Briefly, 330 subjects with respiratory physician-diagnosed COPD were recruited at Hokkaido University Hospital, Sapporo, Japan, and nine affiliated hospitals from May 2003 to May 2005. All were aged 40 years or older and were either current or former smokers with a smoking history of at least 10 pack-years. Subjects with clinically diagnosed asthma were excluded. Thirty subjects were excluded due to consent withdrawal, or were ineligible for inclusion before visit 1, and a total of 300 subjects were followed. During the first follow-up year, the diagnosis of COPD was reconfirmed in 279 subjects based on the spirometric criteria of the Global Initiative for Chronic Obstructive Lung Disease

(GOLD) guidelines (post-bronchodilator FEV_1/FVC <0.70) [1], and the subjects were eligible for subsequent follow-up. In this study, 268 subjects (GOLD 1, 26%; GOLD 2, 45%; GOLD 3, 24%; GOLD 4, 5%) who had clinical data for multiple visits were analyzed. Of the 268 subjects, 184 (69%) completed a 5-year follow-up period. The reasons for dropout of the initial 279 subjects have been described elsewhere [6]. The median follow-up period was 4.97 years. Characteristics of subjects classified by severity of airflow limitation are shown in Table 1. The Ethics Committee of Hokkaido University School of Medicine approved the study protocol, and written, informed consent was obtained from all participants.

Study protocol

The details of the study protocol of the Hokkaido COPD cohort study have been described elsewhere [5, 6]. Most subjects, except for those with GOLD 1, visited outpatient clinics at each hospital monthly or bimonthly for regular clinical checkups (online supplement Table 1). On the first visit, demographic information, including sex, age, height, weight, smoking history, medical history, and medications, and information on pulmonary symptoms were collected. Every 6 months, any changes in smoking status, medical history, and pharmacotherapy were monitored. Health-related quality of life (QOL) assessed by St. George's Respiratory Questionnaire (SGRQ) [7] was examined every year, and blood was also sampled every year for measurements of circulating blood cell counts, serum immunoglobulin E (IgE), and C-reactive protein (CRP). Spirometry both before and after inhalation of a bronchodilator was performed on every visit. Chest CT scans were performed in the supine position with breath held at full inspiration. Severity of emphysema was visually assessed by three independent pulmonologists according to the modified Goddard scoring system [5, 6, 8].

Assessment of exacerbation

In order to collect exacerbation information, reply-paid postcards were sent to all participants every month, and replies were received from almost all participants (reply rate >99%). The questionnaire items in the postcard were described in the online supplement. If exacerbation was suspected, information was always re-confirmed by telephone interview and/or by the medical charts of subjects when they visited a clinic. In addition, the subjects' medical records were periodically checked, and attending

physicians were asked about the subjects' conditions when necessary.

Exacerbation of COPD was defined in several of the following ways: 1) patient's subjective complaint by reply-paid postcard (any clinical symptoms that did not meet symptom definition criteria); 2) worsening or new onset of either two major symptoms (increased dyspnea, change in sputum purulence, increased sputum volume) or any one major symptom plus any minor symptoms (fever, increased cough, wheezing) compared with baseline (symptom definition); 3) symptom criteria plus requiring prescription change (prescription definition); 4) symptom criteria plus antibiotic treatment (antibiotic definition); and 5) symptom criteria plus hospital admission (admission definition). Radiologically proven pneumonia was not excluded from exacerbation events because many of the patients with severe exacerbation are examined by CT scan in Japan and bronchopneumonia is often detected even if chest X-ray is almost normal.

Statistical analysis

The details of statistical analysis are in the online supplement. Differences among the groups were analyzed using the Student's t-test, the Mann-Whitney U test, or the chi-squared test, where appropriate. Bivariate correlations were analyzed using Spearman's rank correlation coefficient. Factors associated with exacerbation-free survival were analyzed using a Cox proportional hazards model and the Kaplan-Meier method with the log-rank test. Factors associated with exacerbation frequency were analyzed using a Poisson regression model. Factors associated with recurrent exacerbation were analyzed using the Prentice, Williams and Peterson (PWP) total time model that is based on the Cox proportional hazards model for recurrent event data [9]. Here, the total time refers to the time interval from time origin 0 to the occurrence of each event. Significant variables in univariate models were included simultaneously in a multivariate model. Statistical significance was defined as $p<0.05$.

RESULTS

The cumulative number of exacerbation events and the number of subjects who experienced exacerbations during the follow-up period differed depending on the definition criteria (Figure 1). Indeed, the number of exacerbation events became much lower compared to the number of patients' subjective complaints when symptoms

were carefully confirmed. There were 16 events of 243 events (6.6%) whose exacerbation was not picked up by subjective complaint in the postcard but by confirmation of symptoms and prescription changes by interview and/or medical records. The COPD exacerbation frequency (events/person/year) during the follow-up period was 0.78 ± 1.16 (subjective complaint), 0.24 ± 0.47 (symptom definition), 0.20 ± 0.43 (prescription definition), 0.13 ± 0.28 (antibiotic definition), and 0.06 ± 0.19 (admission definition), and the exacerbation frequency was higher in subjects with severe airflow limitation (GOLD 3-4) than in those with mild airflow limitation (GOLD 1-2) (Table 2). There were very few subjects who experienced exacerbations twice or more per year (only 3 subjects by symptom or prescription definitions and none of the subjects by antibiotics or admission definitions). Subjects who experienced at least one exacerbation during the follow-up period had lower lung function, more dyspnea, and higher SGRQ total score (i.e. impaired health-related QOL) compared to subjects who had no exacerbation (online supplement Table 2). Among subjects who experienced at least one exacerbation, 50% (symptom definition), 48% (prescription definition), 42% (antibiotics definition), and 25% (admission definition) of subjects developed multiple exacerbation events during the follow-up period (recurrent exacerbation). The number of exacerbation events was higher in the spring months (March to June) and in the autumn months (October to November) (Figure 2).

Subjects who experienced exacerbations within the first year of follow-up had more frequent exacerbations after the first year of follow-up (Figure 3), which confirmed the recurrent nature of COPD exacerbations. On the other hand, the annual decline in FEV_1 was not affected by exacerbation regardless of its definition and the degree of airflow limitation (online supplement Figure 1), whereas subjects who experienced more than one exacerbation defined by admission criteria per year tended to show a more rapid FEV_1 decline compared to subjects with less exacerbations ($p=0.07$) (online supplement Figure 2). There was no significant correlation between the annual decline in FEV_1 and exacerbation frequency at any definition (data not shown).

A multivariate Cox proportional hazards model showed that low BMI and high SGRQ total score were significant and independent predictors for the early development of the first exacerbation event defined as both prescription change and hospital admission (Table 3 and online supplement Tables 3 and 4), and Kaplan-Meier curves for the classification groups by BMI and SGRQ total score were clearly separated (figure 4).

The multivariate Poisson regression model showed that low BMI, high SGRQ total score, low FEV_1, and low Hb were significantly associated with exacerbation frequency defined as prescription change, and low BMI and high SGRQ total score were significantly associated with exacerbations defined as hospital admission (Table 3 and online supplement Tables 5 and 6). Furthermore, the multivariate PWP total time model showed that high SGRQ total score and low Hb were significant predictors for the development of recurrent exacerbations defined as prescription change, and that older age, low BMI, and high SGRQ total score were significant predictors for the development of recurrent exacerbations defined as hospital admission (Table 3 and online supplement Tables 7 and 8).

Since a high SGRQ total score was significantly associated with all of exacerbation-free survival, exacerbation frequency, and the development of recurrent exacerbations, the SGRQ domain scores of Symptoms, Activity, and Impact were also assessed. The SGRQ Activity score was found to be the only domain that was significantly associated with all of the above analyses (online supplement Table 9).

DISCUSSION

In this paper, the intention was to clarify the clinical characteristics and determinants of COPD exacerbations using the Hokkaido COPD cohort study population. The strongest point of this cohort study is that it was very carefully designed and performed, thus making it possible to collect accurate information regarding each patient's complaints, symptoms, and clinical data during COPD exacerbations. Although COPD exacerbation is defined in the GOLD guidelines [1] as an acute event characterized by a worsening of the patient's respiratory symptoms and leads to a change in medication, a general definition for COPD exacerbation has not been accepted; moreover, several levels regarding the severity of exacerbations are required. Therefore, COPD exacerbation was defined in multiple ways in the present study. It was found that the number of exacerbation events and the number of subjects who experienced exacerbations were very different depending on the definition criteria, especially between patients' subjective complaints and confirmed symptoms. Importantly, the same patients seemed to repeatedly complain about their poor physical conditions even if they did not have enough respiratory symptoms, since the number of exacerbation events was less than the number of subjects who experienced

exacerbation events when the symptom definition was applied (Figure 1). Therefore, it is very important for physicians to confirm patients' respiratory symptoms carefully for the diagnosis of COPD exacerbation. On the other hand, it is possible that we missed some symptomatic events even though the symptom information was re-confirmed by telephone interview and/or by the medical charts. Some subjects might have been shy away from declaring their symptoms accurately to medical staffs although they reported the symptoms on the postcards, which may be a characteristic feature of Japanese. Furthermore, some subjects might not be willing to complain in the postcards so that we might have missed actual exacerbations. We think that enhancement and encouragement of reporting using more sensitive tools such as a daily diary or an electronic personal digital assistant would be ideal for more accurate symptom assessment.

A unique finding of this study is the much lower exacerbation frequency during the study period compared to recent large-scale clinical studies such as TORCH [10], UPLIFT [11], and ECLIPSE [4, 12]. Importantly, the present population included patients with mild airflow limitation (GOLD 1), unlike the above clinical studies that did not recruit GOLD 1 patients, and it was confirmed that exacerbations became more frequent as the severity of airflow limitation increased (Table 2), which was consistent with previous studies [4, 13, 14], suggesting that recruitment of patients with milder airflow limitation may contribute to the lower exacerbation frequency. However, the exacerbation frequency in the present study was still lower than that of previous studies even when compared with patients with the same severity of airflow limitation. Specifically, the mean frequency of exacerbations (events/person/year) defined as prescription change in each GOLD category was 0.14 (GOLD 2), 0.30 (GOLD 3), and 0.77 (GOLD 4) in the present study, whereas the mean was 0.7-0.9 (GOLD 2), 1.1-1.3 (GOLD 3), and 1.2-2.0 (GOLD 4) in previous large-scale clinical studies. Similarly, the mean frequency of hospital admission was 0.06 (GOLD 2), 0.10 (GOLD 3), and 0.09 (GOLD 4) in the present study, whereas the mean was 0.11-0.2 (GOLD 2), 0.25-0.3 (GOLD 3), and 0.4-0.54 (GOLD 4) in previous studies [1, 4, 10, 12]. Such a lower frequency of exacerbation was also observed in the subgroup analysis of the Japanese patients participating the UPLIFT study and in another Japanese report [15, 16]. The frequency of chronic bronchitis in our cohort was also lower compared to the other studies [12, 17]. Thus, national characteristics such as the health care system and socioeconomic

status may affect the discrepancy in the frequency of exacerbations and chronic bronchitis between Japan and the other geographical regions. Another possible reason would be a selection bias in our cohort study, since all of the subjects were recruited and treated by respiratory specialists at a university hospital and its affiliated hospitals. Even though the exacerbation frequency was low in the present study, the recurrent nature of exacerbations was confirmed by showing that subjects who experienced exacerbations within the first year of follow-up experienced more frequent exacerbations after the first year of follow-up (Figure 3).

It was found that the number of exacerbation events was higher in the spring and autumn months, but not in the winter (Figure 2), which was an unexpected finding because COPD exacerbations were reported to be more frequent in the winter months [18, 19]. Our cohort study was performed in the north end of Japan, where the winter is very cold and accompanied by significant snowfall; therefore, patients with COPD may tend to stay inside their homes in the winter. Since the trigger for a large part of exacerbations is a respiratory virus infection [20], such patients may have a lower chance of getting a virus infection in the community in the winter. Whatever the reason, the present result indicates that the seasonality of COPD exacerbations can vary depending on where the patients live due to climate differences.

Another notable finding of the present study is that whether subjects experienced exacerbation events or not during the follow-up period did not affect the annual decline in FEV_1, regardless of its definition and the degree of airflow limitation (Figure 4). People may consider that this is an unexpected finding since it has been emphasized that COPD exacerbations accelerate the rate of decline in lung function. The GOLD guideline [1] cited two references for this statement [21, 22]. However, using the Lung Health Study data, Kanner et al. reported that lower respiratory tract illness promoted FEV_1 decline in current smokers with mild COPD, but not in ex-smokers [21]. Furthermore, Donaldson et al. just showed a faster annual decline in FEV_1 in patients with frequent exacerbations defined by symptom-based criteria (>2.92 events/person/year) when compared to patients with infrequent exacerbations (<2.92 events/person/year) [22]. In the present study, 85.1% of the subjects quit smoking during the follow-up period, and the exacerbation frequency was very low; thus, it is reasonable that the effect of exacerbation events on the annual decline in FEV_1 in the present study was small. Moreover, the relationship between exacerbation events and

a decline in FEV_1 does not seem to be simple, since the large-scale UPLIFT study failed to show an improvement in the FEV_1 decline, whereas it did show a significant reduction in the development of exacerbations by drug intervention [11]. On the other hand, there was also a tendency of rapid decline in FEV_1 in subjects who experienced more than one exacerbation defined by admission criteria per year in the present study (online supplement Figure 2). Therefore, the effect of exacerbations on respiratory function seems to be especially larger in patients who experience frequent and more severe exacerbations.

In the multivariate analysis, impaired health-related QOL was significantly associated with exacerbation frequency (Table 3), which is in line with previous studies [2, 4]. The present data extend this observation by showing that impaired health-related QOL was also strongly related to shorter exacerbation-free survival and the development of recurrent exacerbations defined as either prescription change or hospital admission (Table 3). Furthermore, the SGRQ Activity score, closely related to the dyspnea scale and the 6-minute walking distance [7], was the only domain that was significantly associated with all of exacerbation-free survival, the exacerbation frequency, and the development of recurrent exacerbations (online supplement Table 9). One explanation of the association between dyspnea and exacerbations may come from the fact that dyspnea is one of the major symptoms in the symptom definition. It is also possible that reduced activity and poor QOL are just confounders for other factors. However, there are several speculations regarding that reduced activity with dyspnea is a risk factor for exacerbations. First, mucus hypersecretion in subjects with dyspnea may contribute to increase the risk of pulmonary infection that is an important trigger of COPD exacerbation. Second, lung hyperinflation in subjects with dyspnea increases the imbalance of the ventilation/perfusion ratio and may be more susceptible to triggers of exacerbation [23]. It was also found that low BMI was independently associated with COPD exacerbation (Table 3). Poor nutritional status or low BMI has been shown to be associated with increased morbidity and mortality in the natural course of COPD and in patients hospitalized with COPD exacerbation [24, 25]. Therefore, it would be very important to identify patients who have limited physical activities due to dyspnea or weight loss and perform a therapeutic intervention for such patients by medication, rehabilitation, and supporting nutrition in order to reduce the morbidity and mortality from COPD exacerbations.

Although this study was a prospective, observational cohort study, it had several limitations. First, information about exacerbation history before study entry was not obtained. Since it was shown that the best predictor of exacerbations was a history of exacerbations [4], collecting exacerbation history would be important for the clinical management of patients with COPD. Regarding this point, the recurrent nature of exacerbations was confirmed using our prospective data (Figure 3). Second, most subjects were males, and there were no female patients in GOLD 3 and 4 categories. Therefore, the present findings may not simply be applied to female patients with COPD. Third, we were unable to collect accurate information on anxiety and depression that have been reported to be associated with COPD exacerbations [26, 27]. Lastly, the sample size in this study was not as large as previous large-scale clinical studies.

In summary, the clinical characteristics and determinants of COPD exacerbations were identified in the Hokkaido COPD cohort study. In the present population, the exacerbation frequency was very low, while exacerbations appeared to be recurrent. Exacerbation events did not affect the annual decline in FEV_1. Furthermore, poor health-related QOL and weight loss were strong predictors of the development of COPD exacerbations. Identification of patients at high risk for the development of exacerbations and appropriate intervention for such patients are crucial for the prevention of COPD exacerbations.

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Table 1. Characteristics of subjects classified by severity of airflow limitation

	All subjects (N = 268)	GOLD 1 (N = 69)	GOLD 2 (N = 121)	GOLD 3 (N = 65)	GOLD 4 (N = 13)
Age, yr	70 ± 8	67 ± 8	70 ± 8	72 ± 6	70 ± 8
Female sex, N (%)	15 (6)	9 (13)	6 (5)	0 (0)	0 (0)
Body mass index, kg/m^2	22 ± 3	23 ± 3	23 ± 3	21 ± 3	21 ± 4
Current smoker at entry, N (%)	74 (28)	20 (29)	39 (32)	10 (15)	5 (38)
Smoking index at entry, pack-years	62 ± 30	63 ± 34	62 ± 30	64 ± 25	55 ± 22
Post-bronchodilator					
FEV_1, L	1.75 ± 0.67	2.55 ± 0.43	1.76 ± 0.41	1.11 ± 0.19	0.70 ± 0.14
FEV_1, % predicted	65 ± 22	93 ± 11	65 ± 9	42 ± 5	26 ± 4
FVC, % predicted	101 ± 19	118 ± 13	100 ± 14	90 ± 14	70 ± 20
FEV_1/FVC	0.51 ± 0.13	0.64 ± 0.06	0.53 ± 0.08	0.38 ± 0.07	0.31 ± 0.07
Reversibility of FEV_1, %	12 ± 10	6 ± 5	12 ± 8	17 ± 13	14 ± 11
Reversibility of FEV_1, ml	146 ± 105	124 ± 88	162 ± 101	153 ± 127	86 ± 66
Chronic bronchitis, N (%)	29 (11)	2 (3)	15 (12)	11 (17)	1 (8)
MRC dyspnea score ≥2, N (%)	224 (84)	47 (68)	102 (84)	62 (95)	13 (100)
SGRQ total score	32 ± 18	23 ± 14	30 ± 17	41 ± 16	51 ± 14
Blood neutrophil count, cells/mm^3	3519 ± 1113	3597 ± 1220	3421 ± 1155	3580 ± 975	3713 ± 733
Blood eosinophil count, cells/mm^3	198 ± 134	185 ± 130	211 ± 137	184 ± 128	218 ± 152
Blood Hb, g/dl	14 ± 1	14 ± 1	14 ± 1	14 ± 1	14 ± 1
Serum IgE, IU/ml	213 ± 569	278 ± 764	251 ± 606	88 ± 106	140 ± 158
Any cardiovascular disease, N (%)	60 (22)	12 (17)	27 (22)	17 (26)	4 (31)
Ischemic heart disease, N (%)	19 (7)	5 (7)	9 (7)	5 (8)	0 (0)
Diabetes, N (%)	12 (4)	3 (4)	7 (6)	2 (3)	0 (0)

Data are shown as means ± SD or number (%).

Table 2. Exacerbation frequency classified by severity of airflow limitation

	All subjects (N = 268)	GOLD 1 (N = 69)	GOLD 2 (N = 121)	GOLD 3 (N = 65)	GOLD 4 (N = 13)
Exacerbation, events/person/yr					
Subjective complaint	0.78 ± 1.16	0.58 ± 0.79	0.63 ± 0.94	1.09 ± 1.51*†	1.80 ± 1.86*†
Symptom definition	0.24 ± 0.47	0.16 ± 0.29	0.16 ± 0.27	0.37 ± 0.57*†	0.81 ± 1.15*†
Prescription definition	0.20 ± 0.43	0.12 ± 0.26	0.14 ± 0.25	0.30 ± 0.49*†	0.77 ± 1.13*†‡
Antibiotics definition	0.13 ± 0.28	0.09 ± 0.23	0.09 ± 0.22	0.20 ± 0.35*†	0.37 ± 0.42*†‡
Admission definition	0.06 ± 0.19	0.01 ± 0.03	0.06 ± 0.19*	0.10 ± 0.27*†	0.09 ± 0.15*

Data are shown as means ± SD.

*p<0.05 vs. GOLD 1. †p<0.05 vs. GOLD 2. ‡p<0.05 vs. GOLD 3.

Table 3. Significant factors related to COPD exacerbation

A. Factors related to exacerbation-free survival

Multivariate model	Prescription definition		Admission definition	
Variables	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
BMI (1 kg/m^2 increase)	0.93 (0.87-0.99)	0.03	0.86 (0.76-0.96)	0.006
SGRQ total score (4 points increase)	1.12 (1.06-1.19)	<0.001	1.19 (1.08-1.30)	<0.001

(Cox proportional hazards model)

B. Factors related to exacerbation frequency

Multivariate model	Prescription definition		Admission definition	
Variables	Risk ratio (95% CI)	p value	Risk ratio (95% CI)	p value
BMI (1 kg/m^2 increase)	0.95 (0.90-0.99)	0.03	0.87 (0.79-0.95)	0.004
SGRQ total score (4 points increase)	1.09 (1.05-1.14)	<0.001	1.11 (1.03-1.20)	0.008
FEV_1 %predicted (10% increase)	0.89 (0.81-0.97)	0.008	-	-
Hb (1 g/dl increase)	0.84 (0.76-0.93)	0.001	-	-

(Poisson regression model)

C. Factors related to recurrent exacerbation

Multivariate model	Prescription definition		Admission definition	
Variables	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Age (10 years older)	-	-	1.57 (1.00-2.46)	0.049
BMI (1 kg/m^2 increase)	-	-	0.88 (0.80-0.98)	0.02
SGRQ total score (4 points increase)	1.07 (1.03-1.11)	<0.001	1.14 (1.04-1.24)	0.005
Hb (1 g/dl increase)	0.87 (0.78-0.97)	0.02	-	-

(PWP total time model)

Complete data tables including all variables and univariate analyses are shown in the online supplement.

REFERENCES

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease updated 2013. www.goldcopd.org. Date last updated: February 20 2013. Date last accessed: June 25 2013.
2. Seemungal TA, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998; 157: 1418-1422.
3. Soler-Cataluña JJ, Martínez-García MA, Román Sánchez P, Salcedo E, Navarro M, Ochando R. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. *Thorax* 2005; 60: 925-931.
4. Hurst JR, Vestbo J, Anzueto A, Locantore N, Müllerova H, Tal-Singer R, Miller B, Lomas DA, Agusti A, Macnee W, Calverley P, Rennard S, Wouters EF, Wedzicha JA; Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) Investigators. Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med* 2010; 363: 1128-1138.
5. Makita H, Nasuhara Y, Nagai K, Ito Y, Hasegawa M, Betsuyaku T, Onodera Y, Hizawa N, Nishimura M; Hokkaido COPD Cohort Study Group. Characterisation of phenotypes based on severity of emphysema in chronic obstructive pulmonary disease. *Thorax* 2007; 62: 932-937.
6. Nishimura M, Makita H, Nagai K, Konno S, Nasuhara Y, Hasegawa M, Shimizu K, Betsuyaku T, Ito YM, Fuke S, Igarashi T, Akiyama Y, Ogura S; Hokkaido COPD Cohort Study Investigators. Annual change in pulmonary function and clinical phenotype in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2012; 185: 44-52.
7. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. *Am Rev Respir Dis* 1992; 145: 1321-1327.
8. Goddard PR, Nicholson EM, Laszlo G, Watt I. Computed tomography in pulmonary emphysema. *Clin Radiol* 1982; 33: 379-387.
9. Prentice RL, Williams BJ, Peterson AV. On the regression analysis of multivariate failure time data. *Biometrika* 1981; 68: 373-379.

10. Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, Yates JC, Vestbo J; TORCH investigators. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007; 356: 775-789.
11. Tashkin DP, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S, Decramer M; UPLIFT Study Investigators. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med* 2008; 359: 1543-1554.
12. Vestbo J, Edwards LD, Scanlon PD, Yates JC, Agusti A, Bakke P, Calverley PM, Celli B, Coxson HO, Crim C, Lomas DA, MacNee W, Miller BE, Silverman EK, Tal-Singer R, Wouters E, Rennard SI; ECLIPSE Investigators. Changes in forced expiratory volume in 1 second over time in COPD. *N Engl J Med* 2011; 365: 1184-1192.
13. Donaldson GC, Seemungal TA, Patel IS, Lloyd-Owen SJ, Wilkinson TM, Wedzicha JA. Loggitudinal changes in the nature, severity and frequency of COPD exacerbations. *Eur Respir J* 2003; 22: 931-936.
14. de Oca MM, Tálamo C, Halbert RJ, Perez-Padilla R, Lopez MV, Muiño A, Jardim JR, Valdivia G, Pertuzé J, Moreno D, Menezes AM. Frequency of self-reported COPD exacerbation and airflow obstruction in five Latin American cities: the Proyecto Latinoamericano de Investigation en Obstruccion Pulmonar (PLATINO) study. *Chest* 2009; 136: 71-78.
15. Fukuchi Y, Fernandez L, Kuo HP, Mahayiddin A, Celli B, Decramer M, Kesten S, Liu D, Tashkin D. Efficacy of tiotropium in COPD patients from Asia: a subgroup analysis from the UPLIFT trial. *Respirology* 2011; 16: 825-835.
16. Tanabe N, Muro S, Hirai T, Oguma T, Terada K, Marumo S, Kinose D, Ogawa E, Hoshino Y, Mishima M. Impact of exacerbations on emphysema progression in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2011; 183: 1653-1659.
17. Kim V, Criner GJ. Chronic bronchitis and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2013; 187: 228-237.
18. Jenkins CR, Celli B, Anderson JA, Ferguson GT, Jones PW, Vestbo J, Yates JC, Calverley PM. Seasonality and determinants of moderate and severe COPD exacerbations in the TORCH study. *Eur Respir J* 2012; 39: 38-45.
19. Donaldson GC, Goldring JJ, Wedzicha JA. Influence of season on exacerbation characteristics in patients with COPD. *Chest* 2012; 141: 94-100.

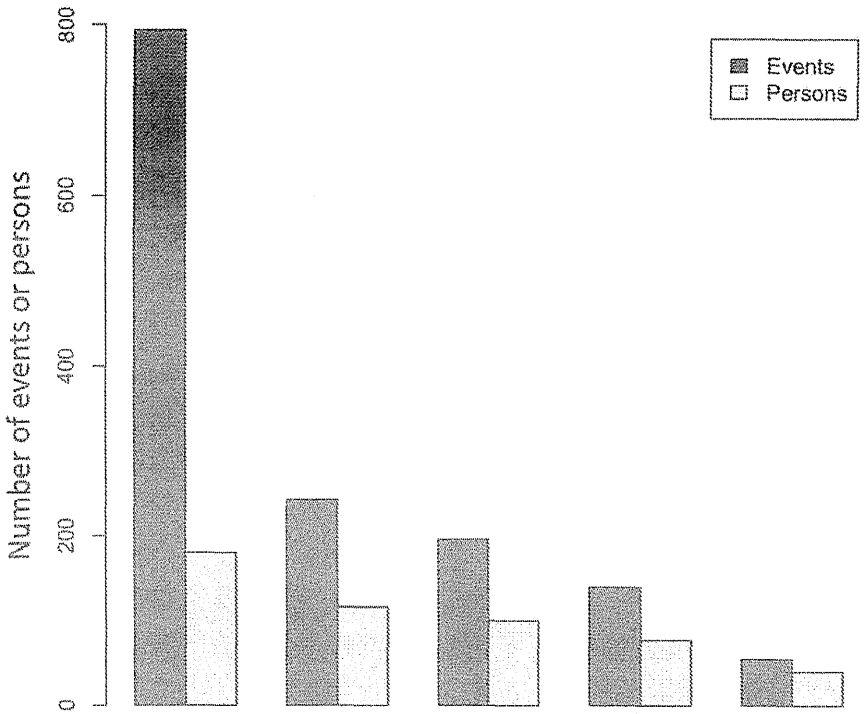
20. Seemungal T, Harper-Owen R, Bhowmik A, Moric I, Sanderson G, Message S, Maccallum P, Meade TW, Jeffries DJ, Johnston SL, Wedzicha JA. Respiratory viruses, symptoms, and inflammatory markers in acute exacerbations and stable chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 164: 1618-1623.
21. Kanner RE, Anthonisen NR, Connett JE; Lung Health Study Research Group. Lower respiratory illnesses promote FEV(1) decline in current smokers but not ex-smokers with mild chronic obstructive pulmonary disease: results from the lung health study. *Am J Respir Crit Care Med* 2001; 164: 358-364.
22. Donaldson GC, Seemungal TA, Bhowmik A, Wedzicha JA. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax* 2002; 57: 847-852.
23. Wedzicha JA, Decramer M, Seemungal TA. The role of bronchodilator treatment in the prevention of exacerbations of COPD. *Eur Respir J* 2012; 40: 1545-1554.
24. Landbo C, Prescott E, Lange P, Vestbo J, Almdal TP. Prognostic value of nutritional status in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; 160: 1856-1861.
25. Lainscak M, von Haehling S, Doehner W, Sarc I, Jeric T, Ziherl K, Kosnik M, Anker SD, Suskovic S. Body mass index and prognosis in patients hospitalized with acute exacerbation of chronic obstructive pulmonary disease. *J Cachexia Sarcopenia Muscle* 2011;2:81-6.
26. Quint JK, Baghai-Ravary R, Donaldson GC, Wedzicha JA. Relationship between depression and exacerbations in COPD. *Eur Respir J* 2008;32:53-60.
27. Xu W, Collet JP, Shapiro S, Lin Y, Yang T, Platt RW, Wang C, Bourbeau J. Independent effect of depression and anxiety on chronic obstructive pulmonary disease exacerbations and hospitalizations. *Am J Respir Crit Care Med* 2008;178:913-20.

FIGURE LEGENDS

Figure 1. Bar plots of the number of exacerbation events or persons during the follow-up period

Exacerbation was defined by patient's subjective complaints, the symptom definition, the prescription definition, the antibiotic definition, and the admission definition.

Figure 1



	Complaint	Symptom	Prescription	Antibiotics	Admission
#Events	794	243	196	139	55
#Persons	190	116	100	77	40