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Negative impacts of unreported COPD exacerbations on health-related quality of life at one year

Wanning Xu[1, 2], Jean-Paul Collet[1,3], Stanley Shapiro[1], Yingxiang Lin[4], Ting Yang[4], Chen Wang[4], Jean Bourbeau[1,2]

Authors' affiliations:

1. Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montréal, Québec, Canada.

2. Respiratory Epidemiology and Clinical Research Unit, Montreal Chest Institute, McGill University, Montréal, Québec, Canada.

3. Child and Family Research institute, Children's and Women's Health Center, Department of Paediatrics and Department of Health Care and Epidemiology, University of British Columbia, Vancouver, British Columbia, Canada.

4. Beijing Institute of Respiratory Medicine, Beijing Chaoyang Hospital, Capital Medical University, Beijing, China.

Joint correspondence to:

Chen Wang, Ph.D.

Beijing Institute of Respiratory Medicine, Beijing Chaoyang Hospital,

No. 8, Bai Jia Zhuang Road, Chaoyang District, Beijing, China, 100020

Telephone: 8610-85231999; Fax: 8610-65060167

E-mail: cyh-birm@263.net

AND

Jean Bourbeau, M.D.

Respiratory Epidemiology and Clinical Research Unit, Montreal Chest Institute,

Room k1.32, 3650 St. Urbain Street, Montréal, Québec, Canada H2X 2P4

Telephone: 514-9341934 ext. 32185; Fax: 514-8432083

E-mail: jean.bourbeau@mcgill.ca

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ABSTRACT

Unreported COPD exacerbations are common but their intermediate to long-term impacts on health-related quality of life (HRQL) are unknown. This study was aimed at examining the impacts of unreported exacerbations on HRQL at 1 year.

A multi-center prospective cohort study in 491 COPD patients was conducted in China. HRQL was measured using the St. George's Respiratory Questionnaire (SGRQ). Other measurements included socio-demographic, clinical, psychosocial and treatment profiles. Patients were monitored monthly for 12 months to document exacerbations (≥1 symptom worsening for ≥48 hours). Patients were categorized into six groups: no exacerbation, 1 unreported exacerbation only, >1 unreported exacerbations only, 1 reported exacerbation only, >1 reported exacerbations only, and both unreported and reported exacerbations. Generalized Estimating Equations were used to estimate adjusted associations between exacerbations and HRQL change.

A total of 466 unreported and 410 reported exacerbations were recorded. Compared with patients with no exacerbation, the change in SGRQ total score was similar among patients with 1 unreported exacerbation (adjusted mean change: 1.22 points; 95% CI: -4.05 to 6.48) but significantly worse among patients with >1 unreported exacerbations (4.61; 0.09 to 9.13).

Development and evaluation of self-management programs emphasizing early recognition of exacerbations and consequent action appear to be warranted.

Key words: Chronic Obstructive Pulmonary Disease (COPD); Exacerbation; Underreporting; Health-related quality of life (HRQL); outcome evaluation; therapy.

INTRODUCTION

Exacerbation is the most important adverse event in the progression of Chronic Obstructive Pulmonary Disease (COPD). It is a common cause of death[1], hospital admission[1], increased healthcare cost[2] and diminished lung function[3]. COPD exacerbation also has immediate[4-6] and sustained[6-10] impacts on health-related quality of life (HRQL). HRQL is an important outcome of clinical care in COPD patients. Clinicians and regulators recognize that measuring HRQL is instrumental in making informed patient management and policy decisions[11, 12]. It is also well accepted that treatment effectiveness should be based on assessment of HRQL rather than on spirometry alone[12].

Previous studies have shown that at least half of all COPD exacerbations identified by symptom worsening were not medically reported[5, 8] and therefore left untreated. Unreported exacerbations were shown to have similar characteristics to the reported exacerbations in the East London cohort[8], but were found to be less severe in terms of the number of symptoms in the Canadian cohort[5]. These exacerbations are associated with symptom worsening[4, 5, 8] and may have important clinical consequences due to delaying or failing to seek treatment[4, 5, 13]. However, the impacts of unreported exacerbations on HRQL have been examined only over a short term (3 months)[5]. This study showed that HRQL declined among patients who had unreported exacerbation(s) as assessed by an increase (deterioration) on the St. George's Respiratory Questionnaire (SGRQ) total score (median: 3.4 points; interquartile range [IQR]: -3.4 to 5.9; n=212). The median change was -2.3 (IQR: -6.1 to 2.4; n=44) in patients who had no exacerbation and 4.3 (IQR: -2.3 to 13.4; n=37) in

those who had reported exacerbation(s)[5]. It suggested that unreported exacerbations have negative impacts on HRQL and thus may represent an unmet healthcare need. However, this study was based on univariate analyses involving neither control group nor confounding adjustment. Moreover, the intermediate to long-term effects of unreported exacerbations on HRQL have not been studied.

China has one of the largest COPD populations in the world, with a prevalence of 8.2% (mean, 12.4%; women, 5.1%)[14] and a huge population of over 1.3 billion. It is responsible for a considerable part of the global burden of this disease. Despite being a major public health problem in China, very little information on this disease and its management in the Chinese population is available.

The main objective of this study was to examine the impacts of unreported exacerbations on the change of HRQL at one year in patients with clinically stable COPD in China. It was hypothesized that patients with unreported exacerbations would have worse HRQL change at one year as compared to patients with no exacerbation.

METHODS

A prospective cohort study with 12-month follow-up was carried out from August 2004 to June 2006 in respiratory divisions of 10 general hospitals in Beijing, China. The study protocol was approved by the Research Ethics Boards of the McGill

University Health Center and all participating hospitals. Written informed consent was obtained from all participants.

Study population

To be eligible, patients were required to satisfy the following criteria[15]: 1) aged ≥30 years with physician-diagnosed COPD; 2) post-bronchodilator forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) ratio < 0.7 and FEV_1 < 80% of predicted value; 3) at clinically stable period of COPD (i.e., no fever, no worsening of respiratory symptoms and no related medication change) within 4 weeks prior to the baseline interview; 4) no primary diagnosis of asthma; 5) no previous lung volume reduction surgery, lung transplantation or pneumonectomy; and 6) expected survival ≥6 months as judged by site investigators according to patients' medical history. In each center, 40 to 60 patients were recruited, at least one-third of whom were females, 40% were Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage II (FEV_1%: 50-79), 40% were stage III (FEV_1%: 30-49), and 20% were stage IV (FEV_1%: <30).

Patient evaluation

Face-to-face interviews were administered at baseline and at the end of the study to assess patients' characteristics and HRQL. Both interviews were administered at least four weeks after an exacerbation (i.e., during a clinically stable period). All interviewers were trained to administer the structured questionnaires in the same manner, and they were blinded to patients' HRQL scores during the follow-up period.

COPD-specific HRQL was measured using the reliable and valid St. George's Respiratory Questionnaire in Mandarin-Chinese (SGRQ-MC)[16]. It covers three domains: symptoms (respiratory symptoms), activity (physical activities that cause or are limited by breathlessness) and impact (social and psychological effects of the disease)[17]. A total score and three sub-scores are calculated, with higher scores indicating worse HRQL[17].

Age, sex, education, employment, marital status, living alone, smoking history and body mass index (weight/height^2) were assessed at baseline. Clinical assessments included spirometric values[18], dyspnea (the 5-grade Medical Research Council [MRC] dyspnea scale)[19], daily productive cough and daily wheeze[20], six-minute walking distance (6MWD)[21], exacerbations and hospitalizations in the previous year, and significant co-morbidities. Psycho-social status was represented by anxiety and depression (Hospital Anxiety and Depression Scale [HADS])[22], self-efficacy (COPD-specific self-efficacy scale, [CSES])[23] and social support (Personal Resource Questionnaire, [PRQ2000])[24]. Treatment profiles were recorded, including long-acting bronchodilators, inhaled corticosteroids, oral mucolytics, vaccinations, long-term oxygen therapy (LTOT) and pulmonary rehabilitation. Full details for these measurements are provided elsewhere[15].

Exacerbations

All patients were monitored monthly by telephone to document the occurrence and characteristics of COPD exacerbations. At each contact, a structured questionnaire

was administered to assess changes in respiratory symptoms and occurrence of medical interventions in the past month. Patients were also encouraged to report to their attending physicians or nurses whenever they experienced symptom worsening. An exacerbation was defined as the worsening of ≥1 key symptom (increased sputum amount, changed sputum color or purulence and increased dyspnea) for at least 48 hours. An exacerbation was considered as "reported" if it was brought to medical attention through scheduled or unscheduled doctor visits, emergency room visits or hospital admissions, and "unreported" if it was not medically reported but identified retrospectively using the monthly follow-up questionnaire. An exacerbation was considered as "treated" if there was a change in ≥1 medication (i.e., antibiotics, corticosteroids and bronchodilators) for the symptom worsening. More details of the determination of exacerbations are provided elsewhere[15].

Statistical analyses

The main outcome of interest was the 1-year change in the SGRQ total score and sub-scores (i.e., the difference between the 1-year and the baseline assessment). Patients were categorized into six exclusive groups according to the combinations of the frequency and the reporting status of exacerbations: no exacerbation (reference group), 1 unreported exacerbation only, >1 unreported exacerbations only, 1 reported exacerbation only, >1 reported exacerbations only, and mixed unreported (≥1) and reported (≥1) exacerbations. Generalized Estimating Equations (GEEs) were used to estimate the adjusted effects of exacerbations on the change of HRQL, taking into account the potential hospital-level clustering effect by modeling the fixed effect and correlation structure separately. The adjusted effect estimates represented the

difference between the average change in HRQL for the patients who had different types of exacerbations and the average change in HRQL for the patients who had no exacerbation. In order to estimate and control for the potential impact of exacerbations that occurred at the end of the study, patients who had at least one exacerbation (regardless of reporting status) in the last three months were included in multivariate models. Similar analyses were repeated for patients who had at least one exacerbation in the last two months. The interactions between exacerbation categories (both unreported and reported exacerbations) and COPD severities (continuous FEV_1%, FEV_1%≥30% vs. <30%, GOLD stage II, III and IV, and dyspnea≥4 vs. <4) were tested in multivariate models. Data analyses were performed using SAS® 9.1.2 (SAS Institute Inc., Cary, NC). The level of significance was set at $p<0.05$.

A priori subject-matter causal knowledge was used to guide the confounder evaluation[25, 26]. Potential determinants for HRQL were identified from a comprehensive literature review. Relevant studies were searched from MEDLINE, EMBASE and The Cochrane Library from 1980 to 2007, using the key words "Chronic Obstructive Pulmonary Disease/COPD", "quality of life/HRQL" and "risk factor/determinant/predictor". For the association under study, the causal relationships of each determinant with the outcome (HRQL), with the exposure (COPD exacerbation) and with other determinants were presented in Directed Acyclic Graphs (DAGs)[25, 26]. The relevant confounders were identified using DAGs, and all identified confounders were adjusted for in multivariate analyses, except for those with low variability (e.g., less than 3% of subjects participated into pulmonary rehabilitation). The confounders adjusted for in the multivariate models were: baseline SGRQ scores, age, sex, marital status, current employment, education, current smoking,

FEV_1%, MRC dyspnea score, 6MWD, daily productive cough, daily wheezing, depression (HADS-depression score ≥8 vs. <8), anxiety (HADS-anxiety score ≥8 vs. <8), self-efficacy score, social support score, significant co-morbidities (yes vs. no), and the use of long-acting bronchodilators (yes vs. no), inhaled corticosteroid (yes vs. no) and long-term oxygen therapy (yes vs. no). Additional details of the DAG and the confounding evaluation are presented in online data supplement A.

Multiple imputation (Markov Chain Monte Carlo method)[27, 28] was employed to impute the missing data. The forty-one missing values for baseline 6MWD (20 with contraindications for the walking test and 21 with unknown reasons) were imputed using all other baseline characteristics (socio-demographical, clinical, psychosocial and treatment profiles). The forty-one missing values for SGRQ scores at the end of the study were imputed using both baseline characteristics and exacerbation characteristics (exacerbation rate and duration). The SAS PROC MI procedure was used to create multiple imputed datasets, and the SAS PROC MIANALYZE procedure was used to combine results after analyses. In order to examine the robustness of the results to the missing values, the multivariate analyses were conducted among 414 patients who had no missing data, among 450 patients who completed the study (only imputing for the baseline 6MWD), and among all 491 patients recruited in the study (imputing for both the baseline 6MWD and the 1-year SGRQ score), respectively. The results were reported for the dataset that provided the more conservative estimates for SGRQ total scores.

RESULTS

Study population

Of the 491 recruited patients, 41 (8%) did not complete the study due to death (n=16), severe co-morbidity (n=1), withdrawal (n=9), being lost to follow-up (n=13), missing the SGRQ questionnaire at 1-year interview (n=1) and other reasons (n=1). The mean follow-up time was 373 (SD 65) days. **Table 1** shows that patients who were lost to follow-up were older, had shorter 6MWD, and had worse spirometric values, dyspnea and SGRQ scores (activity, impact and total) at baseline than those who completed the study ($p<0.05$).

Exacerbations and hospitalizations

As shown in **Table 2**, we recorded a total of 466 unreported exacerbations (rate: 1.01/person-year; 95% CI: 0.92 to 1.09) and 410 reported exacerbations (0.95/person-year; 0.87 to 1.04). When compared with reported exacerbations, unreported exacerbations had a lower median number of key symptoms, a lower proportion of symptom worsening for each key symptom ($p<0.0001$), and a lower proportion of exacerbations with two (12.4% vs. 19.7%; $p=0.0058$) and three key symptoms (4.3% vs. 51.5%; $p<0.0001$). On the other hand, more unreported exacerbations (83.3%) than reported exacerbations (28.8%) had a single symptom worsening ($p<0.0001$). Most of the reported exacerbations (87.1%) were treated using antibiotics, corticosteroid and/or bronchodilators, and 19.9% of unreported exacerbations were also "self-treated" by patients using either medications left from previous prescriptions or certain available over-the-counter antibiotics. Stratified analyses by GOLD stages II, III and IV showed similar patterns (online data supplement B).

Among 450 exacerbations with at least one medication change (regardless of whether physician-treated or self-treated), 183 (40.7%) led to hospitalization. Thirty-percent of all patients were admitted to hospital at least once due to the exacerbation during the study period (i.e.,1 year) (data not shown).

Baseline characteristics for patients with no, unreported and reported exacerbation(s)

Table 3 shows that patients with 1 unreported exacerbation had similar baseline characteristics compared to patients with no exacerbation, except for a better FVC% of predicted value ($p<0.05$). Patients with >1 unreported exacerbations were more likely to be males and had a higher FVC value ($p<0.05$) compared with patients with no exacerbation. Patients with 1 reported exacerbation were older, had less cumulative smoking and reduced 6MWD, and were more likely to be on long-acting bronchodilators and mucolytic agents ($p<0.05$ or $p<0.01$) compared with patients with no exacerbation. Patients with >1 reported exacerbations had less cumulative smoking and more hospital admissions in the past, and were more likely to be on long-acting bronchodilators and mucolytic agents ($p<0.05$ or $p<0.01$).

Change in HRQL among all patients who completed the study and among patients who were in different exacerbation categories

On average, the SGRQ scores improved at the end of the study period (1 year) among all patients who completed the study (n=450). The mean changes (95% CI) of the SGRQ total, activity, impact and symptom scores were -3.40 (-4.88 to -1.92), 0.09 (-1.62 to 1.81), -4.29 (-6.10 to -2.48), and -6.87 (-8.73 to -5.01), respectively. **Table 4**

shows that the improvement was predominant among patients with no exacerbation (n=167) and with 1 unreported exacerbation only (n=30). SGRQ scores improved less in magnitude or deteriorated among patients in other exacerbation categories.

Adjusted effect of unreported and reported exacerbation(s) on HRQL at one year

Multivariate analyses (**Table 5**) show that the 1-year change in SGRQ total score was significantly worse in patients with >1 unreported exacerbations (adjusted β: 4.61; 95% CI: 0.09 to 9.13) as compared with patients with no exacerbation, after adjusting for known confounders. The largest difference was observed for the activity domain (adjusted β: 6.36; 95% CI: 1.28 to 11.44). These estimates were probably clinically significant as the point estimates were greater than the recommended clinically important difference (4 points)[29] and the lower bounds of 95% CIs were over zero. **Table 5** also shows that, when compared to patients with no exacerbation, the 1-year change in SGRQ total score was significantly worse among patients with 1 reported exacerbation (adjusted β: 5.13; 95% CI: 1.15 to 9.11), patients with >1 reported exacerbations (adjusted β: 12.33; 95% CI: 7.72 to 16.95), and patients with mixed unreported (≥1) and reported exacerbations (≥1) (adjusted β: 8.22; 95% CI: 4.46 to 11.98), respectively. The largest differences were observed for the symptom domains. Sensitivity analyses showed similar and even more significant estimates. For instance, adjusted mean change of the SGRQ total score for >1 unreported exacerbations relative to no exacerbation was 4.69 (95% CI: 0.13 to 9.25) among all 491 patients and 4.25 (95% CI: 1.78 to 6.72) among 414 patients without any missing data. The interactions between exacerbation(s) (both unreported and reported) and COPD severity were not statistically significant (all *p* values>0.1). The adjusted estimates

(95% CI) were -1.93 (-6.18 to 2.32), -2.21 (-7.00 to 2.57), -2.49 (-7.72 to 2.73) and 0.23 (-4.82 to 5.29), respectively, for the association between the occurrence of exacerbation(s) in the last three months and the SGRQ total, activity, impact and symptom score. Similar results were observed for exacerbation(s) in the last two months (unpublished data).

DISCUSSION

This study shows that more than half of all exacerbations were not reported for medical attention in a population of COPD patients in China. More than one unreported exacerbations was associated with a significantly (both statistically and clinically) worse HRQL change at one year after adjusting for known confounders. Although this impact seems moderate in magnitude, it is far from negligible. It suggests that unreported exacerbations, despite being associated with fewer symptom worsening as compared to reported exacerbations, may have important intermediate to long-term impact on patients' physical activities (the SGRQ activity domain). In addition, this study shows that the change of HRQL at one year was worse among patients with more frequent and reported exacerbations.

To our knowledge, this is the first prospective study to investigate the independent effect of unreported exacerbations on the change of HRQL in intermediate to long term. Previous studies have focused on the effect of exacerbations reported for medical attention[7, 9] or a combination of unreported and reported exacerbations[8]. One study[13] reported an association between worse HRQL assessed at the beginning

of the study and a higher proportion of untreated exacerbations during the follow-up period. However, this reverse temporal relationship precludes any causal inference for the effect of untreated exacerbations on the change of HRQL. A recent Canadian cohort study[5] has shown that unreported exacerbations may have negative impacts on HRQL in 3 months and suggested that the health impact of this potential unmet healthcare need should be studied over the longer term. The present study, along with previous results, suggests a clinically important health impact of underreporting of exacerbation in patients with COPD.

Selection bias is unlikely to be responsible for the significant association between >1 unreported exacerbations and the change of HRQL. Patients who were lost to follow-up had more severe COPD at baseline than those who completed the study. However, stratified analyses showed that the relation between unreported exacerbations and the change of HRQL is similar across different levels of disease severities. Therefore, there was no evidence that the association between unreported exacerbations and the change of HRQL would be significantly different for patients who were lost to follow-up. Indeed, sensitivity analyses showed very similar and slightly more significant results among all 491 recruited patients.

The causal diagram approach[25, 26] was used for the comprehensive confounding evaluation. As discussed elsewhere[15], this approach is an alternative to other data-driven methods such as stepwise regression and "change-in-estimation" approach)[30-32]. It allows for the consideration of inter-relationships between multiple covariates and explicitly models the causal assumptions between variables which were implied but obscured in most studies[25, 26]. Known confounders identified using our causal

diagrams were controlled for in this study. As with any model there can be no guarantee that our causal diagram is correct or that other models could not be put forward. However, this approach allows us to make our causal assumptions explicit.

In order to avoid the acute effect of the last exacerbation on HRQL measures, the SGRQ was administered at least 4 weeks after the last exacerbation. As a previous study[6] had shown that the effect of a single exacerbation may persist for months, we further included in the multivariate models the occurrence of exacerbations in the last three months and two months, respectively. There were no significant effects on the change of HRQL after adjusting for the frequency and the reporting status of exacerbations. This result suggests that a 1-month wash-out period appears to be appropriate in therapeutic evaluations to preclude the acute effect of recent exacerbations.

Due to the expected poor compliance to the patient-kept diary card approach[5, 8] in this relatively lower-educated population (i.e., 35.5% primary school or no education), a monthly follow-up using a standardized questionnaire was employed to trace unreported exacerbations. As patients with COPD often under-recognize their symptom changes, a less strict criterion (i.e., ≥1 key symptom change) was used to capture as many unreported exacerbations as possible. The Canadian cohort study[5, 8], one of the two previous studies that investigated the underreporting of COPD exacerbations, used a similar definition. The incidence rate of all exacerbations in the present study (1.95 per person-year)[15] was lower than what was observed using diary card in the Canadian cohort (2.7 per person-year)[5, 8]. This difference may be explained by the different inclusion criteria in these two studies. In order to be

included in the Canadian cohort, patients needed to have a history of at least 10 pack-years smoking and two exacerbations in the previous 3 years. In the present study, however, 27.3% of patients had never smoked and 16.5% patients had no exacerbation in the previous year. On the other hand, it may indicate that patients who underwent monthly follow-up didn't recall mild symptom worsening in the past month. Closer investigation revealed that, as compared to the Canadian cohort, the present study had a lower rate (number per person-year) of unreported exacerbation (1.01 vs. 1.9) and a higher rate of reported exacerbation (0.95 vs. 0.8)[5, 8]. Indeed, patients in the present study were encouraged to report their symptoms worsening to the research team. There was also a possibility that patients' awareness of the symptoms change increased gradually during the study period, partly due to the monthly follow-up. Therefore, more reported exacerbations (i.e., reduced unreported exacerbations) might be observed than what would be found in routine clinical settings. However, this is more likely to have lead to an underestimate of the negative impacts of unreported exacerbations in current clinical care, although the impacts of reported exacerbations might be exaggerated. In future research, applying different detection approaches in at least a sample of the study population would be helpful to directly evaluate the difference between these approaches.

Monthly follow-up showed that 87.1% of reported exacerbations were treated and 12.9% were not treated based upon clinicians' judgments. On the other hand, 19.9% of unreported exacerbations were shown to be self-treated by patients. These self-treatments may be related to the use of medications left from the previous prescription and certain available over-the-counter antibiotics in China. The rate of hospital admission is relatively high in this study, that is, 40.7% of exacerbations with at least

one medication change led to hospitalization and 30.0% of patients were admitted to hospital at least once due to the exacerbation during the 1 year. These observations suggest potential unmet health needs or less-than-optimal health resource utilization in the management of COPD exacerbations.

The main limitation of this study is that patients were only monitored for one year and HRQL during the period of clinical stability was measured only at two time points (at recruitment and the end of the study). As a consequence, the fluctuation of HRQL during the 1-year follow-up period was unknown. A longer follow-up time and more frequent HRQL measures would allow for a more thorough investigation of the long-term impact of unreported exacerbations on the evolution of HRQL. Periodic measures of HRQL during the period of clinical stability would also allow for a better use of the exacerbation and HRQL data that were collected before the loss to follow-up. The limited number of patients with one (n=30) and more than one (n=45) unreported exacerbations only is another concern. Multiple testing could be an issue, as several exacerbations groups were compared to the no-exacerbation group. It might increase the chance of incorrectly rejecting the null hypothesis.

On average, the SGRQ total, impact and symptom scores improved significantly at the end of the study among patients who completed the follow-up. The overall improvement of HRQL at one year is not unexpected, as it has been a universal finding in the placebo arm of major intervention trials[33, 34] and in longitudinal observational studies[7]. Patients usually benefit from the participation in clinical studies since this is associated with better decision-making in regard to the therapy and patient care. This study allowed for the standard treatments such as

bronchodilators and inhaled steroids based upon clinical judgment and allowed for the treatments being optimized throughout the study. Although the change of treatments was not recorded, it may partly explain the overall improvement in HRQL. A closer investigation revealed that the improvement was predominant among patients who had no exacerbation and those who had 1 unreported exacerbation. However, the effect of having >1 unreported exacerbations was to reduce HRQL improvement. This finding concurs with an observational study investigating the effect of reported exacerbations on the evolution of HRQL over two years[7].

In conclusion, unreported exacerbations, although associated with fewer symptoms worsening than reported exacerbations, have a non-negligible negative impact on the change of HRQL at one year. The development of self-management programs has been recommended[35], emphasizing early recognition of exacerbation (symptoms worsening) and consequent action. Intervention trials seem to be warranted to evaluate the intermediate to long-term health benefit of these strategies. Given the large proportion of unreported exacerbations (associated with symptom change but usually not medication change) and their negative impacts on patients' health over the intermediate to long term, the frequency of unreported exacerbations should also be monitored and evaluated as an important outcome in future intervention trials (or a part of treatment benefits may be unrevealed). The intermediate to long-term HRQL impacts of both unreported and reported exacerbations call for further investigations of modifiable risk factors for COPD exacerbations, as well as interventional strategies that prevent the occurrence of COPD exacerbations.

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TABLES

Table 1. Baseline characteristics of the study population

	All patients (n=491)	Patients completed the study (n=450)	Patients lost to follow-up (n=41)	*P* values*
Age, years, mean (SD)	65.7 (10.7)	65.2 (10.6)	70.7 (10.1)	0.002
Male sex, n (%)	338 (68.8)	309 (68.7)	29 (70.7)	0.78
BMI, kg/m^2, mean (SD)	23.9 (4.2)	24.0 (4.2)	23.0 (4.0)	0.15
Cumulative smoking, pack-years, mean (SD)	26.8 (29.2)	26.5 (29.0)	31.0 (31.6)	0.33
MRC dyspnea grade ≥ 4, n (%)	123 (25.0)	103 (22.9)	20 (48.8)	0.001
6MWD†, meters, mean (SD)	384.6 (135.9)	392.4 (132.7)	287.2 (141.0)	0.0002
Spirometric values (post-BD), mean (SD)				
FEV_1, L	1.16 (0.47)	1.18 (0.47)	0.96 (0.36)	0.005
FEV_1 , % of predicted value	47.6 (15.9)	47.2 (15.8)	40.9 (16.5)	0.009
FVC, L	2.35 (0.80)	2.37 (0.79)	2.07 (0.79)	0.02
FVC, % of predicted value	75.8 (19.6)	76.5 (19.2)	67.8 (22.3)	0.02
FEV_1/FVC	0.49 (0.10)	0.49 (0.10)	0.47 (0.10)	0.10
GOLD stage (FEV_1%), n (%)				
II (50-79%)	211 (42.9)	199 (44.2)	12 (29.3)	0.02
III (30-49%)	204 (41.6)	188 (41.8)	16 (39.0)	
IV (< 30%)	76 (15.5)	63 (14.0)	13 (31.7)	
SGRQ scores, mean (SD)				
Symptom	61.7 (18.9)	61.3 (18.5)	66.4 (21.9)	0.15
Activity	56.1 (21.9)	55.1 (21.7)	68.0 (21.7)	0.0007
Impact	35.7 (22.3)	35.2 (22.1)	42.3 (23.7)	0.07
Total	46.3 (18.9)	45.6 (18.6)	54.1 (20.2)	0.01

* Unpaired 2-tailed t-test and Chi-square test were used to compare continuous variables (compare two means) and categorical variables (compare two proportions), respectively, between patients who completed the study and patients who lost to follow-up.

† Analyses were conducted among patients who had complete baseline data on 6MWD.

BMI=Body Mass Index; 6MWD=6-minute walking distance; MRC=Medical Research Council; BD=bronchodilator; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; SGRQ=St. George's Respiratory Questionnaire; GOLD=Global Initiative for Chronic Obstructive Lung Disease.

Table 2. Characteristics of unreported and reported exacerbations[*]

	Unreported exacerbations	Reported Exacerbations
Number of exacerbations	466	410
Rate of exacerbations, number/person-year (95% CI)	1.01 (0.92-1.09)	0.95 (0.87-1.04)
Total number of key symptoms, median (range)	1 (1-3)	3 (1-3)
Type of key symptoms, n (%)		
Sputum amount	213 (45.7)	292 (71.2) [†]
Sputum color	72 (15.5)	268 (65.4) [†]
Dyspnea	279 (59.9)	353 (86.1) [†]
One symptom	388 (83.3)	118 (28.8) [†]
Two symptoms	58 (12.4)	81 (19.7) [‡]
Three symptoms	20 (4.3)	211 (51.5) [†]
Proportion of treated and untreated exacerbations, n (%)		
Untreated exacerbations	373 (80.1)	53 (12.9)
Treated exacerbations	93 (19.9)	357 (87.1)

[*] Analyses were conducted among all 491 patients.

[†] *P* value<0.0001 and [‡] *p* value<0.01 for comparisons of proportions between reported and unreported exacerbations, which were estimated from Generalized Estimating Equations using each symptom as the dependent variable and the reporting status as the independent variable, taking into account the potential individual-level clustering effect.

Table 3. Baseline characteristics of patients according to exacerbation groups (n=450)

	No exacerbation (n=167)	1 unreported exacerbation only (n=30)	>1 unreported exacerbation only (n=45)	1 reported exacerbation only (n=70)	>1 reported exacerbation only (n=46)	Mixed unreported (≥1) and reported (≥1) exacerbation (n=92)
Age, years, mean (SD)	64.8 (11.4)	63.0 (10.8)	63.5 (10.8)	68.6 (8.9) *	65.7 (9.9)	64.7 (10.3)
Male sex, n (%)	110 (67.0)	21 (70.0)	37 (82.2) *	38 (54.3)	33 (71.7)	70 (73.6)
Cumulative smoking, pack-years, mean (SD)	29.1 (34.9)	25.6 (20.4)	20.1 (23.8)	21.7 (24.1) *	18.0 (24.9) *	29.1 (27.2)
MRC dyspnea score ≥ 4, n (%)	29 (17.6)	7 (23.3)	7 (15.5)	19 (27.1)	11 (23.9)	30 (31.5) *
6MWD‡, meters, mean (SD)	398.7 (139.3)	369.7 (85.6)	437.2 (130.7)	348.6 (119.2) *	356.6 (121.5)	414.2 (138.1)
Spirometric values (post-BD), mean (SD)						
FEV_1, L	1.19 (0.47)	1.32 (0.55)	1.28 (0.42)	1.10 (0.45)	1.06 (0.53)	1.19 (0.46)
FEV_1 , % over predicted	48.3 (15.1)	53.7 (18.4)	48.1 (14.6)	49.6 (16.1)	44.3 (15.5)	47.5 (16.0)
FVC, L	2.34 (0.79)	2.62 (0.78)	2.65 (0.69) *	2.13 (0.79)	2.20 (0.83)	2.47 (0.77)
FVC, % over predicted	74.9 (19.6)	84.0 (19.8) *	78.0 (17.5)	75.0 (20.9)	74.9 (16.7)	78.2 (18.6)
FEV_1/FVC	0.51 (0.10)	0.48 (0.11)	0.50 (0.10)	0.52 (0.09)	0.47 (0.10)	0.48 (0.12) *
Hospital admission for the last exacerbation, n (%)	66 (40.2)	9 (30.0)	23 (51.1)	33 (47.1)	28 (60.9) *	53 (55.7) *
Significant co-morbidities≥1, n (%)	23 (14.0)	6 (20.0)	6 (13.3)	12 (17.1)	7 (15.2)	19 (20.0)
Treatment profile, n (%)						
LABD	62 (37.8)	13 (43.3)	17 (37.8)	42 (60.0) †	31 (67.4) †	46 (48.4)
ICS	50 (30.5)	9 (30.0)	8 (17.8)	26 (37.1)	17 (37.0)	32 (33.7)
Mucolytics	74 (45.1)	10 (33.3)	20 (44.4)	43 (61.4) *	32 (70.0) †	45 (47.3)
No medication¶	47 (28.1%)	10 (33.3%)	15 (33.3%)	15 (21.4%)	4 (8.7%)	25 (27.2%)

[*]*P* value<0.05; [†]*P* value<0.01; Unpaired 2-tailed t-test and Chi-square test were used to compare the continuous variables (compare two means) and categorical variables (compare two proportions), respectively, between different exacerbation categories and no exacerbation category (reference).

[‡] Analyses were conducted among patients who had complete baseline data on 6MWD.

[¶] No use of LABD, ICS and mucolytics.

SD=standard deviation; 95%CI=95% confidence interval; MRC=Medical Research Council; 6MWD=6-minute walking distance; BD=bronchodilator; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; LABD=long-acting bronchodilator; ICS=Inhaled corticosteroid.

Table 4. Change of HRQL at one year of patients according to exacerbation groups (n=450)

	No exacerbation (n=167)	1 unreported exacerbation only (n=30)	>1 unreported exacerbation only (n=45)	1 reported exacerbation only (n=70)	>1 reported exacerbation only (n=46)	Mixed unreported (≥1) and reported (≥1) exacerbation (n=92)
1-year change of SGRQ scores†, mean (SD)						
SGRQ symptom	-13.0 (19.2)	-16.2 (18.0)	-7.2 (18.5)	-2.1 (18.5) ‡	2.9 (14.6) ‡	-0.8 (21.0) ‡
SGRQ activity	-3.7 (19.4)	-4.4 (18.8)	1.1 (17.2)	2.2 (17.2) *	7.4 (17.6) †	2.8 (17.1) †
SGRQ impact	-6.6 (20.6)	-6.8 (18.3)	-1.5 (17.2)	-3.8 (18.9)	2.5 (18.7) †	-3.7 (18.8)
SGRQ total	-6.8 (16.7)	-7.7 (13.1)	-1.6 (15.3)	-1.7 (15.0) ‡	4.1 (14.6) ‡	-1.2 (15.0) †
1-year change of SGRQ scores≥4†, n (%)						
Symptom	22 (13.4)	2 (6.7)	9 (20.0)	27 (38.6) ‡	26 (56.5) †	39 (41.0) ‡
Activity	47 (28.6)	7 (23.3)	19 (42.2)	27 (38.6)	28 (60.9) †	44 (46.3) †
Impact	38 (23.2)	6 (20.0)	14 (31.1)	19 (27.1)	20 (43.5) ‡	30 (31.6)
Total	32 (19.5)	3 (10.0)	13 (28.9)	21 (30.0)	23 (50.0) †	28 (29.5) *

* *P* value<0.05; † *P* value<0.01; ‡ *P* value <0.0001; Unpaired 2-tailed t-test and Chi-square test were used to compare the continuous variables (compare two means) and categorical variables (compare two proportions), respectively, between different exacerbation categories and no exacerbation category (reference category).

SD=standard deviation; 95%CI=95% confidence interval; SGRQ=St. George's Respiratory Questionnaire.

Table 5. Adjusted associations between unreported and reported exacerbations and the 1-year change of SGRQ scores among patients who completed the study (n=450)

	No. of patients	SGRQ domains			
		Total	Activity	Impact	Symptom
		Adjusted† β* (95% CI)			
No exacerbation	167	0 (reference)	0 (reference)	0 (reference)	0 (reference)
1 unreported exacerbation only	30	1.22 (-4.05, 6.48)	3.40 (-2.54, 9.34)	1.30 (-5.16, 7.76)	-3.38 (-9.65, 2.88)
>1 unreported exacerbations only	45	4.61 (0.09, 9.13)	6.36 (1.28, 11.44)	3.17 (-2.37, 8.71)	3.62 (-1.76, 8.99)
1 reported exacerbation only	70	5.13 (1.15, 9.11)	3.99 (-0.50, 8.48)	3.37 (-1.50, 8.24)	11.73 (7.01, 16.45)
>1 reported exacerbations only	46	12.33 (7.72, 16.95)	10.78 (5.57, 16.00)	11.33 (5.67, 16.99)	17.28 (11.80, 22.77)
≥1 unreported plus ≥1 reported exacerbations	92	8.22 (4.46, 11.98)	9.34 (5.11, 13.57)	5.53 (0.92, 10.14)	13.99 (9.51, 18.46)

* The estimate of β represents the mean change of SGRQ scores at one year for patients with exacerbations compared with patients with no exacerbation. For instance, 4.61 means that the mean change of the SGRQ total score at one year is 4.61 points worse for patients with >1 unreported exacerbations compared with patients with no exacerbation.

† Adjusted for baseline SGRQ scores, age, sex, marital status, current employment, education, current smoking, FEV_1%, MRC dyspnea, 6MWD, daily productive cough, daily wheezing, depression, anxiety, self-efficacy, social support, the use of long-acting bronchodilators and inhaled corticosteroid, long-term oxygen therapy, significant co-morbidities, and the occurrence of at least one exacerbation (regardless of reporting status) during the last 3 months of follow-up. Other statistically significant (p<0.05) estimates (adjusted β; 95% CI) in multivariate models are:

1) In the model for the SGRQ total score: anxiety (Hospital Anxiety and Depression scale (HADS)-Anxiety score ≥8 vs. <8) (5.23; 0.05 to 10.42), every 10-unit increase in self-efficacy score (0.74; 0.10 to 1.37); current smoking (3.66; 0.28 to 7.04); 50-meter increase in 6MWD (-0.70; -1.32 to -0.08); every 1-grade increase in MRC dyspnea scale (1.63; 0.23 to 3.03), baseline SGRQ total score (-0.52; -0.62 to -0.42).

2) In the model for the SGRQ activity score: Depression (HADS-depression score≥8 vs. <8) (4.69; 0.52 to 8.86); self-efficacy (0.73; 0.01 to 1.45); every 10% increased in FEV1% (-1.43; -2.38 to -0.47); current smoking (4.29; 0.46 to 8.12); every 50-meter increase in 6MWD (-0.87; -1.56 to -0.18); dyspnea (1.66; 0.05 to 3.28), baseline SGRQ activity score (-0.59; -0.68 to -0.50).
3) In the model for the SGRQ impact score: Anxiety (7.08; 0.67 to 13.49); self-efficacy (1.10; 0.32 to 1.87); dyspnea (1.97; 0.30 to 3.64), baseline SGRQ impact score (-0.54; -0.64 to -0.44).
4) In the model for the SGRQ symptom score: every 1-year older in age (-0.19; -0.38 to -0.01), depression (4.64; 0.25 to 9.03), dyspnea (1.59; 0.01 to 1.38), daily productive cough (4.26; 0.66 to 7.86), baseline SGRQ symptom score (-0.63; -0.73 to -0.53).

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