Depression, but not sleep disorder, is an independent factor affecting exacerbations and hospitalization in patients with chronic obstructive pulmonary disease

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ABSTRACT

Background and objective: Patients with chronic obstructive pulmonary disease (COPD) may experience depression and sleep disorders, which can adversely affect their health-related quality of life (HRQOL). The aim of this study was to investigate depression and sleep disorders among 85 COPD patients and 46 control subjects, aged 40 years and over.

Methods: Patients underwent spirometry and arterial blood gas analysis, self-completed St. George's Respiratory Questionnaire and were assessed on the Center for Epidemiologic Studies Depression (CES-D) and the Pittsburgh Sleep Quality Index (PSQI). The frequency of exacerbations among COPD patients was prospectively monitored for 12 months.

Results: The prevalence of depression and sleep disorders was significantly higher among COPD patients than control subjects. The relative risks (95% confidence interval) of depression and sleep disorders were 7.58 (1.03 to 55.8) and 1.82 (1.03 to 3.22), respectively, in COPD patients compared with control subjects. Among COPD patients, there was a correlation between CES-D and PSQI. Lower body mass index, more severe dyspnoea, poorer HRQOL, lower partial pressure of arterial oxygen and higher partial pressure of arterial carbon dioxide were significantly associated with depression and sleep disorders among COPD patients. Exacerbations and hospitalizations were more frequent among COPD patients with depression than those with sleep disorders alone or those without depression or sleep disorders.

Conclusions: Depression and sleep disorders are very common co-morbidities among COPD patients and significantly reduce activities and HRQOL among these patients. Depression, but not sleep disorder, is an independent risk factor for exacerbations and hospitalization among COPD patients.

Key words: chronic obstructive pulmonary disease, depression, sleep disorder.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by chronic airflow limitation and is recognized as a major cause of chronic morbidity and mortality throughout the world.1 COPD exacerbations are one of the most important adverse events and lead to increased mortality and frequent hospitalization, with serious negative impacts on lung function,2 health-related quality of life (HRQOL)3 and socioeconomic costs.4 The Global Strategy for the Diagnosis, Management, and Prevention of COPD (GOLD) guidelines emphasize the importance of treatment to reduce both the frequency and severity of COPD exacerbations.1

The increase in the number of individuals in the general population who experience depression and anxiety is a significant social problem, because these
psychological disorders not only degrade the individual’s HRQOL but also increase the likelihood of suicide. Depressive disorders have been associated with sleep disorders,\(^5,6\) and conversely, sleep disorders may lead to depression.\(^7,8\) Difficulty in falling asleep may be a predictor for the development of depression in elderly people, including patients with COPD.\(^7\) Patients with more severe COPD have a higher incidence of psychological disorders.\(^10,11,14\) There is increasing evidence that psychological disorders may have a direct impact on HRQOL and the frequency of exacerbations and hospitalizations in patients with COPD.\(^10-14\) Depression and sleep disorders may affect exacerbations, hospitalizations and mortality.\(^12,14\) However, the effects of depression and sleep disorders on patients with COPD are still unclear.

It has been suggested that there is a close association between sleep disorders and depression, and that each of these conditions is a risk factor and predictor for the other.\(^5,15,16\) The objective of this study was to investigate the prevalence of depression and sleep disorders in patients with mild to very severe COPD and in control subjects and to assess whether depression and sleep disorders are independent risk factors for exacerbations, hospitalization and mortality due to COPD.

METHODS

Participants

The subjects enrolled in this study were outpatients or healthy volunteers. COPD patients (n = 85) and healthy control subjects (n = 46) were randomly enrolled between 1 September 2009 and 31 August 2010. All the patients had had stable COPD for at least 4 weeks prior to the baseline assessments. Individuals with asthma, bronchiectasis, interstitial pneumonia, tuberculosis, pneumoconiosis, respiratory tract infections, ischaemic heart disease, chronic heart disease, renal or liver failure, active malignancies of any organ, sleep apnoea syndrome, central nervous system disorders, including cerebrovascular disease, or previous or active psychological diseases, such as major depression, bipolar disorder, schizophrenia or anxiety, were excluded. Subjects who had undergone lung volume reduction surgery, lung transplantation or pneumonectomy were also excluded. When worsening of respiratory symptoms and respiratory infections occurred, patients were enrolled 4 weeks after the improvement of their symptoms.

Among the COPD patients and control subjects, 29 and 17, respectively, had hypertension, 10 and 7, respectively, had hyperlipidaemia and 21 and 6, respectively, had diabetes mellitus (P > 0.05 for all). There were no significant differences in the incidence of these co-morbidities between the COPD patients and control subjects. As reported previously,\(^14,17-20\) the sample sizes for the COPD patients and healthy volunteers were >86 and >43, respectively, for depression, and >127 and >64, respectively, for sleep disorders, giving a COPD patient : control subject sample ratio of 2:1 (power = 80%; α error = 5%; β error = 80%). However, the sample size in this study was small.

Diagnosis and severity of COPD

The diagnosis and staging of COPD were in accordance with the GOLD guidelines, and the criteria included a post-bronchodilator ratio of forced expiratory volume in 1 s (FEV\(_1\))/forced vital capacity of <70%, reversibility of decrease in FEV\(_1\) after bronchodilator administration of <200 mL or <12% and GOLD stage I (%FEV\(_1\) > 80), GOLD stage II (%FEV\(_1\): 50–79), GOLD stage III (%FEV\(_1\): 30–49) or GOLD stage IV (%FEV\(_1\) < 30) COPD at baseline, as previously reported.\(^12,21\)

Study protocol

This prospective cohort study and 12-month follow up were conducted between September 2009 and August 2011 at the Respiratory Disease Center of Kurume University Hospital, Yanagawa Nagata Hospital, and Social Insurance Tagawa Hospital, in southwestern Japan. The study protocols were approved by the research ethics boards at each institution, and written informed consent was obtained from all participants.

Information on age, gender, smoking status (current, ex- or non-smoker), cumulative smoking history (pack-years), body mass index (BMI) (weight/height\(^2\)), co-morbidities, history of pharmacological and physiological treatments, and prescription of long-term oxygen therapy or non-invasive positive pressure ventilation was obtained at the screening visit. Electrocardiography, chest radiography, chest computed tomography and arterial blood gas analyses were also performed at the screening visit.

Assessments conducted at baseline, after the screening visit, included spirometry and bronchodilator responsiveness using an electronic spirometer (Chestgraph Jr HI-101, CHEST Ltd, Tokyo, Japan), in accordance with the American Thoracic Society recommendations.\(^22\) Predicted values for spirometry parameters were calculated using the prediction equations of the Japanese Respiratory Society, as reported previously.\(^21\) Dyspnoea was assessed using the five-grade Medical Research Council dyspnoea scale.\(^24\) Depression and sleep disorders were assessed using the validated Japanese Center for Epidemiologic Studies Depression scale (Saccess Bell Co., Ltd, Tokyo, Japan)\(^25,26\) and the Pittsburgh Sleep Quality Index,\(^27,28\) respectively. In order to include patients with pre- or early-phase illness, the scores selected as indicative of depression or sleep disorder were Center for Epidemiologic Studies Depression ≥ 16 and Pittsburgh Sleep Quality Index > 5.5, respectively, which have been shown to be reliable for detecting patients with early-phase illness, including those with probable or clinically mild disorders.\(^25–28\) The HRQOL of all participants was assessed using the validated Japanese St. George’s Respiratory Questionnaire.\(^29,30\) The
St. George’s Respiratory Questionnaire contains three subscales (symptoms, activity and impact), and the total score ranges from 0 to 100, with higher scores indicating poorer HRQOL.30

12-month prospective follow up of patients with COPD

All COPD patients visited their chief physician once a month and their baseline treatments were maintained for 12 months. Eight COPD patients without depression but with a sleep disorder, six COPD patients with depression alone and five COPD patients with a sleep disorder alone had undergone pneumococcal vaccination within the 5 years before enrolment. All COPD patients received vaccinations against seasonal and H1N1 influenza during the study period.

Chief physicians were unaware of the baseline Center for Epidemiologic Studies Depression and Pittsburgh Sleep Quality Index scores for each COPD patient and reviewed the changes in symptoms that had occurred over the previous month. Each patient was individually educated about exacerbations by their chief physician, and diaries of COPD symptoms were self-reported by each patient on a daily basis.

COPD patients were able to visit the emergency department when they experienced a worsening of symptoms, including increased sputum production, a change in sputum quality or increasing dyspnoea. The severity of exacerbations was graded as mild (controlled by inhalation of short-acting β₂-agonists or by education), moderate (controlled by treatment with antibiotics or systemic corticosteroids) or severe (requiring hospitalization, increased use of supplemental oxygen, change in non-invasive positive pressure ventilation mode or resulting in death). When patients showed signs of infection, such as a high body temperature, chest computed tomography was performed.

Data on the time to first exacerbation and hospitalization, the frequency of exacerbations and hospitalization (episodes per patient per year), the severity of exacerbations and mortality were analysed and compared between the patients with or without depression, with or without sleep disorders and GOLD stages I, II, III or IV COPD.

Eleven of the 14 COPD patients with depression agreed to consult psychologists, but the remaining three patients opted not to do so. Three and 11 of the 14 COPD patients had been receiving antidepressants and hypnotic drugs, respectively.

Statistical analyses

Data are expressed as means ± standard deviation, and comparisons were performed using the parametric Student’s t-test or one-way analysis of variance, and the non-parametric Wilcoxon rank sum or Kruskal–Wallis tests, as appropriate. Correlations were analysed using non-parametric Spearman’s correlation. Differences in frequencies between the groups were evaluated using the chi-square test. Times to initial exacerbation were compared by means of Kaplan–Meier curves and the log-rank test. Univariate and multivariate logistic regression was used to analyse associations among individual parameters and the incidence of exacerbations or hospitalizations. Data analyses were performed using JMP version 7 software (SAS Institute Inc., Cary, NC, USA). The level of significance was set at P < 0.05.

RESULTS

Characteristics of the subjects

The numbers of patients with GOLD stages I, II, III and IV COPD were 18 (21.2%), 33 (38.8%), 24 (28.2%) and 10 (11.8%), respectively. Nine and two of the COPD patients received long-term oxygen therapy and non-invasive positive pressure ventilation, respectively. The control subjects were matched with the COPD patients for age and BMI, but not gender (Table 1).

Prevalence of depression and sleep disorders in COPD patients

The mean total Center for Epidemiologic Studies Depression and Pittsburgh Sleep Quality Index scores were significantly higher in the COPD patients than in the control subjects (P = 0.0002 and P = 0.0076, respectively). The non-parametric Spearman’s test revealed a weak but significant positive correlation between the Center for Epidemiologic Studies Depression and Pittsburgh Sleep Quality Index scores in the COPD patients (r = 0.22, P = 0.044). The prevalence of depression and sleep disorders was 16.5% and 43.5%, respectively, in the 85 COPD patients and 2.2% and 23.9%, respectively, in the 46 control subjects (CI: 1.82, 1.03 to 3.22, P = 0.0419), respectively, in the COPD patients compared with the control subjects (Table 2). The numbers of patients with depression and GOLD stages I, II, III or IV COPD were two (11.1%), three (9.1%), four (16.7%) and five (50.0%), respectively, while the numbers of patients with sleep disorders and GOLD stages I, II, III or IV COPD were seven (21.2%), 12 (36.4%), 13 (38.9%) and 11 (30.6%), respectively.

Characteristics of the COPD patients with depression and sleep disorders

The patients with COPD were divided into three groups: those without depression or sleep disorders (n = 46), those with sleep disorders alone (n = 25) and those with depression, with or without sleep disorders (n = 14) (Table 3). Twelve of the 14 COPD patients with depression also had a sleep disorder, whereas only two COPD patients had depression alone. COPD
Patients with depression had a significantly lower mean BMI ($P < 0.05$), pre- and post-bronchodilator lung function (forced vital capacity, $P < 0.01$; FEV$_1$, $P < 0.05$), partial pressure of arterial oxygen ($P < 0.05$) and HRQOL ($P < 0.001$), and a higher partial pressure of arterial carbon dioxide ($P < 0.01$) and Medical Research Council dyspnoea score ($P < 0.01$) than those without depression or sleep disorders. COPD patients with depression also had significantly lower lung function (post-bronchodilator forced vital capacity, $P < 0.05$) and HRQOL ($P < 0.001$), and a higher partial pressure of arterial carbon dioxide ($P < 0.05$) and Medical Research Council dyspnoea score ($P < 0.05$) than those with COPD and sleep disorders alone. There were no differences in mean age, gender distribution, current smoking habit or smoking index among the three groups (Table 3).

The results of the analysis of risk factors for depression and sleep disorders in patients with COPD are presented in the online supporting information and Table S1.

### Table 1 Characteristics of the COPD patients and control subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>COPD ($n = 85$)</th>
<th>Control ($n = 46$)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>70.0 ± 7.9</td>
<td>67.3 ± 9.6</td>
<td>NS</td>
</tr>
<tr>
<td>Gender, % males</td>
<td>90.6</td>
<td>73.9</td>
<td>0.0227*</td>
</tr>
<tr>
<td>Body mass index, kg/m$^2$</td>
<td>22.1 ± 3.7</td>
<td>23.0 ± 2.6</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non / Ex / Current, n</td>
<td>0/61/24</td>
<td>38/7/11</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking index, pack-years</td>
<td>57.2 ± 31.0</td>
<td>16.5 ± 24.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lung function</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Pre-bronchodilator</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVC, L</td>
<td>3.3 ± 0.9</td>
<td>3.3 ± 0.8</td>
<td>NS</td>
</tr>
<tr>
<td>FEV$_1$, L</td>
<td>1.5 ± 0.7</td>
<td>2.6 ± 0.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Post-bronchodilator</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVC, L</td>
<td>3.3 ± 0.9</td>
<td>3.4 ± 0.8</td>
<td>NS</td>
</tr>
<tr>
<td>FEV$_1$, L</td>
<td>1.6 ± 0.7</td>
<td>2.6 ± 0.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FEV$_1$ / FVC, %</td>
<td>47.1 ± 13.9</td>
<td>78.0 ± 6.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Arterial blood gas analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaO$_2$, mm Hg</td>
<td>75.2 ± 10.3</td>
<td>88.6 ± 7.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PaCO$_2$, mm Hg</td>
<td>41.2 ± 4.8</td>
<td>41.4 ± 3.2</td>
<td>NS</td>
</tr>
<tr>
<td>MRC dyspnoea scale</td>
<td>1.9 ± 1.4</td>
<td>0.1 ± 0.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SGRQ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score, units</td>
<td>33.6 ± 20.0</td>
<td>10.5 ± 9.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Symptom score, units</td>
<td>42.4 ± 21.5</td>
<td>23.0 ± 15.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Activity score, units</td>
<td>44.5 ± 27.7</td>
<td>9.9 ± 13.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Impact score, units</td>
<td>22.3 ± 19.2</td>
<td>6.9 ± 9.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CES-D score, points</td>
<td>12.5 ± 6.8</td>
<td>8.7 ± 4.5</td>
<td>0.0002</td>
</tr>
<tr>
<td>PSQI score, points</td>
<td>5.5 ± 3.3</td>
<td>4.1 ± 2.6</td>
<td>0.0076</td>
</tr>
</tbody>
</table>

*Chi-square test was used to compare data between the two groups. All data are means ± standard deviation and Student’s $t$-test was used to compare data between the two groups.

COPD, chronic obstructive pulmonary disease; Ex, ex-smokers; FEV$_1$, forced expiratory volume in 1 s; FVC, forced vital capacity; MRC, Medical Research Council; Non, non-smokers; NS, not significant; PaCO$_2$, partial pressure of arterial carbon dioxide; PaO$_2$, partial pressure of arterial oxygen; PSQI, Pittsburgh Sleep Quality Index; SGRQ, St. George’s Respiratory Questionnaire.

### Table 2 Relative risks of depression and sleep disorders in COPD patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>COPD ($n = 85$)</th>
<th>Control ($n = 46$)</th>
<th>Relative risk</th>
<th>95% CI</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CES-D $&gt; 16$, $n$</td>
<td>14</td>
<td>1</td>
<td>7.58</td>
<td>1.03 to 55.8</td>
<td>0.0303</td>
</tr>
<tr>
<td>PSQI $&gt; 5.5$, $n$</td>
<td>37</td>
<td>11</td>
<td>1.82</td>
<td>1.03 to 3.22</td>
<td>0.0419</td>
</tr>
</tbody>
</table>

Data are expressed as relative risk and 95% confidence interval (CI) using the chi-square test.

COPD, chronic obstructive pulmonary disease; PSQI, Pittsburgh Sleep Quality Index.

Patients with depression had a significantly lower mean BMI ($P < 0.05$), pre- and post-bronchodilator lung function (forced vital capacity, $P < 0.01$; FEV$_1$, $P < 0.05$), partial pressure of arterial oxygen ($P < 0.05$) and HRQOL ($P < 0.001$), and a higher partial pressure of arterial carbon dioxide ($P < 0.01$) and Medical Research Council dyspnoea score ($P < 0.01$) than those without depression or sleep disorders. COPD patients with depression also had significantly lower lung function (post-bronchodilator forced vital capacity, $P < 0.05$) and HRQOL ($P < 0.001$), and a higher partial pressure of arterial carbon dioxide ($P < 0.05$) and Medical Research Council dyspnoea score ($P < 0.05$) than those with COPD and sleep disorders alone. There were no differences in mean age, gender distribution, current smoking habit or smoking index among the three groups (Table 3).

The results of the analysis of risk factors for depression and sleep disorders in patients with COPD are presented in the online supporting information and Table S1.

**12-month prospective study of exacerbations and hospitalizations**

Nine of the 85 COPD patients withdrew from the study during the 12-month follow-up period. The
Table 3  Comparisons among COPD patients with depression, COPD patients with sleep disorders, and COPD patients without depression or sleep disorders

<table>
<thead>
<tr>
<th>Parameter</th>
<th>COPD without depression or sleep disorders (n = 46)</th>
<th>COPD with sleep disorders alone* (n = 25)</th>
<th>COPD with depression† (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>67.8 ± 8.4</td>
<td>73.8 ± 6.3</td>
<td>70.4 ± 6.5</td>
</tr>
<tr>
<td>Gender, % males</td>
<td>91.3</td>
<td>96.0</td>
<td>78.6</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>22.8 ± 3.7</td>
<td>22.1 ± 2.9</td>
<td>19.7 ± 4.1*</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ex / Current, n</td>
<td>33/13</td>
<td>17/8</td>
<td>10/4</td>
</tr>
<tr>
<td>Smoking index, pack-years</td>
<td>63.6 ± 33.1</td>
<td>47.9 ± 26.1</td>
<td>52.7 ± 28.7</td>
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<tr>
<td>Lung function</td>
<td></td>
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<tr>
<td>Pre-bronchodilator</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVC, L</td>
<td>3.5 ± 0.8</td>
<td>3.3 ± 0.8</td>
<td>2.6 ± 1.1**</td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>1.7 ± 0.7</td>
<td>1.5 ± 0.6</td>
<td>1.2 ± 0.8*</td>
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<tr>
<td>Post-bronchodilator</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>FVC, L</td>
<td>3.5 ± 0.8</td>
<td>3.3 ± 0.8</td>
<td>2.6 ± 1.2**</td>
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<tr>
<td>FEV₁, L</td>
<td>1.7 ± 0.7</td>
<td>1.6 ± 0.6</td>
<td>1.2 ± 0.8*</td>
</tr>
<tr>
<td>FEV₁ / FVC, %</td>
<td>48.8 ± 13.5</td>
<td>46.6 ± 13.6</td>
<td>42.2 ± 15.3</td>
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<tr>
<td>Arterial blood gas analysis</td>
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</tr>
<tr>
<td>PaO₂, mm Hg</td>
<td>78.1 ± 8.2</td>
<td>73.0 ± 10.1</td>
<td>69.9 ± 13.6*</td>
</tr>
<tr>
<td>PaCO₂, mm Hg</td>
<td>39.7 ± 4.1</td>
<td>40.7 ± 3.7</td>
<td>46.3 ± 9.8**</td>
</tr>
<tr>
<td>MRC dyspnoea scale</td>
<td>1.6 ± 1.2</td>
<td>1.9 ± 1.3</td>
<td>3.0 ± 1.7***</td>
</tr>
<tr>
<td>SGRQ</td>
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</tr>
<tr>
<td>Total score, units</td>
<td>29.4 ± 16.4</td>
<td>28.7 ± 15.9</td>
<td>56.1 ± 23.0******##</td>
</tr>
<tr>
<td>Symptom score, units</td>
<td>38.7 ± 20.7</td>
<td>39.5 ± 21.5</td>
<td>59.5 ± 16.5***##</td>
</tr>
<tr>
<td>Activity score, units</td>
<td>39.7 ± 23.9</td>
<td>40.8 ± 24.5</td>
<td>67.3 ± 34.6***###</td>
</tr>
<tr>
<td>Impact score, units</td>
<td>20.7 ± 14.4</td>
<td>18.4 ± 13.3</td>
<td>48.6 ± 24.2***#####</td>
</tr>
</tbody>
</table>

*P < 0.05, **P < 0.01, ***P < 0.001 compared with COPD without depression or sleep disorders; †P < 0.05, ‡P < 0.01, ###P < 0.001 compared with COPD with sleep disorders.

All data are expressed as means ± standard deviation, and one-way analysis of variance was performed to compare data among the groups.

*Subjects categorized as having sleep disorders (PSQI > 5.5), but not depression (CES-D < 16).

†Twelve of 14 subjects with depression also had a sleep disorder. Only two subjects had depression alone.

CES-D, Center for Epidemiologic Studies Depression scale; COPD, chronic obstructive pulmonary disease; Ex, ex-smokers; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; MRC, Medical Research Council; PaCO₂, partial pressure of arterial carbon dioxide; PaO₂, partial pressure of arterial oxygen; PSQI, Pittsburgh Sleep Quality Index; SGRQ, St. George’s Respiratory Questionnaire.

reasons for withdrawal included loss to follow up (five patients), lung cancer (two patients), colon cancer (one patient) and hepatocellular carcinoma (one patient). Therefore, complete data were available for 76 COPD patients. Among these patients, 14 had depression, 24 had sleep disorders alone and 38 had neither depression nor sleep disorders. Twelve of the 14 COPD patients with depression also had a sleep disorder. Only two patients had depression alone. The mortality rate was 1.31%, as one patient without depression or a sleep disorder died due to exacerbation of disease, 336 days after providing informed consent. The annual frequencies of pneumonia episodes in the COPD patients with depression, those with sleep disorders alone and those without depression or sleep disorders were 0.1 ± 0.2, 0.1 ± 0.2 and 0.1 ± 0.3, respectively, with the differences being non-significant.

The mean (± standard deviation) annual number of exacerbations per patient was significantly higher in the COPD patients with depression (3.3 ± 3.5 episodes) than in the COPD patients with sleep disorders alone (0.7 ± 1.3) or those without depression or sleep disorders (0.6 ± 1.3) (P = 0.0002 and P < 0.0001, respectively) (Fig. 1). There was no significant difference in the annual number of exacerbations between COPD patients with sleep disorders alone and those without depression or sleep disorders (Fig. 1). With regard to the severity of exacerbations, the COPD patients with depression had a significantly higher frequency of mild (1.1 ± 1.5 episodes/year) and severe (0.6 ± 0.6), but not moderate, exacerbations compared with those with sleep disorders alone (0.2 ± 0.5, P < 0.01 and 0.1 ± 0.3, P < 0.05, respectively) and those without depression or sleep disorders (0.1 ± 0.3, P < 0.001 and 0.0 ± 0.2, P < 0.001, respectively).

The mean (± standard deviation) annual number of hospitalizations per patient was significantly higher in the COPD patients with depression (0.5 ± 0.7 episodes) than in the COPD patients with sleep disorders alone (0.1 ± 0.3, P = 0.0009) or those without depression or sleep disorders (0.0 ± 0.2, P < 0.0001) (Fig. 2). There was no significant difference in the annual
number of hospitalizations between COPD patients with sleep disorders alone and those without depression or sleep disorders (Fig. 2).

Kaplan–Meier curves showed that COPD patients with depression had a significantly shorter time to first exacerbation than those with sleep disorders or those without depression or sleep disorders ($P < 0.0001$ for both) (Fig. 3a). In a proportional hazards model based on GOLD stage, COPD with depression was also significantly associated with a shorter time to first exacerbation than COPD with sleep disorders alone and COPD without depression or sleep disorders (adjusted relative risk 4.63, $P = 0.006$ and relative risk 4.45, $P = 0.0025$, respectively). The COPD patients with depression also had a significantly shorter time to first hospitalization than those with sleep disorders alone or those without depression or sleep disorders ($P < 0.0001$ for both) (Fig. 3b). In a proportional hazards model based on GOLD stage, COPD with depression was also significantly associated with a shorter time to first hospitalization than COPD with sleep disorders alone or COPD without depression or sleep disorders (relative risk 2.29, $P = 0.1069$ and relative risk 2.97, $P = 0.0152$, respectively). There was no significant difference in the time to first exacerbation and hospitalization between COPD patients with sleep disorders alone and those without depression or sleep disorders.

Risk factors for exacerbations and hospitalization in COPD patients

As shown in Table 4, univariate analysis showed that the risk factors for exacerbations and hospitalization were depression, low BMI ($<20$ kg/m$^2$), having GOLD stage III or IV COPD, requirement for long-term oxygen therapy or non-invasive positive pressure ventilation and regular use of inhaled corticosteroids. Univariate analysis showed that a partial pressure of
arterial oxygen < 70 mm Hg and a partial pressure of arterial carbon dioxide > 45 mm Hg were risk factors for hospitalization, but not exacerbations. Multivariate analysis showed that depression and a high partial pressure of arterial carbon dioxide were independent risk factors for hospitalization. Interestingly, low BMI and FEV₁ were not independent risk factors. Multivariate analysis showed that the adjusted relative risks (95% CI) for depression and a partial pressure of arterial carbon dioxide > 45 mm Hg were 34.8 ($P = 0.0076$) and 25.6 ($P = 0.026$), respectively, whereas there were no independent factors predis-

Table 4  Univariate and multivariate analyses of risk factors for exacerbations and hospitalization among patients with chronic obstructive pulmonary disease

<table>
<thead>
<tr>
<th></th>
<th>Exacerbations RR (95% CI) P value</th>
<th>Hospitalization RR (95% CI) P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>4.88 (1.37 to 17.4) 0.0098</td>
<td>14.8 (3.07 to 70.9) &lt;0.0001</td>
</tr>
<tr>
<td>Sleep disorder</td>
<td>1.66 (0.66 to 4.18) NS</td>
<td>4.59 (0.88 to 23.7) 0.0517</td>
</tr>
<tr>
<td>Body mass index, &lt;20 kg/m²</td>
<td>3.43 (1.16 to 10.1) 0.0220</td>
<td>4.73 (1.12 to 20.0) 0.0242</td>
</tr>
<tr>
<td>Current smoker</td>
<td>0.38 (0.12 to 1.21) NS</td>
<td>0.31 (0.04 to 2.70) NS</td>
</tr>
<tr>
<td>GOLD stage III or IV</td>
<td>5.00 (1.86 to 13.4) 0.0023</td>
<td>14.3 (1.69 to 121) 0.0025</td>
</tr>
<tr>
<td>PaO₂, &lt;70 mm Hg</td>
<td>1.78 (0.99 to 3.16) 0.0918</td>
<td>5.66 (1.20 to 26.6) 0.0238</td>
</tr>
<tr>
<td>PaCO₂, &gt;45 mm Hg</td>
<td>1.69 (0.89 to 3.20) NS</td>
<td>9.00 (2.45 to 33.0) 0.0037</td>
</tr>
<tr>
<td>Requirement for LTOT or NPPV, n</td>
<td>15.3 (1.80 to 130) 0.0018</td>
<td>19.7 (3.75 to 103) 0.0002</td>
</tr>
<tr>
<td>Regular use of ICS, n</td>
<td>4.86 (1.75 to 13.4) 0.0026</td>
<td>4.70 (1.07 to 20.7) 0.0268</td>
</tr>
</tbody>
</table>

**Univariate**

<table>
<thead>
<tr>
<th></th>
<th>Exacerbations RR (95% CI) P value</th>
<th>Hospitalization RR (95% CI) P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>1.85 (0.40 to 8.21) NS</td>
<td>34.8 (3.66 to 1009) 0.0076</td>
</tr>
<tr>
<td>Body mass index, &lt;20 kg/m²</td>
<td>1.98 (0.50 to 7.70) NS</td>
<td>4.16 (0.37 to 59.1) NS</td>
</tr>
<tr>
<td>GOLD stage III or IV</td>
<td>3.36 (0.94 to 12.2) 0.0622</td>
<td>2.86 (0.28 to 38.9) NS</td>
</tr>
<tr>
<td>PaO₂, &lt;70 mm Hg</td>
<td>NA</td>
<td>1.08 (0.08 to 14.2) NS</td>
</tr>
<tr>
<td>PaCO₂, &gt;45 mm Hg</td>
<td>NA</td>
<td>25.6 (1.90 to 875) 0.0260</td>
</tr>
<tr>
<td>Requirement for LTOT or NPPV, n</td>
<td>1.55 (0.32 to 7.29) NS</td>
<td>1.20 (0.02 to 65.1) NS</td>
</tr>
<tr>
<td>Regular use of ICS, n</td>
<td>2.93 (0.77 to 11.2) NS</td>
<td>7.09 (0.19 to 389) NS</td>
</tr>
</tbody>
</table>

All data are expressed as relative risk (RR) with 95% confidence interval (CI). Univariate analyses were performed using the chi-square test. Multivariate analysis was performed to identify significant parameters, including depression, BMI, GOLD stage, requirement for LTOT and NPPV, and regular use of ICS, in patients who experienced exacerbations and hospitalization.

GOLD, Global Strategy for the Diagnosis, Management, and Prevention of COPD; ICS, inhaled corticosteroid; LTOT, long-term oxygen therapy; NA, not available; NPPV, non-invasive positive pressure ventilation; NS, not significant; PaCO₂, partial pressure of arterial carbon dioxide; PaO₂, partial pressure of arterial oxygen.
posing patients to exacerbations. Multivariate sub-
analysis of the frequencies of exacerbations and hospitalizations showed that the adjusted relative risks (95% CI) of depression associated with >1, >2 or >3 exacerbations annually were 1.85 (0.40 to 8.21, \( P > 0.05 \)), 16.2 (3.37 to 90.7, \( P = 0.0005 \)) and 29.1 (4.62 to 202, \( P = 0.0002 \)), respectively (Table S2 in the online supporting information). The adjusted relative risks of depression associated with >1 or >2 hospitalizations annually were 16.0 (1.77 to 206, \( P = 0.0137 \)) and 13.5 (1.81 to 125, \( P = 0.0132 \)), respectively.

**DISCUSSION**

To our knowledge, this is the first prospective study investigating the interactions between depression, sleep disorder without sleep apnoea syndrome, exacerbations and hospitalization among COPD patients. In this study, we showed that COPD patients with depression had significantly more severe dyspnoea, a lower HRQOL and more frequent exacerbations and hospitalization than COPD patients with sleep disorders. Patients with COPD who have depressive symptoms may have severe disabilities, sleep disorders and a poor prognosis. Depression, but not sleep disorder, was an independent risk factor for frequent exacerbations (>2 episodes per patient per year) and hospitalization. Surprisingly, about 90% (12/14) of the COPD patients with depression also had some symptoms of sleep disorder. These findings confirm the close association between depression and sleep disorders in COPD patients, as demonstrated in previous studies of the general population.5–9 The presence of sleep disorders, as well as depression, is thus an important consideration in the management of patients with COPD.

Recent studies have demonstrated that the prevalence of depression is between 11% and 30% in patients with mild to severe COPD, although there is no evidence of sleep disorder in COPD patients without sleep apnoea syndrome.17,31–33 Patients with sleep apnoea syndrome were excluded from this study, because it is well known that sleep apnoea syndrome is an independent risk factor for low HRQOL and a poor prognosis in patients with COPD.34 The prevalence of depression and sleep disorders among patients with COPD was 16.5% and 43.5%, respectively, being significantly higher than in the control subjects. In addition, one third of the COPD patients with sleep disorders had depressive symptoms, and most of those with depression also had some symptoms of sleep disorder. Factors shown to be correlated with the development of depression and anxiety among patients with COPD include female gender, older age, low BMI, FEV1 predicted < 50%, oxygen dependency, end-stage disease and the presence of advanced co-morbidities such as cancer, acquired immune deficiency syndrome, heart disease and renal disease.35,36 Therefore, COPD patients with advanced co-morbidities were carefully excluded from this study. There were no significant differences in age or BMI between the COPD patients and control subjects. The prevalence of depression and sleep disorders was higher in COPD patients than in the control subjects, although the proportion of males was higher among the COPD patients (90.6%) than among the control subjects (73.9%) (Table 1). Patients with severe or very severe COPD (GOLD stages III or IV), requirement for long-term oxygen therapy, and requirement for regular inhaled corticosteroid therapy appeared to be at risk of developing depression, although severity of COPD did not contribute to the risk of developing both depression and sleep disorders. Moreover, among the 18 patients with mild COPD (GOLD stage I), two (11.1%) and seven (38.9%) experienced depression and sleep disorders, respectively. These results suggest that COPD may be an important risk factor for depression and sleep disorders.

Exacerbation is thought to be one of the most important adverse events in patients with COPD, leading to a decline in lung function, increased mortality and frequent hospitalization.9 There is little evidence to suggest that depression and sleep disorders affect exacerbations, hospitalization and mortality among COPD patients, whereas repeated exacerbations and hospitalization are associated with the development of depression and anxiety.12–15 In this study, the prospective 12-month follow up showed that exacerbations and hospitalizations occurred significantly more rapidly and more frequently among COPD patients with depression than among those without depression. The COPD patients with sleep disorders showed a non-significant trend towards frequent and more rapid exacerbations and hospitalizations than those without sleep disorders. The proportion of COPD patients who experienced at least one exacerbation in the 12-month period was 40.8% (31 of 76 patients), and the annual number of exacerbations per patient was 1.12 (95% CI: 0.64–1.60). The annual number of exacerbations was significantly greater among the COPD patients with depression than among those without depression (3.29, 95% CI: 1.28–5.29 vs 0.63, 95% CI: 0.31–0.95). A recent meta-analysis of previous cohort studies demonstrated that the number of annual exacerbations ranged from 0.67 to 3.43, and it was estimated that the annual event-based exacerbation frequencies, in terms of GOLD stage, were 0.82 (95% CI: 0.46–1.49) for mild COPD, 1.17 (95% CI: 0.93–1.50) for moderate COPD, 1.61 (95% CI: 1.51–1.74) for severe COPD and 2.10 (95% CI: 1.51–2.94) for very severe COPD.37 Thus, the frequency of exacerbations in COPD patients with depression may be equal to, or higher than that in patients with GOLD stage IV COPD, although these results cannot be compared directly with those from the present study.

In summary, the present study showed that the prevalence of depression and sleep disorders in Japanese patients with COPD was higher than that in control subjects without COPD. Twelve of the 14 COPD patients with depression had symptoms of sleep disorder, although the sample size was small. The interaction between depression and sleep disorders therefore appears to be strong in patients with COPD. Detection of sleep disorders may help in the early identification of depression among such
patients.7 COPD patients with depression had a lower HRQoL, more severe disability and more frequent exacerbations and hospitalizations than the control subjects. Depression may be an independent predictor of early and more frequent exacerbations and hospitalizations, and a risk factor for poor prognosis among COPD patients. However, previous studies have indicated that depression and anxiety among patients with COPD often remain untreated or undertreated.37–39 In addition, there is little evidence for the efficacy of physiological or pharmacological treatments in COPD patients with depression and sleep disorders.35,40,41 Prospective studies should be undertaken to evaluate whether treatment of depression affects disease activity in patients with COPD.

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**SUPPORTING INFORMATION**

Additional Supporting Information may be found in the online version of this article:

**Table S1** Relative risks of depression and sleep disorder in patients with COPD.

**Table S2** Multivariate analysis of correlation between depression and annual total number of exacerbations or hospitalizations.

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