Editorial

# Clinical impact of preoperative immunonutritional status in patients undergoing surgical resection of lung cancer

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Predictions of postoperative major complications and prognosis in surgically resected non-small cell lung cancer (NSCLC) patients according to the preoperative sarcopenia status have been reported by Nakamura *et al.* (1). The leading cause of cancer-related death in the world is lung cancer. The outcomes of early-stage NSCLC after curative surgery remain poor compared with those of other organ cancers. Moreover, the age of population in the world is rapidly increasing, and lung cancer patients are also aging. Therefore, it is necessary to improve the prognosis of not only patients with early-stage lung cancer but also older patients with lung cancer. In addition to prognostic factors such as primary tumor characteristics, the immunonutritional status of organ malignancies patients is also a significant predictor of patient outcomes. In general, cancer cells change the host's metabolic condition and grow by taking nutrition from the host. Body weight loss or malnutrition in the pretreatment period increases treatment-related adverse events or complications, shortens the treatment response time and overall survival (OS), and worsens the quality of life. The clinical significance of the immunonutritional status and the importance of immunonutritional support for patients with cancer are now widely recognized.

## Assessment of preoperative nutritional status

Several studies have shown that the nutritional status in preoperative period is closely connected with comorbidities in postoperative period and outcomes of NSCLC patients (2-4). Sánchez-Lara *et al.* (5) reported that the performance status and malnutrition were associated with poor outcomes in patients with inoperable lung cancer. Some other studies have shown that a preoperative low body weight and low body mass index were poor prognostic factors in patients with operable lung cancer (6,7). In addition to the performance status and body mass index, sarcopenia and immunonutritional parameters such as the modified Glasgow prognostic score (mGPS), prognostic nutritional index (PNI), Controlling Nutritional Status (CONUT) score, and geriatric nutritional risk index (GNRI) are objective tools with which to assess the preoperative immunonutritional condition in patients with cancer.

## Sarcopenia

Sarcopenia is a clinically important condition defined as progressive loss of skeletal muscle mass, muscle strength, and physical performance (8). Cancer is a major cause of secondary sarcopenia, and many studies of the association between cancer and sarcopenia have been highlighted. Sarcopenia can predict survival in patients with various kinds of cancer, including advanced lung cancer (9). Pretherapeutic sarcopenia is highly recognized in cancer patients; it is independently related to poor prognosis during treatment of cancer and influences postoperative

comorbidities, toxicity induced by chemotherapy, and outcomes. Thus, it is recommended that the sarcopenia status is screened before cancer treatment (10).

## Immunonutritional parameters

Immunonutritional parameters including the mGPS, PNI, CONUT score, and GNRI can be calculated based on hematological and anthropometric data. These immunonutritional parameters were recently identified as prognostic markers for several malignancies, including lung cancer.

### *mGPS*

The mGPS is calculated using the serum C-reactive protein (CRP) level and serum albumin level as follows. Patients with an abnormal CRP level (>1.0 mg/dL) and serum abnormal albumin level (<3.5 g/dL) are categorized as a score of 2, patients with only an abnormal CRP level (>1.0 mg/dL) are categorized as a score of 1, and patients with a normal CRP level (≤1.0 mg/dL) and serum normal albumin level are categorized as a score of 0 (11).

### *PNI*

The PNI is calculated based on two parameters (the total lymphocyte count in peripheral blood and the serum albumin level) and thus reflects both the immune response to cancer cells and the nutritional status. The PNI formula is as follows: 10 × serum albumin level (g/dL) + 0.005 × total peripheral blood lymphocyte count (per $mm^3$) (12).

### *CONUT score*

The CONUT is scored by three items including the serum albumin level, peripheral lymphocyte count, and total cholesterol level (13). The CONUT score thus can reflect the reserve condition of the protein, calorie insufficiency, and immune defenses and may consequently reflect the immunological and nutritional statuses, thus serving as a useful immunonutritional marker. Briefly, these parameters are scored as follows: serum albumin level (g/dL) ≥3.50 [0], 3.00–3.49 [2], 2.50–2.99 [4], and <2.50 [6]; total peripheral lymphocyte count (per $mm^3$) ≥1,600 [0], 1,200–1,599 [1], 800–1,199 [2], and <800 [3]; and serum total cholesterol level (mg/dL) ≥180 [0], 140–179 [1], 100–139 [2], and <100 [3]. The CONUT score is calculated from the sum of these three items.

### *GNRI*

The GNRI is calculated from the serum albumin level and body weight. The GNRI is calculated using the following formula: GNRI = 14.87 × serum albumin level (g/L) + 41.7 × preoperative weight/ideal weight (kg). Ideal body weight formula is as follows: ideal body weight = 22 × height ($m^2$). In hospitalized older patients, the GNRI is a useful and simple parameter can predict the risk of complications and outcomes (14).

## Relationship between sarcopenia and immunonutritional parameters

The evaluation of sarcopenia in patients with NSCLC is associated with several problems. First, although skeletal muscle in the region of the third lumbar vertebra (L3) is generally assessed to detect sarcopenia, not all patients with NSCLC undergo computed tomography (CT) that includes the L3 region. Second, various methods such as bioelectrical impedance analysis, dual X-ray absorptiometry, CT, and magnetic resonance imaging are used for detection of the sarcopenia status. To diagnose the sarcopenia condition, The European Working Group on Sarcopenia in Older People recommends the measurement and evaluation of muscle by CT or magnetic resonance imaging. In contrast, the Asian Working Group on Sarcopenia recommends judgment of sarcopenia by bioelectrical impedance analysis. However, these methods require expensive instruments and complicated software analysis procedures, and patients are exposed to radiation for measurement of the skeletal muscle area.

To overcome these disadvantages, we investigated whether immunonutritional parameters are useful for detecting the sarcopenia status instead of the above-described methods. Thus, we retrospectively investigated the correlation between the existence of preoperative sarcopenia and immunonutritional parameters in patients with pathological stage I NSCLC (15). In this study, the existence of preoperative sarcopenia was significantly correlated with the preoperative GNRI and CONUT score in patients undergoing surgical resection of pathological stage I NSCLC. These results suggest that preoperative immunonutritional parameters could be used as a simple method for assessing the risk of preoperative sarcopenia based on hematological data or anthropometric

 

measurements such as body height and weight, rather than by the more complex and time-consuming method of measuring skeletal muscle in CT images.

## Preoperative immunonutritional status of patients with early-stage lung cancer

In general, patients who have cancer of an operable stage and adequate organ function that can tolerate operative stress are considered operable patients. However, one study showed that among 90 operable patients with pathological stage I NSCLC, 38 (42.2%) patients were preoperatively diagnosed with sarcopenia (16). This prevalence of sarcopenia is similar to that reported in a systematic review, which showed a 38.6% prevalence of pretherapeutic sarcopenia in patients with cancer (10). This unexpectedly high prevalence was found even in patients with early-stage lung cancer. Moreover, patients with sarcopenia had worse outcomes than patients without sarcopenia, and sarcopenia was an independent prognostic factor (16). A recent systematic review and meta-analysis concluded that sarcopenia independently could predict unfavorable prognosis even in early-stage NSCLC patients undergoing surgical resection (17).

Jin *et al.* (18) reported that mGPS might have prognostic value in all stages of lung cancer and is significantly associated with poor OS. However, other studies showed that a low PNI was significantly associated with both postoperative recurrence and poor prognosis in patients with early-stage NSCLC. Recurrence-free survival (RFS) in patients with abnormal PNI was significantly shorter than that in those with normal PNI (19,20). Therefore, the preoperative PNI is a simple and useful parameter could predict recurrence in patients with early-stage lung cancer. A high CONUT score was also positively associated with postoperative recurrence (21). In the multivariate analysis, the preoperative CONUT score was an independent prognostic factor. In addition, patients with an abnormal CONUT score had significantly shorter RFS, cancer-specific survival (CS), and OS. Thus, the preoperative CONUT score can predict postoperative recurrence and is a prognostic parameter in early-stage NSCLC patients undergoing surgical resection. An abnormal preoperative GNRI was also significantly associated with postoperative recurrence and was an independent prognostic factor (22). In the Kaplan-Meier analysis of RFS, CS, and OS by preoperative GNRI, the patients with an abnormal preoperative GNRI had significantly shorter RFS, CS, and OS. Thus, these three immunonutritional parameters (preoperative PNI, CONUT score, and GNRI) are novel prognostic factors for early-stage NSCLC patients and can identify patients at high-risk of postoperative recurrence and cancer-related death.

In summary, the sarcopenia status cannot be confirmed using only the patient's appearance or organ function. We must pay attention to the existence of preoperative sarcopenia and abnormal immunonutritional parameters in patients with early-stage lung cancer.

## Older patients with operable NSCLC

The utility of immunonutritional parameters for older patients with surgically resected lung cancer is unknown. We investigated whether these immunonutritional parameters can predict postoperative complications or outcomes of older NSCLC patients. For this purpose, we performed a multicenter retrospective study to analyze the correlation between immunonutritional parameters such as PNI, CONUT and GNRI, and postoperative complications or outcomes of older NSCLC patients (23). Our data showed that both the PNI and GNRI could predict postoperative complications. In addition, among the three immunonutritional parameters, only the GNRI was a prognostic factor in older patients with surgically resected NSCLC and identified an independent poor prognostic factor in older patients with surgically resected NSCLC. Furthermore, OS in patients had an abnormal preoperative GNRI was significantly shorter. Thus, the preoperative GNRI could predict surgical outcomes of high-risk older NSCLC patients. Therefore, preoperative GNRI is both a predictor for postoperative comorbidities and a prognostic factor for high-risk older NSCLC patients. Watanabe *et al.* (24) demonstrated that both the 5-year CS and OS of abnormal preoperative PNI patients were lower than those of normal preoperative PNI patients. They concluded that the preoperative PNI might be useful for treatment planning in older patients with lung cancer. Thus, these three immunonutritional parameters may be useful and promising markers even in older patients with lung cancer.

## Future directions

As indicated by the above-described results, preoperative immunonutritional support can potentially improve the postoperative outcome or prevent postoperative complications in patients with early-stage NSCLC or older

 

patients with NSCLC. Actually, several clinical studies have been performed to evaluate the benefits of preoperative immunonutritional support mainly in patients with digestive or head and neck cancers. Most of these prospective researches examined arginine, glutamine, or omega-3 fatty acids such as eicosapentaenoic acid and docosahexaenoic acid as immunonutritional supplements or regimens. One study showed that preoperative immunonutritional support containing these agents could decrease the postoperative comorbidities in surgically resected NSCLC patients (25). Many types of immunonutritional support for digestive cancers are started before surgery. Therefore, a prospective research to analyze whether a preoperative immunonutritional program provided these agents could reduce postoperative complications and surgical outcomes in NSCLC patients with abnormal immunonutritional parameters is needed. This study might contribute the production of an immunonutritional support regimen could bring about benefits for patients in sarcopenia or abnormal immunonutritional condition with early-stage NSCLC or older patients with NSCLC who undergo thoracic surgery.

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## Footnote

*Conflicts of Interest:* The author has no conflicts of interest to declare.

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