Editorial

Editorial on "Albumin-to-fibrinogen ratio as a prognostic biomarker to predict clinical outcome of non-small cell lung cancer individuals"

Takuro Miyazaki, Takeshi Nagayasu

Department of Surgical Oncology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

Correspondence to: Takuro Miyazaki, MD, PhD. Department of Surgical Oncology, Nagasaki University Graduate School of Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan. Email: miyataku@nagasaki-u.ac.jp.

Provenance: This is an invited article commissioned by the Section Editor Shuangjiang Li (Department of Thoracic Surgery and West China Medical Center, West China Hospital, Sichuan University, Chengdu, China).

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As shown in "Albumin-to-fibrinogen ratio as a prognostic biomarker to predict clinical outcome of non-small cell lung cancer individuals", by Li *et al.*, the albumin/fibrinogen ratio (AFR) is a valuable addition to the tools used to assess systemic inflammatory response (SIR) and/or nutrition status in patients with cancer and other serious diseases.

These SIR evaluation tools also include the neutrophil/lymphocyte ratio (1), platelet/lymphocyte ratio (2), monocyte/lymphocyte ratio (3), Glasgow prognostic score (GPS) (4,5), and prognostic nutritional index (6,7), which are prognostic predictors for cancer patients (8,9), as is the advanced lung cancer inflammation index (ALI; *Table 1*) (10,11). They are all conveniently based on information available from routine blood and laboratory tests.

Several mechanisms for the relationship between cancer and inflammatory response have been suggested (4,8,9,12,13). Briefly, cancer growth and invasion damage local tissue, which disrupts homeostasis and incites systemic acute-phase responses, including progressive release of proinflammatory cytokines (13), immunovascular cells (neutrophils and lymphocytes), C-reactive protein (CRP), albumin, etc.—all SIR markers.

The prognostic value of SIR markers has also been verified in systematic review and meta-analysis. Dolan *et al.* (8,9) evaluated the use of SIR tools in predicting outcomes for patients with operable cancers, through a systematic review and meta-analysis of 244 papers. They found neutrophil to lymphocyte ratio (NLR), GPS and mGPS (among many SIR markers) to predict overall survival (OS) and cancer-specific survival (CSS) significantly. Moreover, the GPS, mGPS and NLR were shown to have prognostic value in randomized clinical trials for patients with non-small cell lung cancer (NSCLC) or cancers of the esophagus, pancreas, prostate, etc. (9)

Among SIR tools, GPS and CRP/albumin ratio are useful prognostic predictors for elderly patients with clinical stage I NSCLC who undergo pulmonary resection (4,12). NSCLC remains the most common cause of cancer death globally, and as median age increases worldwide, so will the number of elderly patients with potentially resectable lung cancer. Surgeons are sometimes reluctant to perform pulmonary resections in older patients because of their higher surgical mortality and morbidity, and their likelihood of death from coincidental natural causes. For these patients, SIR indices are very helpful in selecting appropriate treatments.

Elderly patients may display frailty (low ability to adapt to stress), as shown by physiological deterioration, and decreased nutritional status and immune function (14). Heightened inflammation, marked by increased inflammatory molecules and white blood cell counts, is often found in frail older adults (15). Lealdini *et al.* reported that patients with both abnormal CRP and albumin levels had significantly higher frailty scores among 52 cancer

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Table 1 Systematic inflammatory response evaluation tools

Marker	Name	Formula
AFR	Albumin/fibrinogen ratio	–
ALI	Advanced lung cancer inflammation index	BMI (kg/m^2) × Alb/NLR
CAR	CRP/albumin ratio	–
GPS	Glasgow prognostic scale	Albumin (<35 or ≥35 g/L), CRP (<10 or ≥10 mg/L)
mGPS	modified GPS	–
MLR	Monocyte/lymphocyte ratio	–
NLR	Neutrophil/lymphocyte ratio	–
PLR	Platelet/lymphocyte ratio	–
PNI	Prognostic nutritional index	10× albumin (g/dL) +0.005× total lymphocyte count/mm^3

BMI, body mass index; CRP, C-reactive protein.

patients (median age: 72.5 years), and concluded that inflammatory parameters correlated with frailty, more advanced clinical stage and poor functional status (14). The review by McMillan *et al.* of >60 papers with >30,000 cancer patients reported that increased GPS was associated with loss of weight and muscle, poor performance scores, increased comorbidity, greater pro-inflammatory and angiogenic cytokine levels, and higher complication rates (16). Overall, these results indicate a meaningful relationship among frailty, aging, nutrition, and SIR scores.

Li *et al.* reported that pretreatment AFR could predict efficacy of surgical resection and adjuvant chemo-radiotherapy for patients with NSCLC (13). Notably, their study evaluated lung cancer patients comprehensively—that is, not only those treated with surgery, but also those treated with chemotherapy and radiotherapy, and patients with NSCLC of various stages and histologies (patients with abnormal liver function, infections, inflammation-related, autoimmune or hematological diseases, or other malignancies were excluded, to avoid biasing the results). Their study might enable us to select NSCLC patients who would likely benefit from surgery and adjuvant chemo-radiotherapy, and predict their survival.

AFR reflects nutrition status, coagulation conditions and systemic inflammation. Fibrinogen, as an essential protein in coagulation, is an acute-phase reactant in inflammatory environments, where it promotes synthesis of pro-inflammatory cytokines and indicates systemic inflammation; it also accumulates at tumor sites and affects cancer progression (13,17-19).

The prognostic use of AFR in lung cancer has been studied. Sheng *et al.* (19) reported that serum fibrinogen levels were positively correlated with serum CRP, and patients with operable NSCLC and hyperfibrinogenemia had higher risks of disease progression and death. Similarly, Chen *et al.* (17) reported that among propensity-score matched patients with NSCLC, pre-resection AFR was predictive of OS, CSS, and pathological stage. This predictive utility of AFR has also been reported for other cancers (18).

Although we greatly admire the study by Li *et al.*, we would have changed a few things. First, as the authors mentioned themselves, the study is limited by the small number of centers (only two) and the lack of a validation cohort. Second, the relatively long time-frame for this study—10 years—has seen many advances, including diagnostic techniques (positron emission tomography and endobronchial ultrasound), less invasive surgery (robotic and video-assisted thoracoscopic surgery), postoperative intensive care, various improvements in chemotherapy (platinum doublet adjuvant therapy), targeted therapies (epidermal growth factor receptor biologics) and immune-check point inhibitors; this long period of time might be another limitation. Third, CSS was not evaluated; we speculate that AFR might help predict it. Finally, 3 years seems a rather short period to evaluate OS; in further studies of long-term survival, 5-year OS seems more appropriate.

Among the many prognostic markers and indices based on SIR and nutritional status, identifying the most reliable one for lung cancer patients would be valuable. In particular, cut-off values for SIR tools vary among studies, which affects results and conclusions. Standardizing these

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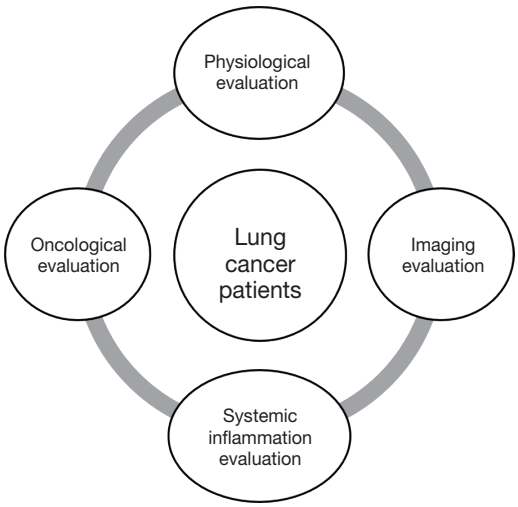

Figure 1 Key map for the treatment strategy for lung cancer patients.

cut-off values is a creditable goal that warrants wider study.

In any case, we recommend that use of SIR tools should form part of routine pre- and post-procedure evaluations, not only for surgery but also for other treatments, such as chemotherapy and radiotherapy (*Figure 1*).

Future prospective studies and the accumulation of clinical data are needed to address these limitations and improve treatment and management of patients with NSCLC. Such studies would also help determine whether SIR scoring tools could be applied in clinical practice to guide treatment decisions for lung cancer patients with various backgrounds.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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