Clinical biopsychosocial risk factors for depression in lung cancer patients: a comprehensive analysis using data from the Lung Cancer Database Project

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Background: Various risk factors for depression in lung cancer patients have been suggested but have been examined separately in studies with relatively small sample sizes. The present study examined the biopsychosocial risk factors of depression in lung cancer patients, focusing on psychological factors in the largest patient sample reported to date.

Patients and methods: A total of 1334 consecutively recruited lung cancer patients were selected, and data on cancer-related variables, personal characteristics, health behaviors, physical symptoms, and psychological factors were obtained. The participants were divided into groups with or without depression using the Hospital Anxiety and Depression Scale.

Results: Among the recruited patients, 165 (12.4%) manifested depression. The results of a binary logistic regression analysis were significant (overall R², 36.5%), and a greater risk for depression was strongly associated with psychological factors, such as personality characteristics (neuroticism) and coping style (low fighting spirit, helplessness/hopelessness, and anxious preoccupation). Although the contributions of cancer-related variables, personal characteristics, health behaviors, and clinical state were relatively low, cancer stage, cancer type, sex, and age correlated significantly with depression.

Conclusion: Depression was most strongly linked with personality traits and coping style, and using screening instruments to identify these factors may be useful for preventive interventions.

Key words: coping, depression, lung carcinoma, personality, quality of life, supportive care.

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introduction

Lung cancer is the most common form of cancer and is the most common cause of cancer-related deaths worldwide [1]. As lung cancer is a life-threatening disease, its impact on patients’ psychological well-being has been widely studied. As shown by the results of many observational studies [2–14], lung cancer patients have high rates (9%–53%) of clinically significant depression. Depression in cancer patients creates great suffering, and many patients with depression develop suicidal ideation or suicidal behavior [15, 16]. Also, depression has a negative impact in terms of patient quality of life [17], patient decision making regarding cancer treatment [18], length of hospital stay [19], and caregiver distress [20] and may even affect survival [21].

Consideration of a wide range of risk factors, including biopsychosocial dimensions, and understanding which factors are strongly related to depression are critical for ongoing care and to identify patients who are at risk for depression, in addition to finding clues for effective interventions [22, 23]. Many studies have attempted to identify a set of factors that are consistently correlated, but problems regarding sampling have been encountered. Most previous studies have had a small sample size, with the exception of one study that simply combined data from three separate randomized clinical trials, creating a potential sampling bias [2].

Based on the results of previous studies, cancer-related variables such as cancer stage [11, 14], cell type [small-cell lung cancer (SCLC) or non-SCLC] [2], or performance status (PS) [2]; personal characteristics such as age [11, 24], sex [25], marital status [25], living alone [25], presence of a confidant [14, 25, 26], employment status [27], or educational status [12]; health behaviors such as alcohol intake [11], smoking [28], or body weight [29]; and physical symptoms such as pain [11], dyspnea [30], or fatigue [2, 31] have been suggested as risk factors for depression in patients with lung cancer.

Psychological factors also have been studied in lung cancer patients, and a few studies have suggested that personality traits or coping patterns [25, 32–34] are correlated with depression. Adaptation to a major illness is readily understood in terms of stress and coping theory [35, 36], and individual personality or coping style may determine whether patients achieve a good psychological appraisal or develop depression. Bardwell et al. [37] showed that in breast cancer patients, psychological factors are strongly linked with depression, while other variables such as cancer-related variables, personal characteristics, and physical symptoms have a minimal contribution. Based on these perceptions, we hypothesized that psychological factors such as personality traits or coping patterns may have a greater association with depression than other variables in lung cancer, but few studies have simultaneously examined biopsychosocial factors to decide which variables have the strongest correlations.

The purpose of this study was to obtain an understanding of the biopsychosocial risk factors associated with depression in lung cancer patients, focusing on psychological factors. Previously reported multifactorial variables were combined together into an integrated model, and we attempted to clarify which ones have the most profound effects on depression. As this study was carried out using the largest consecutive sampling reported to date, conclusive results regarding the biopsychosocial factors that are correlated with depression in lung cancer patients were anticipated, providing clues for efficient ongoing care.

patients and methods

participants

The data were obtained from the Lung Cancer Database Project at the National Cancer Center, Japan; Nakaya et al. [38] previously reported the study design in detail. Between July 1999 and July 2004, a total of 1622 consecutive patients who were newly diagnosed as having lung cancer were enrolled in the study after the disclosure of their diagnosis by their attending physician. Of these, written informed consent was not obtained from 41 patients; consequently, 1581 patients were included in the present analysis. These patients were asked to complete the questionnaires by themselves at home before their admission to the hospital. However, we excluded 247 patients with missing responses for the items related to the subscales of this study. Finally, we analyzed 1334 out of 1622 patients (82.2%) in the present study.

The group of patients who were excluded (n = 247) did not differ significantly from the group of patients who participated (n = 1581) in terms of sex, age, PS, or cancer stages.

measurements

cancer-related variables, personal characteristics, health behaviors, and clinical state

Information, including the age at diagnosis, sex, socioeconomic variables (educational level, employment, marital status, cohabitation, and presence of a confidant), smoking status, and severity of clinical symptoms (self-reported dyspnea, pain, and dullness) was obtained from the self-administered questionnaires. The alcohol variable was calculated based on the responses to a semiquantitative food frequency questionnaire created for a population-based prospective study in Japan [39].

Medical information such as the clinical stage, weight and height, PS, and cancer type was obtained from the patients’ medical charts by attending physician, and the body mass index (BMI) was calculated (kg/m²). The clinical stage of the lung cancer was classified according to the TNM (tumour–node–metastasis) classification of the International Union Against Cancer. The PS was assessed by the attending physician of each patient using the Eastern Cooperative Oncology Group criteria [40]. Self-reported dyspnea, pain, and fatigue at the time of diagnosis were self-graded using a five-point scale: 1 (absent), 2 (little), 3 (moderate), 4 (severe), or 5 (very severe).

psychological aspects

Eysenck personality questionnaire—revised. Personality traits were measured using the Japanese version of the Eysenck Personality Questionnaire—Revised (EPQ-R) [41, 42]. The EPQ-R measures four personality dimensions labeled as Psychoticism (P), Extraversion/Introversion (E), Neuroticism (N), and Lie (L), each containing 12 items. Each item is answered as ‘yes’ or ‘no’ and coded as 1 or 0, respectively, with the total subscale scores for the items ranging from 0 to 12. The Psychoticism scale is a measure of tough-mindedness, aggressiveness, coldness, and egocentricity. The Extraversion scale represents sociability, liveliness, and surgency, and the Neuroticism scale describes emotional instability and anxiousness. Finally, the Lie scale is a measure of dissimulation.
The Japanese version of the EPQ-R was developed by Hosokawa et al. [42], and its reproducibility and validity was examined among 329 college students and 253 adults. The Cronbach coefficient, a measure of internal consistency, was >0.70 for all subscales except psychotism (0.42 for college students and 0.48 for adults). Test–retest reliability coefficients for the four subscales over a 6-month period ranged from 0.70 to 0.85, indicating substantial stability. A confirmatory factor analysis supported the original theoretical structure of the four scales proposed by Eysenck et al. [41].

mental adjustment to cancer scale

The coping style was measured using the Japanese version of the Mental Adjustment to Cancer (MAC) scale [43, 44], a 40-item self-rated scale. The scale consists of five subscales: fighting spirit (16 items), anxious preoccupation (9 items), fatalism (8 items), helplessness/hopelessness (6 items), and avoidance (1 item). The patients were asked to rate each question on a scale of 1 (definitely does not apply to me) to 4 (definitely applies to me), and higher scores indicate a greater tendency of the patients to adopt the mental adjustment style.

In a previous study, we developed the Japanese version of the MAC and examined its reproducibility and validity among 455 cancer patients [43]. The Cronbach coefficient was >0.60 for all subscales. The test–retest reliability coefficients of the five subscales over a 6-month period were >0.64, indicating substantial stability. A confirmatory factor analysis supported the original theoretical structure of the five scales proposed by Watson et al. [44].

hospital anxiety and depression scale

Depressive symptoms were measured using the Japanese version of the Hospital Anxiety and Depression Scale (HADS) [45, 46]. We used the depression subscale, which contains seven questions; each question is rated on a four-point scale of 0–3. Higher scores indicate greater depressive symptoms. In this study, subscale scores ≥11 were defined as depression, as this threshold was correlated with the presence of major depressive disorder [46].

statistical analysis

All the patients were divided into depressed or not depressed groups and their characteristics were compared using \( \chi^2 \), Mann–Whitney \( U \), and \( t \)-tests. Binary logistic regression was used to identify risk factors in a multivariate analysis (Nagelkerke’s \( R^2 \) parameter was used to gauge model fit). Following the method used by Bardwell et al. [37] in study examining depression in breast cancer patients, a hierarchical design (forced entry) was chosen for the binary logistic regression model. Cancer-related variables were first entered to determine whether they were capable of explaining the significant variance in depressive symptoms by themselves. Personal characteristics (block 2), health behaviors (block 3), and physical symptoms (block 4) were subsequently entered. Finally, because they were expected to explain the most variance, psychological factors were entered last (block 5).

In all the statistical evaluations, \( P \) values of <0.05 were considered to be statistically significant; all the \( P \) values were two-tailed. SPSS20 J for Windows statistical software (SPSS Japan Institute Inc., Tokyo, Japan, 2010) was used for all the data analyses.

results

participant demographics

The participants averaged 64.2 years of age (range = 26–88 years) and 71.4 % were men; 82.8 % were married. The mean BMI was 22.3 kg/m². Regarding education, 32.1 % had ≤9 years of education and 67.9 % had >10 years of education. As for the clinical stage, 38.3 % were diagnosed as having stage I, 7.0 % had stage II, 8.9 % had stage IIIA, 19.5 % had stage IIIB, and 26.3 % had stage IV. Regarding cancer type, 11.6 % of the patients had SCLC, whereas 88.4 % had other types of cancer. Regarding smoking status, 50.7 % were current smokers, 26.2 % were ex-smokers, and 23.1 % were nonsmokers. As for alcohol intake, 67.1 % reported an ethanol intake of <150 g/week, 13.7 % reported an intake of 150–300 g/week, and 19.2 % reported an intake of >300 g/week.

t, Mann–Whitney, and \( \chi^2 \) tests

Among the 1334 participants, 165 (12.4 % ) were classified as depressed and the other 1169 (87.6 % ) were classified as not depressed. Regarding cancer-related variables, the depressed group had a more advanced cancer stage and a severer PS (supplemental Table S1, available at Annals of Oncology online). However, no significant difference according to cancer type was observed. The groups did not differ with regard to personal characteristics including age, sex, marital status, cohabitation, existence or nonexistence of a confidant, education level, employment status, and BMI. As for health behaviors, the groups did not differ with regard to alcohol intake and smoking. Also, the depressed group had more severe dyspnea, pain, and dullness. Moreover, the depressed group had lower scores for fighting spirit and higher scores for helpless/hopeless, anxious preoccupation, and fatalism in the MAC scale. Additionally, the depressed group had greater introversion and neurotic scores and lower lie score on the EPQ-R.

binary logistic regression

The binary logistic regression was significant (\( R^2 = 36.5 \% \); \( P < 0.05 \)) (Table 1). The variance in the depressed or nondepressed groups was explained by each block of variables as follows: cancer-related, 5.2 % ; personal characteristics, additional 2.5 % ; health behavior, additional 0.5 % ; physical symptoms, additional 3.7 % ; and psychological factors, additional 24.6 % .

Before including psychological factors in the analysis of blocks 1–4, the following factors explained a significant portion of the variance in the depressed and nondepressed statuses: cancer stage, cancer type, dyspnea, and dullness (Table 1). After the inclusion of psychological factors, cancer stage, sex, and dullness from blocks 1–4, and among the psychological factors, fighting spirit, helpless/hopeless, anxious preoccupation, and neuroticism were significantly associated (Table 1).

discussion

In the present study, 12.4 % of the studied patients developed depression after the disclosure of their diagnosis of lung
cancer, and the biopsychosocial-associated factors of depression were comprehensively investigated in this group of lung cancer patients, who were the largest consecutive patient sample size reported to date. Changes in the variance of the multivariate analysis suggested that the associations of cancer-related variables, personal characteristics, or physical symptoms were comparatively small, whereas the associations of psychological factors, such as coping styles or personality factors, were much greater. Patients with a fighting spirit may be able to adjust to their situation, whereas neurotic patients may tend to feel anxious or helplessness/hopelessness and may develop severe depression.

In general, the underlying personality is a well-known and significant concomitant of depression. Neuroticism is especially promising with regard to its relationship to the phenomenology and outcome of depression and may represent an underlying

<table>
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<tr>
<th>Block</th>
<th>Nagelkerke’s $R^2$</th>
<th>Categories</th>
<th>Variables</th>
<th>Before entry of psychosocial variables</th>
<th>After entry of psychosocial variables</th>
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<td>Change</td>
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<td>OR (95% CI)</td>
<td>$P$</td>
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<td>Age 50–60 years</td>
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<td>Age &gt;60</td>
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<td>Sex</td>
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<td>Married (yes/no)</td>
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<td>Living alone (yes/no)</td>
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<td>Confident person (yes/no)</td>
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<td>Education (&lt;9/≥9)</td>
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<td>Education (&lt;9/unknown)</td>
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<td>Employment (fulltime/others)</td>
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<td>BMI &lt;25 (reference)</td>
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<td>BMI 25–30</td>
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<td>BMI &gt;30</td>
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<td>Alcohol 150–300</td>
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<td>Alcohol &gt;300</td>
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<td>Smoking status: current smoker</td>
<td>0.90 (0.60–1.35)</td>
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<td>Smoking status: ex-smoker</td>
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<td>1.61 (1.07–2.43)</td>
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<td>Pain (moderate–very severe/absent–little)</td>
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<td>Fatigue (moderate–very severe/absent–little)</td>
<td>2.19 (1.48–3.27)</td>
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<td>Block 5</td>
<td>0.365</td>
<td>0.246</td>
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<td>Fighting spirit</td>
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<td>Helpless/hopeless</td>
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<td>Anxious preoccupation</td>
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<td>Avoidance</td>
<td>0.92 (0.77–1.10)</td>
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<td>EPQ-R (continuous variable) Extraversion/introversion</td>
<td>0.99 (0.93–1.05)</td>
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<td>Neuroticism</td>
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<td>Lie</td>
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<td>Psychoticism</td>
<td>1.01 (0.89–1.15)</td>
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</table>

BMI, body mass index; CI, confidence interval; EPQ-R, the Eysenck Personality Questionnaire—Revised; HADS-D, the Hospital Anxiety and Depression Scale (scores ≥11 indicate clinically significant depressive symptoms); MAC Scale, the Mental Adjustment to Cancer Scale; OR, odds ratio; PS, performance status.

Table 1. Results of binary logistic regression analysis: risk factors versus HADS-D status (depressed/not depressed)
heritable trait of etiologic significance [22, 23, 47]. Our results supported these speculations in lung cancer patients, and even after various factors were considered, the association between personality and depression was especially large.

Moreover, a recent study has shown that neuroticism exerts huge economic costs on health care [48]. As personality traits are generally thought to remain unchanged, neurotic patients should be regarded as having a very high risk of depression. Preventive strategies or the early detection of depression should be considered and this may reduce subsequent economic costs. Examining depression and personality traits by using such scales as the State and Trait Anxiety Inventory may be important to elucidate discriminative traits in detail [49].

Also, how patients cope with and adjust to threats is reportedly associated with depression. A fighting spirit has been consistently shown to be correlated with fewer symptoms of depression [44, 50], whereas individuals with hopelessness or anxious preoccupation are more likely to be depressed [51]. In our study, the significance of coping style was also supported in a multivariate analysis and accounted for a large part of the risk of depression. Unlike personality, coping is considered to be changeable and should be targeted by interventions such as cognitive behavioral therapy [52].

Compared with psychological variables, the lower significance of cancer-related variables, personal characteristics, and physical symptoms was suggested by a hierarchical binary logistic regression, as the model fit of these blocks was comparatively lower. Among them, however, cancer stage, cancer type, and sex remained significant in the final multivariate analysis, and we should take these factors into consideration as part of a comprehensive model. In breast cancer patients, none of the cancer-related variables or personal characteristics were associated after the psychological factors were taken into consideration [37], and differences among the cancer sites were noted. When caring for cancer patients, the specific nature of each cancer site should be considered.

Concerning the cancer stage, only patients with stage IIIIB had a significantly higher risk of depression than patients with stage I in a multivariate analysis; for stage IV, only a tendency toward a risk was noted, although the odds ratio was sufficiently high. Although our sample size was comparatively large, it may be insufficient to show the difference for each stage. Although the interpretation of the present data is debatable, we consider our results to support the idea that patients with advanced stages of cancer tend to be affected by depression more commonly than patients with early disease, as reported previously [11, 14].

Regarding cancer type, our results showed that patients with SCLC had a lower risk of depression than those with non-SCLC, contrary to our expectation. The poor prognosis of SCLC is likely to create a larger physical and psychological burden for patients, and a previous study has shown that patients with SCLC tended to be affected by depression [2]. Our surprising finding may represent a type I error, and further validation is needed.

Many factors previously suspected of being risk factors for depression were not replicated in our study. Among them, frequently reported factors, such as PS, dyspnea, pain, and dullness, were correlated in a univariate analysis, but the correlations disappeared when all the variables were entered into a multivariate analysis. These factors may have had little true relation and should be excluded from a comprehensive model.

Our study had several limitations. First, a sampling bias was present in the data because all the subjects attended a single institution and thus were not representative of lung cancer patients in general. Second, our results provide a snapshot of distress and coping mechanisms soon after cancer diagnosis. Depression and coping styles may evolve naturally over time once patients begin treatment, and the present results may not be applicable to other settings. Third, we used a self-administered questionnaire, which may create a response bias. We did not use a structured psychiatric interview in this study (such as the Structured Clinical Interview for DSM-IV, a widely recognized standard). HADS has been shown to be a reliable and valid screening tool for detecting depression in patients with cancer [46, 53] and is widely used in the field of oncology [54]. However, depressed patients tend to be more likely to report negatively on other self-report questionnaires [55], such as the EPQ-R or MAC. Finally, a causal relationship between factors and depression could not be confirmed because of the cross-sectional design of this study. To clarify the independent effects of each factor, a further longitudinal study is needed.

In conclusion, our study using a large-scale registry enabled a comprehensive understanding of the clinical biopsychosocial-associated factors for depression in lung cancer patients. When caring for lung cancer patients, the specific nature of each patient should be considered. In the present model, psychological factors had a larger association with depression than other variables. Strategies targeting patients with neurotic personality traits and providing cognitive behavioral therapy focusing on their coping styles, such as hopelessness or anxious preoccupation, may be reasonable for alleviating depression [52].

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disclosure

The authors declare no conflicts of interest.
references

Deterioration in quality of life (QoL) in patients with malignant ascites: results from a phase II/III study comparing paracentesis plus catumaxomab with paracentesis alone


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Background: Malignant ascites (MA) is associated with poor prognosis and limited palliative therapeutic options. Therefore, quality of life (QoL) assessment is of particular importance to demonstrate new treatment value. Following the demonstration of the superiority of catumaxomab and paracentesis over paracentesis on puncture-free survival, this analysis aimed at comparing deterioration in QoL between both the treatment options.

Patients and methods: In a randomised, multicentre, phase II/III study of patients with MA due to epithelial cell adhesion molecule (EpCAM) positive cancer, the QoL was evaluated using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 items (EORTC QLQ-C30) questionnaire at screening, 1, 3 and 7 months after treatment and in the case of re-puncture on the day of paracentesis. Time to first deterioration in QoL was defined as a decrease in the QoL score of at least five points and compared between the catumaxomab (n = 160) and control (n = 85) groups using the log-rank test and Cox proportional hazards models adjusted for baseline score, country and primary tumour type.

Results: Deterioration in QoL scores appeared more rapidly in the control than in the catumaxomab group (median 19–26 days versus 47–49 days). The difference in time to deterioration in QoL between the groups was statistically significant for all scores (P < 0.01). The hazard ratios ranged from 0.08 to 0.24 (P < 0.01).

Conclusions: Treatment with catumaxomab delayed deterioration in QoL in patients with MA. Compared with paracentesis alone, catumaxomab enabled patients to benefit from better QoL for a prolonged survival period.

Key words: deterioration, malignant ascites, quality of life

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