Original Article

Fatigue in Ambulatory Patients with Advanced Lung Cancer: Prevalence, Correlated Factors, and Screening

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Abstract

Although it has been indicated that patients with lung cancer experience higher level of fatigue than patients with other cancers, few published studies have focused on the characteristics of this fatigue and how it interferes with daily activities. The purpose of this study was to clarify fatigue prevalence and the factors correlated with fatigue, and to develop a screening method for fatigue in patients with advanced lung cancer. One hundred fifty-seven patients completed two fatigue scales (Cancer Fatigue Scale [CFS], and Fatigue Numerical Scale [FNS]) plus other measures, along with a self-administered questionnaire asking whether fatigue had interfered with any of 7 areas of daily activities. Fifty-nine percent of patients had experienced clinical fatigue, which was defined as fatigue that interfered with any daily activities. Logistic regression analysis demonstrated that symptoms of dyspnea on walking, appetite loss, and depression were significant correlated factors. Both CFS and FNS were found to have sufficient sensitivity and specificity for use as a screening tool. The results indicated that fatigue is a frequent and important symptom, which is associated with both physical and psychological distress in this population. The CFS and FNS were confirmed to have sufficient screening ability. J Pain Symptom Manage 2001;22:554–564. © U.S. Cancer Pain Relief Committee, 2001.

Key Words

Fatigue, lung cancer, pain, dyspnea, depression, QOL, screening, symptom management, Cancer Fatigue Scale

Introduction

Fatigue has been recognized as one of the most frequent symptoms experienced by patients with cancer. In addition, fatigue is also experienced following various active treat-
ments such as surgery, chemotherapy, radiotherapy, and bone marrow transplantation.

Activities and quality of life (QOL) in cancer patients is deleteriously affected by fatigue. Ferrell et al., in a descriptive study investigating the impact of fatigue on cancer patients, found that fatigue interfered with physical, psychological, social, and spiritual dimensions of well-being. Vogelzang et al. conducted a telephone survey of 419 patients with a variety of cancers and reported that the impact of fatigue on daily routines was rated as significant by 32% of patients and as moderate by 39% of patients. Recently, in a study of patients with various cancers, Ashbury et al. reported that fatigue was the most frequent symptom, and was most likely to interfere with their normal daily activities.

Lung cancer is the most frequent cause of cancer death in the world and is one of the most prevalent cancers. In Japan, the incidence of lung cancer is increasing, and was the cause of death in approximately 51,000 people in 1998. For all cancer mortality in Japan, lung cancer is the commonest cause and accounts for 18% of all cancer deaths.

Advanced lung cancer (III, IV) is difficult to cure (survival rate within 5 years of diagnosis is about 7% and 1%, respectively), and it is important to improve the QOL in this patient population.

Some studies have indicated that fatigue is a critical problem in lung cancer patients. One study, looking at the findings from 2390 cancer patients in 10 clinical trials, has reported that patients with lung or ovarian cancer experienced greater fatigue than those with other cancers. Other studies have shown that fatigue was one of the most distressing symptoms in 60 women with advanced lung cancer, that there was a significant correlation between fatigue and QOL in 127 patients with small-cell lung cancer, and that fatigue was associated with depression in three palliative treatment trials in 987 lung cancer patients. On the other hand, a small study, conducted in 26 lung cancer patients, reported that although fatigue was perceived as the highest intensity symptom, it was ranked as the second lowest in importance compared with other symptoms.

Only a few studies have focused on fatigue in this population. Hickok et al. conducted a retrospective review of medical records in 50 lung cancer patients receiving radiotherapy, and found that fatigue is a frequent symptom (78%) and is not correlated with either disease or treatment variables. However, this study had serious methodological flaws, in that symptoms, including fatigue, were assessed retrospectively and objectively, rather than subjectively using a valid assessment method. In addition the number of participants was small. Blesch et al. reported that pain and mood, as measured by Profile of Mood States, were significantly correlated with fatigue in lung cancer patients, although the use of a convenient and small sample (n = 33) limited the interpretation, and symptoms other than pain and sleep disturbance were not assessed. Furthermore, neither of these studies assessed interference with daily life due to fatigue.

In summary, many patients with lung cancer experience fatigue as a distressing symptom. However, no well-designed studies have yet been conducted in this population investigating the prevalence of fatigue, factors correlated with this symptom, and how fatigue interferes with daily activities. This cross-sectional study was conducted to determine 1) the prevalence of patients with advanced lung cancer who had interference with daily activity due to fatigue, 2) the correlated factors of such patients, and 3) methods to detect such patients. Fatigue in advanced lung cancer patients was assessed using two fatigue scales (Cancer Fatigue Scale and Fatigue Numerical Scale) along with a self-administered questionnaire asking whether fatigue had interfered with any of 7 domains of their daily activities. In addition, a broad range of biopsychosocial factors, including cancer information and previous anti-cancer treatment history, psychological distress, and demographical and social support status were assessed using a review of medical records, a self-administered questionnaire, and a structured interview.

Methods

Subjects

The study subjects were consecutive ambulatory patients with advanced lung cancer at the Thoracic Oncology Division of the National Cancer Center Hospital East, and the National Cancer Center Hospital, Japan. The eligibility criteria for patients were a) to have clinically in advanced stage of disease (clinical stage; unre-
sectable IIIA, IIIB, or IV) or recurrent disease, b) to have had no active anti-cancer treatment such as surgery, chemotherapy, or radiotherapy in the preceding 4 weeks, c) to be informed of the cancer diagnosis, d) to be well enough to complete the questionnaire and participate in a brief interview, and e) not to be suffering from severe mental or cognitive disorders.

This study was approved by the Institutional Review Board and the Ethics Committee of the National Cancer Center, Japan. Full written consent was obtained from each patient after being fully informed of the study.

Procedure

Consecutive outpatients who met the criteria were invited to participate in the study. After informed consent had been obtained, structured interviews were held to obtain sociodemographic data and information on regular medication. A physical examination, including measurement of height, weight, temperature, heart rate, respiratory rate, and SpO\textsubscript{2} (oxygen-saturated hemoglobin measured by finger pulse oximeter) was conducted. The patients were given simple instructions, and were requested to complete the self-administered questionnaires at home on the hospital-visit day and to mail them back by the following day. Returned questionnaires were checked and if any questions had not been answered, telephone inquiries were made to obtain the missing answers, as the participants had been informed already. Subjects received a 500-yen prepaid telephone-card for participating in this study.

Thirty-seven consecutive patients, selected from the entire patient sample, participated in the test on two occasions in order to assess the reliability of the definition of clinical fatigue and that of the Fatigue Numerical Scale. These patients completed the survey by mail with an average 7.0-day window between the first and second response (SD = 1.27, median = 7 days).

Measures

Definition of Clinical Fatigue. Using a questionnaire, patients were asked whether fatigue had interfered, in the previous 24 hours, with the 7 domains of daily activity: walking ability, sleep, normal work, mood, relations with other people, enjoyment of life, and general activities of life. Each category was scored as ‘present’ or ‘absent.’ The 7 domains are those used by Cleeland et al. in the Brief Pain Inventory,\textsuperscript{22} and have been investigated in pain research.\textsuperscript{23} Patients who complained of interference with at least one domain were defined as having clinical fatigue.

We examined the psychometric properties of this classification. The test–retest reliability was investigated calculating Cohen’s kappa coefficient.\textsuperscript{24} This indicates the stability of distinguishing between case and non-case, and was found to be sufficient (coefficient = 0.68). Discriminant validity was investigated by the Mann–Whitney test comparing performance status between the two groups, and a significant difference was found ($z = -2.87, P = 0.004$).

Cancer Fatigue Scale (CFS). The CFS is a 15-item self-rating scale for assessing fatigue in cancer patients.\textsuperscript{25} This scale consists of 3 subscales (physical, affective, and cognitive aspect of fatigue), and can assess the multi-dimensional nature of fatigue. Patients are asked to circle the one number that describes their current state, on a scale of 1 (not at all) to 5 (very much). The possible response range for each subscale score is 0 to 28 for the physical, and 0 to 16 for each of the affective and cognitive subscales. Total fatigue is calculated as the sum of these aspects. The maximum total score is 60, with the higher scores indicating more severe fatigue. The reliability and validity of this scale in cancer patients has been established by a previous study.\textsuperscript{25}

Fatigue Numerical Scale (FNS). The FNS is a 0 to 10 numerical rating scale, ranging from zero (‘no fatigue’) to 10 (‘fatigue as bad as you can imagine’). Patients are asked to circle a number to express the intensity of their fatigue in the previous 24 hours, thus expressing a global sensation of fatigue. The advantages of using numerical rating scales have been discussed elsewhere.\textsuperscript{26} The most important characteristic of FNS is its simplicity, making it easier both to administer to patients and for clinicians to collect and interpret the data. We investigated the validity and reliability of this scale in the present study. Pearson’s correlation coefficients between FNS and CFS total score, which indicates convergent validity, was 0.69 ($P < 0.001$). The test–retest correlation coefficient was 0.60 ($P < 0.001$).
Assessment of Pain, Dyspnea and Interference with Daily Life Activities Caused By These Symptoms.

Pain and dyspnea were compared with fatigue using similar 0–10 numerical scales, the Pain Numerical Scale (PNS) and the Dyspnea Numerical Scale (DNS). In addition, interference with daily activities, due to these symptoms, was also investigated using the same format as that for fatigue.

Hospital Anxiety and Depression Scale (HADS). The HADS, developed by Zigmond et al., consists of a 7-item anxiety subscale and a 7-item depression subscale. It assesses psychological distress over the preceding week. A characteristic of this scale is that it does not include questions about physical symptoms. We have established the reliability and validity of the Japanese version of this questionnaire in cancer patients.

Ad-Hoc Self-Administered Questionnaire. An ad-hoc self-administered questionnaire was used to investigate physical symptoms in the preceding 24 hours. This included questions on cough, sputum, dyspnea at rest and while walking, appetite, nausea, constipation, sleep, and pain. These categories were assessed using the 4-point Likert scale, rating 0 (not at all) to 3 (very much).

Medical information was obtained from the patients’ medical records. Their laboratory data were also obtained from the medical records if they were available within a week. On the day of the hospital visit, the attending physician clinically judged the performance status (PS), as defined by the Eastern Cooperative Oncology Group (ECOG). Each of the attending physicians had been engaged in thoracic oncology for over 5 years.

Statistical Analysis

To compare the prevalence of interference with daily life activity due to fatigue, dyspnea, and pain, we conducted a Friedman test in each domain. If significant difference was found, further analysis was conducted using the Wilcoxon ranked test.

A logistic regression analysis was carried out to determine the potential correlated factors. Factors having a $P$ value of less than 0.05 were retained as independent variables, and subjected to logistic regression analysis. Inter-group comparisons of categorical, nonparametric, and continuous variables were examined using the chi-square test, Wilcoxon’s rank sum test, and unpaired $t$-test, respectively.

The cut-off point for screening patients with clinical fatigue, using both the CFS and FNS, was determined utilizing the Receiver Operating Characteristic Curves (ROC curves). The optimal cut-off point was determined by two criteria. Firstly, it was chosen in order to minimize the sum of false-positive ($1 - \text{sensitivity}$) and false-negative ($1 - \text{specificity}$) test results. Secondly, a consideration of the balance between sensitivity and specificity was made in cases where the sensitivity was considerably lower than the specificity. Acceptable levels of sensitivity and specificity depend on the purpose for which a scale is being utilized. Since we considered that over-diagnosis of clinical fatigue is less harmful than missing it completely by using a cut-off point that is set too high, we determined it to provide enough sensitivity.

For all analyses, a $P$ value less than 0.05 was required for significance. All statistical procedures were performed using SPSS 8.0J for Windows statistical software (SPSS Japan Institute Inc., 1998).

Results

Subjects

One hundred and seventy-one consecutive outpatients were initially considered as candidates for the study between May and July 1998. Eight of these patients were ineligible due to their severe physical ill health and/or cognitive dysfunction. Two patients (1%) declined because of lack of time or feeling too ill, and four (2%) were excluded because they failed to complete the questionnaires. The sociodemographic and clinical characteristics of the remaining 157 patients are shown in Table 1. About 80% of the subjects had physical impairments, with a performance status of 1 or more. Non-participants had a worse performance status ($z = -3.80, P < 0.001$, Mann–Whitney test) and were of a higher education level ($z = -2.06, P = 0.04$, Mann–Whitney test) when compared with participants.
Prevalence of Clinical Fatigue and Interference with Daily Activities; A Comparison with Pain and Dyspnea

The FNS, DNS and PNS results showed that 81.5% of subjects experienced some degree of fatigue, 74.5% experienced dyspnea, and 65.0% experienced pain. Figure 1 shows the percentage of patients who reported interference with each daily life activity due to fatigue, dyspnea, or pain. From this it can be seen how fatigue impinges on various domains of daily activity.

Fig. 1. Percentage of patients who reported interference with daily life activities due to fatigue; comparison with that due to pain and dyspnea (n = 157). Percentages of patients who reported interference with each daily activity, due to fatigue, dyspnea, and pain, are shown. From this it can be seen how fatigue impinges on various domains of daily activity.

by pain (19.7%, $z = -3.61, P < 0.001$ and 21.7%, $z = -2.60, P = 0.01$).

About half of the patients were found to have clinical fatigue (51.3%)—that is, they complained of interference with at least one domain of daily living activity. Patients with clinical fatigue had significantly greater CFS and FNS scores than those where clinical fatigue was absent (mean CFS score [SD] = 25.4 [9.2] and 14.7 [6.9], respectively (Figure 2); $t = 8.26, P < 0.001$; mean FNS score [SD] = 4.0 [1.9] and 1.1 [1.2], respectively; $t = 11.1, P < 0.001$, unpaired t-test).

Factors Correlated with Clinical Fatigue

A comparison of patients’ characteristics between patients with and those without clinical fatigue is shown in Tables 2 and 3. There was a significant difference between the two groups in performance status, symptoms of sputum, cough, dyspnea, appetite loss, sleep, pain, de-
pression, and anxiety. However, no significant difference was found in the sociodemographic, disease, and treatment characteristics. Before these variables were subjected into logistic regression analysis, correlations among independent variables were noted. There were three correlation coefficients above 0.30: depression and anxiety; sputum and cough; and appetite loss and nausea. Only variables with a strong correlation with other dependent variables were selected for logistic regression analysis. The results of this analysis are shown in Table 4. Patients with clinical fatigue had significantly more severe dyspnea on walking, more severe appetite loss, and more severe depression than those where clinical fatigue was absent. Recent laboratory data were available in 81 patients (37 patients with clinical fatigue and 44 without it). There were no significant differences in white blood cell count, albumin, and hemoglobin between the two groups.

Screening for Clinical Fatigue

Figure 3 shows the ROC curve for screening for clinical fatigue in this population. For the CFS, the optimal cut-off point was 18/19, and this was associated with 71.3% sensitivity and 74.0% specificity. For the FNS, the optimal cut-off point was 2/3, which gave 76.3% sensitivity and 87.0% specificity. In addition, we investigated the association between fatigue intensity measured by FNS and the number of interfered domains, similar to Mendoza et al.30 The optimal cut-off points are associated with a large increase in the number of interfered domains, since the ideal cut-off point between each severity group should yield the greater discrepancy in the number of interfered domains. This result is preliminary because of the limited accuracy of the data, since there were only a small number of patients with fatigue scores of 6 or more (17 patients, 10.8%). However, there are steep slopes between 2 and 3 and also between 4 and 5 (Figure 4). This may indicate that a cut-off point of 4/5 could be useful in distinguishing severe clinical fatigue from mild clinical fatigue.

Discussion

This study investigated the prevalence of clinical fatigue and correlated factors, and the
screening ability of the CFS and FNS in ambulatory patients with advanced lung cancer.

Our results indicated that about half of these patients suffered from clinical fatigue. The impact on daily activities extended into both physical and emotional areas. The problem of fatigue is as great as that of pain and dyspnea. Health care professionals therefore need to pay more attention to fatigue and its impact on patients’ QOL.

Dyspnea on walking, appetite loss, and depression were significantly correlated with clinical fatigue in ambulatory patients with advanced lung cancer. A greater awareness of these factors may contribute to better understanding and treatment of fatigue in this population. Stone et al. also found an association between fatigue and dyspnea, and suggested that there might be a similar underlying physiological process. We were unable to find any significant association between fatigue and SpO2. Although dyspnea is as poorly understood as fatigue, a more detailed study focusing on this issue is needed. For example, other processes such as anemia should be studied to clarify this phenomenon, although our preliminary results failed to show any association between fatigue and low hemoglobin levels.

The association between fatigue and appetite loss was also an important finding. This relationship was independent of depression. Appetite loss may cause malnutrition, and so induce fatigue. Alternatively, both appetite loss and fatigue may lead to the same biological process such as cachexia, although studies have failed to show such an association.

Depression was also a correlated factor for fatigue. This suggests that the development of fatigue is associated with both physical and psychological factors, and this finding is consistent with other studies. In the general population, it is recognized that depression contrib-
utes to fatigue. Derogatis et al. reported that about 42% of cancer patients suffer from major depression or adjustment disorders. In some studies in lung cancer patients, the prevalence of depression has been reported as to be 15%. Psychological distress need to be taken into account when attempting to ameliorate fatigue, since treatment of depression is effective in most cases. On the other hand, 21.5% of patients in this study complained that fatigue had interfered with their mood. These results show the complexity of this association, since fatigue and depression might partly cause and partly result from each other, as Stone et al. have suggested. To investigate this complex phenomenon, further research is required.

Some other physical factors, such as low performance status, sputum, nausea, insomnia, and pain, appear to be strongly associated with fatigue. It is possible that the effect of other symptoms of cancer may promote the development of secondary fatigue, as suggested by Winningham et al. We consider that decreasing these correlated factors might also contribute to ameliorating fatigue in this population.

From a clinical standpoint, it is desirable to establish a method for screening for clinical fatigue. The present study indicated that both the CFS and FNS had well-accepted screening ability in patients with advanced lung cancer. Fatigue is often overlooked and may be underestimated by both physicians and cancer patients. Vogelzang et al. reported on the perception of fatigue by both patients and oncologists in heterogeneous cancer patients. In their study, 32% of cancer patients reported that fatigue affected their daily

<table>
<thead>
<tr>
<th>Sample Characteristics</th>
<th>With Clinical Fatigue (n = 80)</th>
<th>Without Clinical Fatigue (n = 77)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Performance Status (ECOG&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>0  9 (11)  21 (27)  0.01&lt;sup&gt;f&lt;/sup&gt;</td>
<td>1  64 (80)  54 (70)  0.76&lt;sup&gt;e&lt;/sup&gt;</td>
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<tr>
<td>1  64 (80)  54 (70)</td>
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<td>2  6 (8)  1 (1)  0.007&lt;sup&gt;f&lt;/sup&gt;</td>
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<tr>
<td>3  1 (1)  0 (0)  0.001&lt;sup&gt;f&lt;/sup&gt;</td>
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<tr>
<td>4  0 (0)  1 (1)  0.009&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>Body Temperature (°C)</td>
<td>0.32&lt;sup&gt;g&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>&lt;37.0  70 (88)  63 (82)  0.32&lt;sup&gt;g&lt;/sup&gt;</td>
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<tr>
<td>≥37.0  10 (13)  14 (18)  0.001&lt;sup&gt;g&lt;/sup&gt;</td>
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<tr>
<td>mean  SD  mean  SD  0.50&lt;sup&gt;e&lt;/sup&gt;</td>
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<tr>
<td>SpO&lt;sub&gt;2&lt;/sub&gt;&lt;sup&gt;b&lt;/sup&gt;</td>
<td>96.2  1.9  96.4  1.5  0.50&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>Heart Rate</td>
<td>83.0  13.0  82.3  13.7  0.98&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>Respiratory Rate</td>
<td>18.4  3.0  18.4  3.1  0.001&lt;sup&gt;f&lt;/sup&gt;</td>
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<tr>
<td>Sputum&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2.1  0.8  1.8  0.6  0.007&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>Cough&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2.1  0.8  2.0  0.6  0.14&lt;sup&gt;f&lt;/sup&gt;</td>
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<tr>
<td>Dyspnea at Rest&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.2  0.5  1.1  0.3  0.03&lt;sup&gt;f&lt;/sup&gt;</td>
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<tr>
<td>Dyspnea on Walking&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td>Appetite&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td>Nausea&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.3  0.6  1.1  0.3  0.009&lt;sup&gt;f&lt;/sup&gt;</td>
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<tr>
<td>Constipation&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.6  0.9  1.4  0.6  0.13&lt;sup&gt;f&lt;/sup&gt;</td>
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<td></td>
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<tr>
<td>Sleep&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.8  0.9  1.3  0.5  0.001&lt;sup&gt;f&lt;/sup&gt;</td>
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<td></td>
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<tr>
<td>Panic&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.7  0.8  1.4  0.6  0.001&lt;sup&gt;f&lt;/sup&gt;</td>
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<tr>
<td>WBC (10&lt;sup&gt;9&lt;/sup&gt; count/mm&lt;sup&gt;3&lt;/sup&gt;)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>60.3  19.1  62.8  23.9  0.001&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>Hemoglobin (g/dl)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>12.0  2.1  12.1  2.0  0.001&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>Albumin (g/dl)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>3.8  0.5  3.9  0.8  0.001&lt;sup&gt;d&lt;/sup&gt;</td>
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<tr>
<td>Psychological</td>
<td></td>
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<tr>
<td>Depression&lt;sup&gt;e&lt;/sup&gt;</td>
<td>6.9  3.8  3.8  3.0  0.001&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>Anxiety&lt;sup&gt;e&lt;/sup&gt;</td>
<td>5.1  3.5  2.9  2.4  0.001&lt;sup&gt;e&lt;/sup&gt;</td>
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</table>

<sup>a</sup>Defined by Eastern Cooperative Oncology Group.
<sup>b</sup>Oxygen-saturated hemoglobin measured with a finger pulse-oximeter.
<sup>c</sup>Symptoms were assessed by a 4-point Likert scale—1 = not at all to 4 = very much.
<sup>d</sup>Laboratory data were obtained from 81 patients.
<sup>e</sup>Hospital Anxiety and Depression Scale.
<sup>f</sup>Wilcoxon’s rank sum test.
<sup>g</sup>Chi-squared test.
routines significantly, but 74% considered fatigue to be a symptom that had to be endured. On the other hand, most oncologists (80%) believed that fatigue is generally overlooked or under-treated. Since fatigue may be sufficiently severe to interfere with daily life activities, it is essential for medical staff to be alert to the possibility of fatigue in these patients.

Recently Mendoza et al. suggested that a score of 7 or more on the 0–10 numerical scale in the Brief Fatigue Inventory (BFI) indicates severe fatigue.\textsuperscript{30} We were unable to examine the BFI classification since only 7.0% of participants in this study met Mendoza’s criteria, probably because subjects in this study were outpatients. It may also be questionable whether the number of interfered domains, used to define clinical fatigue, truly reflects the severity of fatigue. Further studies are required to establish a detailed severity classification for fatigue.

We conclude that fatigue is one of the most critical problems for ambulatory patients with advanced lung cancer. Dyspnea on walking, appetite loss, and depression are major factors that correlate with fatigue. This study has revealed that the CFS and FNS are useful screening tools for clinical fatigue. It is hoped that these findings will contribute to a better understanding of fatigue in this population, and facilitate earlier detection and treatment.

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References


25. Okuyama T, Akechi T, Kugaya A, et al. Develop-


