Evaluation of a prognostic scoring system based on the systemic inflammatory and nutritional status of patients with locally advanced non-small-cell lung cancer treated with chemoradiotherapy

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ABSTRACT

Systemic inflammation and poor nutritional status have a negative effect on the outcomes of cancer. Here, we analyzed the effects of the pretreatment inflammatory and nutritional status on clinical outcomes of locally advanced non-small-cell lung cancer (NSCLC) patients treated with chemoradiotherapy. We retrospectively reviewed 89 patients with locally advanced NSCLC treated with chemoradiotherapy between July 2006 and June 2013. Serum C-reactive protein (CRP) was assessed as an inflammatory marker, and serum albumin, body mass index (BMI) and skeletal mass index were assessed as nutritional status markers. The relationships between these markers and overall survival (OS) were assessed. The median OS was 24.6 months [95% confidence interval (CI): 19.4–39.3 months]. During follow-up, 58 patients (65%) had disease recurrence and 52 patients (58%) died. In multivariate Cox hazard analysis, CRP levels and BMI approached but did not achieve a significant association with OS (P = 0.062 and 0.094, respectively). Recursive partitioning analysis identified three prognostic groups based on hazard similarity (CRP-BMI scores): 0 = CRP < 0.3 mg/dl and BMI ≥ 18.5 kg/m², 1 = CRP ≥ 0.3 mg/dl and BMI ≥ 18.5 kg/m², and 2 = CRP ≥ 0.3 mg/dl and BMI < 18.5 kg/m². The CRP-BMI score was significantly associated with OS (P = 0.023). Patients with scores of 0, 1 and 2 had median OS of 39.3, 24.5 and 14.5 months, respectively, and the scores also predicted the probability of receiving salvage treatment after recurrence. The CRP-BMI score is thus a simple and useful prognostic marker of clinical outcome for patients with locally advanced NSCLC treated with chemoradiotherapy.

Keywords: systemic inflammatory response; nutritional status; non-small-cell lung cancer; chemoradiotherapy; recursive partitioning analysis

INTRODUCTION

Lung cancer is the most common cause of cancer-related death worldwide [1]. Non-small-cell lung cancer (NSCLC) accounts for at least 80% of all lung cancer cases and presents as locally advanced disease in 25–30% of cases. Chemoradiotherapy or radiotherapy is a standard regimen for treatment of inoperable locally advanced NSCLC [2]; however, the prognosis for these patients is poor, with an estimated 5-year overall survival (OS) rate of <20% (range 15–40%) [3]. Treatment of patients with NSCLC is mainly based on the TNM staging system [2]. However, this system provides limited information on the best treatment option, and, in some patients, the disease progresses within a few months. Thus, identification of more sensitive prognostic factors would help to optimize the therapeutic approach for patients with NSCLC.
Systemic inflammation, poor nutritional status, and sarcopenia are increasingly recognized to be associated with low survival rates in various malignancies [4–7]. The effect of systemic inflammation on OS has been examined in early stage NSCLC patients treated with surgery or radiotherapy and in advanced stage NSCLC patients treated with chemotherapy [8–10]. A few studies have also evaluated the influence of poor nutritional status and sarcopenia on OS in NSCLC patients treated with surgery or chemotherapy [11, 12]. However, the effect of the pretreatment systemic inflammatory and nutritional status on clinical outcomes of locally advanced NSCLC patients treated with chemoradiotherapy has not been examined.

A combination of factors reflecting systemic inflammatory and nutritional status is widely used as a prognostic factor and is considered to have greater sensitivity and precision than single prognostic factors [4, 6, 9]. However, the specific parameters used to generate the combination score differ with the type of cancer and treatment [13, 14], and methods for calculating combination scores also differ [15]. Thus, there is a need to identify the most appropriate combination score to predict prognosis in specific cancers [14, 16]. Although serum C-reactive protein (CRP) is widely used as a systemic inflammatory response index, the optimal nutritional index to create combination scores has yet to be identified; those used to date include serum albumin (Alb), body mass index (BMI) and skeletal mass index (SMI). Accordingly, the nutritional index that best predicts outcomes for locally advanced lung cancer after chemoradiotherapy is unclear [10, 13, 17]. Here, we tested CRP and the nutritional indexes Alb, BMI and SMI to determine the optimal combination for predicting the prognosis of patients with locally advanced NSCLC treated with chemoradiotherapy.

**MATERIALS AND METHODS**

**Patients**

Patients who were treated with definitive chemoradiotherapy for locally advanced NSCLC were eligible for this retrospective review. Exclusion criteria included: treatment with radiotherapy alone, treatment with surgery after chemoradiotherapy, history of other malignancies within 5 years, or patients that we couldn’t follow up due to them not being available. The diagnosis of NSCLC was confirmed by histological evaluation. All patients were staged with thoracoabdominal computed tomography (CT) and magnetic resonance imaging or CT of the brain. The clinical stage at presentation was subsequently categorized according to the TNM classification of malignant tumors (7th edition).

Medical records and clinical laboratory data for the patients were retrospectively collected and anonymized to exclude personal information. The study protocol was approved by the Institutional Review Board of R0718.

**Treatments and outcomes**

Patients received radical radiotherapy and chemotherapy consisting of vinorelbine plus cisplatin or paclitaxel plus carboplatin with each combination being administered either concurrently or sequentially. The prescribed radiation dose was 50–66 Gy delivered in 2.0 Gy daily fractions, five times a week. Patients were treated with elective nodal irradiation therapy, which prophylactically targeted uninvolved mediastinal nodal regions. A shrinking field technique was used, with opposed anterior/posterior fields covering the primary tumor and elective mediastinal nodes, followed by cone-down fields angled off the spinal cord. Patients were followed up at an outpatient clinic every 3 months for the first year and every 6 months thereafter. Telephone interviews were carried out for patients who failed to attend the outpatient clinic.

**Data collection**

OS was defined as the time from the date of first treatment to the date of death or date of last contact if the exact date of death was unavailable. Progression-free survival (PFS) was defined as the time from the date of first treatment to the date of disease progression or death from any cause.

Age, gender, height, weight, clinical stage, tumor histology, performance status (Eastern Cooperative Oncology Group, ECOG-PS), history, laboratory data, and clinical outcome data were retrospectively obtained from hospital-based registries and medical records. Blood samples were also obtained before treatment for measurement of serum CRP and Alb. The cut-offs for abnormal elevation of serum CRP and Alb were 0.3 mg/dl and 3.5 g/dl, respectively, based on the reagent instruction manual or past studies [18]. BMI was calculated as: weight (kg)/height² (m²). Patients were classified according to the World Health Organization system as underweight at BMI < 18.5 kg/m² [19].

**Table 1. Clinicopathological patient characteristics**

| Characteristic | n (%) |
|----------------|-------|
| Median age (years) | 66 (42–81) |
| Gender | |
| Male | 67 (75) |
| Female | 22 (25) |
| PS | |
| 0 | 50 (56) |
| 1 | 36 (41) |
| 2 | 3 (3) |
| Histology | |
| SqCC | 40 (45) |
| Adenocarcinoma | 36 (40) |
| Others | 13 (15) |
| cStage | |
| IIIA | 34 (38) |
| IIIB | 55 (62) |

Age is presented as years (range); all other data are presented as the number (and %) of patients (n = 89). PS = performance status, ECOG-PS = Eastern Cooperative Oncology Group PS, SqCC = squamous cell carcinoma, cStage = clinical stage.
Sarcopenia (loss of skeletal muscle mass) was assessed by measuring the total psoas muscle area at the L3 level on the pretreatment CT, which is significantly related to whole-body tissue mass in healthy adults and cancer patients [20–22]. Measurements were performed with manual outlining of the psoas muscle border and setting the density threshold at between −30 and 110 Hounsfield units. This value was normalized to the square of body height to provide the skeletal mass index (SMI), calculated as: total psoas muscle area at L3 (cm²)/height² (m²) [22, 23]. When stratified by gender, the mean adjusted SMI was significantly lower for women than for men. The thresholds were set at the lowest quartile SMI for men and women [24].

Statistical analysis
For univariate analysis, relationships between systemic inflammatory or nutritional status and OS were assessed using the Kaplan–Meier method and a log-rank test. Multivariate survival analysis and calculation of hazard ratios (HR) was performed using Cox regression analysis. Fisher’s exact test, the Chi-square test, and the log-rank trend test were used to assess the association between scores and clinical characteristics. For regression tree growing during recursive partitioning analysis, the log rank test was used as the splitting criterion [25, 26]. The dichotomous prognostic parameter that resulted in the largest separation of survival at each node with P < 0.05 was selected as the criterion for that node. All analyses were carried out with EZR ver. 2.2-3 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [27], with P < 0.05 (two-tailed) considered significant.

RESULTS
Eighty-nine patients received definitive chemoradiotherapy and follow-up after initial treatments for locally advanced NSCLC at our institution between July 2006 and June 2013. Characteristics of the 89 included patients are shown in Table 1. Chemotherapy and radiotherapy were given concurrently to 85 patients (96%), of whom 46 (52%) received cisplatin-based chemotherapy and 39 (44%) received carboplatin-based chemotherapy. The 4 patients (4%) received carboplatin-based chemotherapy sequentially. Most patients (n = 84; 94%) received a total radiation dose of at least 60 Gy (range 50–66 Gy) in 2.0 Gy daily fractions.

The median follow-up period was 21 months (range 2–103 months). In total, 58 (65%) had disease recurrence and 52 patients (58%) died during follow-up. The median OS and PFS were 24.6 months [95% confidence interval (CI): 19.4–39.3] and 12.1 months (95% CI: 9.0–16.3), respectively. In univariate analysis, there was a significant association between OS and gender (P = 0.02).

The relationships between pretreatment systemic inflammatory and nutritional status and OS are shown in Table 2. The thresholds of SMI were set at 3.73 cm²/m² for men and 2.45 cm²/m² for women. On univariate analysis, CRP was significantly associated with OS (P = 0.046). On multivariate analysis, elevated CRP (≥0.3 mg/dl) and low BMI (<18.5 kg/m²) were correlated with shorter OS. Alb and SMI were not correlated with OS.

Recursive partitioning analysis
Recursive partitioning analysis for OS was performed with stepwise variable selection of inflammatory and nutritional status factors:

Table 2. Univariate and multivariate analysis of the association between overall survival and systemic inflammatory and nutritional status

| Characteristic | Number of patients n (%) | Univariate survival analysis | Multivariate survival analysis |
|----------------|--------------------------|-----------------------------|--------------------------------|
|                |                          | HR (95% CI)                 | P value | HR (95% CI) | P value |
| CRP (mg/dl)    |                          |                             |         |             |         |
| <0.3           | 36 (40)                  |                             | 0.046   | 0.062       |         |
| ≥0.3           | 53 (60)                  | 1.85 (1.01–3.37)            | 1.74 (0.97–3.12) |         |
| Alb (g/dl)     |                          |                             | 0.91    |             |         |
| <3.5           | 16 (18)                  |                             |         |             |         |
| ≥3.5           | 73 (82)                  | 1.34 (0.57–3.16)            |         |             |         |
| BMI (kg/m²)    |                          |                             | 0.223   | 0.094       |         |
| <18.5          | 24 (27)                  |                             |         |             |         |
| ≥18.5          | 65 (73)                  | 0.65 (0.33–1.29)            | 0.60 (0.33–1.09) |         |
| SMI (cm²/m²)   |                          |                             | 0.873   |             |         |
| <threshold     | 22 (25)                  |                             |         |             |         |
| ≥threshold     | 67 (75)                  | 0.94 (0.45–1.94)            |         |             |         |

HR = hazard ratio, CI = confidence interval, CRP = C-reactive protein, Alb = albumin, BMI = body mass index, SMI = skeletal muscle index. SMI thresholds were 3.73 cm²/m² for men and 2.45 cm²/m² for women.
CRP (<0.3 or ≥0.3 mg/dl), Alb (<3.5 or ≥3.5 g/dl), BMI (<18.5 or ≥18.5 kg/m²) and SMI (<threshold or ≥threshold). The regression tree obtained is shown in Fig. 1. The top node contained CRP as the predictor variable. For patients with elevated CRP, BMI became the prognostic factor. The CRP-BMI scores were defined as: 0 = CRP < 0.3 mg/dl, 1 = CRP ≥ 0.3 mg/dl and BMI ≥ 18.5 kg/m², and 2 = CRP ≥ 0.3 mg/dl and BMI < 18.5 kg/m². Figure 2 shows the Kaplan–Meier curves for OS stratified by the CRP-BMI scores. There was a significant trend between the CRP-BMI score and OS rate using the log-rank trend test (P = 0.023). The 2-year OS rates and median OS times for patients with CRP-BMI scores of 0, 1 and 2 were 63.7% and 39.3 months, 50.1% and 24.5 months, and 26.9% and 14.5 months, respectively. Correlations between the CRP-BMI score and clinical characteristics are shown in Table 3. Only gender significantly correlated with the CRP-BMI score (P = 0.001). We assessed CRP-BMI score separately in each gender group. The higher CRP-BMI tended to be associated with worse OS for each gender. The Kaplan–Meier curves for OS stratified by the CRP-BMI scores are shown in Fig. 3a for men and Fig. 3b for women. The higher CRP-BMI tended to be associated with worse OS for each gender (P = 0.070 for men and 0.191 for female).

Recurrence

Of the 58 patients with recurrent disease, 27 (30.3%) developed local recurrence, 16 (18.0%) developed regional recurrence (defined as lymph node recurrence in the mediastinum) and 41 (46.1%) developed distant metastasis, including overlapping recurrence (Table 4). After disease recurrence, salvage treatment was prescribed

Table 3. Relationships between C-reactive protein–body mass index score and clinical characteristics

| Characteristic | CRP-BMI score |
|----------------|---------------|
|                | 0 | 1 | 2 | P value |
| Age (years)    |   |   |   | 0.469   |
| ≥70            | 16 (43) | 12 (33) | 9 (24) |
| <70            | 20 (38) | 27 (52) | 5 (10) |
| Gender         | 0.001 |
| Male           | 20 (30) | 33 (49) | 14 (21) |
| Female         | 16 (73) | 6 (27) | 0 (0) |
| PS             | 0.362 |
| 0              | 24 (48) | 20 (40) | 6 (12) |
| 1              | 12 (33) | 17 (52) | 7 (19) |
| 2              | 0 (0) | 2 (67) | 1 (33) |
| Histology      | 0.753 |
| SqCC           | 15 (38) | 20 (50) | 5 (12) |
| Adenocarcinoma | 15 (42) | 14 (39) | 7 (19) |
| Others         | 6 (46) | 5 (38) | 2 (15) |
| cStage         | 0.371 |
| IIIA           | 15 (44) | 16 (47) | 3 (9) |
| IIIB           | 21 (38) | 23 (42) | 11 (20) |

CRP-BMI = C-reactive protein–body mass index score, PS = performance status, ECOG-PS = Eastern Cooperative Oncology Group PS, SqCC = squamous cell carcinoma, cStage = clinical stage.
for 46 patients (79.3%). Significantly more patients who received salvage treatment had CRP-BMI scores of 0 or 1 than a score of 2 ($P < 0.01$). Of the 9 patients who developed recurrence and had a CRP-BMI score 2, 6 could not receive salvage treatments because of their medical condition or history, such as interstitial pneumonia or renal failure. The median survival time after recurrence was longer for patients with CRP-BMI scores of 0 or 1 than for those with a score of 2.

**DISCUSSION**

The TNM staging system, which classifies cancer mainly according to the size and extension of the primary tumor, its lymphatic involvement, and the presence of metastases, is used in clinical practice to determine treatment for lung cancer patients [2, 28, 29]. However, this staging system sometimes fails to predict patient prognosis and may not offer appropriate clinical practice guidance. Indeed, patients at the same TNM stage may have other conditions that influence treatment outcomes. Thus, there is a need to identify more sensitive and convenient pretreatment prognostic factors to enable more personalized treatment. Many studies have examined the relationships between pretreatment systemic inflammatory status, nutritional status, and skeletal muscle mass and the outcomes of treatment for cancer [18, 30]. Although this has also been examined in NSCLC, most studies have involved surgical treatments [8, 11, 31]. In this study, we evaluated these relationships in patients with locally advanced NSCLC treated with chemoradiotherapy.

|                | Total       | CRP-BMI score |
|----------------|-------------|---------------|
|                | Total       | 0             | 1             | 2             |
| n = 89 (%)     | n = 36 (%)  | n = 39 (%)    | n = 14 (%)    |
| Total recurrence | 58 (65)     | 24 (67)       | 25 (64)       | 9 (64)        |
| Local recurrence | 27 (30)     | 10 (28)       | 12 (31)       | 5 (36)        |
| Regional recurrence | 16 (18)   | 8 (22)        | 6 (15)        | 2 (14)        |
| Metastasis      | 41 (46)     | 16 (44)       | 18 (46)       | 7 (50)        |
| Salvage treatment for recurrence | 46 (79)   | 23 (96)       | 20 (80)       | 3 (33)        |
| Median survival time after recurrence (months) | 10.3     | 12.3          | 10.2          | 5.2           |

CRP-BMI = C-reactive protein–body mass index.
Several serum markers have been investigated as predictors of systemic inflammatory status and prognosis of patients with NSCLC, but none are available for use in daily practice. Serum CRP level is widely used in the diagnosis of acute and chronic systemic inflammation and is a prognostic factor for patients with malignant tumors such as hepatocellular carcinoma, esophageal cancer, and colon cancer [32–34]. Some studies of NSCLC patients treated with surgery or chemotherapy have also assessed CRP as an independent risk factor [35–37]. In the present study, elevated pretreatment serum CRP tended to correlate with poor OS, consistent with previous studies. Thus, CRP may be a prognostic factor for locally advanced NSCLC patients treated with chemoradiotherapy.

Serum Alb is commonly used to assess nutritional status. Hypoalbuminemia (Alb < 3.5 g/dl) often reflects malnutrition and may be a predictor of survival in patients with NSCLC after curative pulmonary resection [38]. However, in our study, hypoalbuminemia was not a prognostic factor in univariate analysis. Recovery of Alb level is important after surgery [39], but radical chemoradiotherapy is a less invasive treatment than surgery. This may explain why hypoalbuminemia was not associated with a risk of complication and thus did not affect the post-chemoradiotherapy outcome.

BMI is also widely used to evaluate nutritional status [40]. A Phase III trial of first line systemic chemotherapy for advanced NSCLC in 2684 patients showed that BMI ≥ 18.5 kg/m2 indicated a better prognosis than BMI < 18.5 kg/m2 [41]. This may be related to the difference in rates of treatment discontinuation due to disease progression or death in that study, which were 52.3% for the underweight patients and 42.3% for the obese patients. In our study, a similar trend was found for the relationship between BMI and discontinuation of treatment at the time of recurrence. The OS for patients with BMI < 18.5 kg/m2 was also worse than for those with BMI ≥ 18.5 kg/m2.

Sarcopenia, which reflects degenerative loss of skeletal muscle mass, is an objective indicator of cancer cachexia and a predictor of worse clinical outcomes in several studies of malignancy [42, 43]. This condition may reflect increased metabolic activity of more aggressive tumors, leading to systemic inflammation and muscle wasting [44]. However, in our study, SMI was not a significant prognostic factor for OS. The reason for this result is unclear, but most studies have examined SMI in the context of postoperative complications in abdominal surgery, and SMI obtained by measuring the total psoas muscle area at L3 may have little relationship to outcomes of thoracic cancer treated with chemoradiotherapy.

One merit of the CRP-BMI score is that it is easy to acquire in clinical practice. Another merit is that it can be used to predict whether salvage treatment can be received at the time of recurrence. Although the recurrence rate for each CRP-BMI score group was almost the same, the rate of administration of salvage treatment for recurrence and the median survival time after recurrence were different for patients with scores of 0, 1 and 2. More than 50% of patients with a score of 2 were unable to receive salvage therapy after recurrence because of their general conditions, which were worse than those of patients with scores of 0 or 1 at the time of recurrence. Therefore, the pre-chemotherapy CRP-BMI score may be useful for determining whether salvage treatment after recurrence might be possible. This score had a statistically significant relationship with gender; however, there was a trend that high CRP-BMI score tended to show a worse OS rate, regardless of gender. To our knowledge, this is the first study to identify the CRP-BMI score as a prognostic factor in patients with advanced NSCLC.

The CRP-BMI score was significantly correlated with gender. Considering this correlation, we analyzed OS rates separately for each gender with CRP-BMI score. Even though they were analyzed separately, the higher CRP-BMI tended to be associated with worse OS for each gender. We concluded that the CRP-BMI score may be a prognostic factor in patients with advanced NSCLC regardless of gender, though it was not proved in this study.

Some limitations of this study should be acknowledged. First, the study was performed retrospectively in a small population of 89 patients. We think that a further study on a large number of patients is needed to clarify the issues. Second, there was some heterogeneity in the patient treatments, which may have led to different clinical prognoses. Thus, further studies are needed to examine the relationship between pretreatment systemic inflammatory and nutritional status and the prognosis of patients with locally advanced NSCLC treated with chemoradiotherapy.

In conclusion, the results of this study indicate that the CRP-BMI score that is based on pretreatment systemic inflammatory and nutritional status is associated with clinical outcome of NSCLC patients treated with chemoradiotherapy and the probability of receiving salvage treatment after recurrence. We think that further large-scale prospective studies are required in order to establish the CRP-BMI score as a guide for selection of patients for treatment.

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CONFLICT OF INTEREST
The authors declare no conflicts of interest with regard to the work in the manuscript.

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