Editorial

The pretreatment circulating albumin-to-fibrinogen ratio in patients with non-small cell lung cancer: a simple, economical, and effective biomarker

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

Comment on: Li SQ, Jiang YH, Lin J, *et al.* Albumin-to-fibrinogen ratio as a promising biomarker to predict clinical outcome of non-small cell lung cancer individuals. Cancer Med 2018;7:1221-31.

Submitted Jan 05, 2019. Accepted for publication Jan 19, 2019.
doi: 10.21037/jtd.2019.01.83
View this article at: http://dx.doi.org/10.21037/jtd.2019.01.83

Lung cancer is among the most prevalent malignant diseases and the leading cause of cancer-related death worldwide. Disease progression in patients with various types of carcinomas, including lung cancer, is dependent on an intricate interaction among the tumor, host inflammatory response, and nutritional status. There is substantial evidence that the systemic inflammatory response and nutritional status of patients with carcinomas are important predictors of the outcome. The roles of biochemical or hematological markers, such as hypoalbuminemia, elevated C-reactive protein (CRP) levels, or others, have been studied by many researchers.

Proinflammatory cytokines are released as part of the systemic inflammatory response to the tumor. Interleukin (IL)-6 is produced by the tumor or surrounding cells and can stimulate the liver to produce acute-phase reaction proteins, such as CRP and fibrinogen. Moreover, lower serum albumin concentrations may be caused by IL-6 that modulates albumin production by hepatocytes (1). The association among IL-6, CRP, albumin, and fibrinogen was investigated by Yanagawa *et al.* (2). They measured IL-6 levels in serum from patients with benign or malignant lung disease. Although IL-6 was not detected in patients with benign lung disease, 39% of patients with lung cancer expressed IL-6. Serum CRP and plasma fibrinogen levels were significantly higher, and the serum albumin concentration was significantly lower, in IL-6-expressing lung cancer patients.

Serum albumin is a common biomarker used to assess the nutritional status in cancer patients. A review of 29 studies investigating the association between pretreatment serum albumin levels and survival in different types of cancer was reported by Gupta *et al.* (1). The authors stated that serum albumin levels (considered either alone or combined with other factors) provide useful prognostic information in several cancers. In most studies on lung cancer, higher serum albumin levels were associated with better survival; this was similar to that in other types of cancers such as gastrointestinal.

Combinations of biochemical and hematological markers for inflammatory and nutritional factors have been used to derive simple inflammation-based prognostic scores, such as the Glasgow Prognostic Score (GPS), modified GPS (mGPS), neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and prognostic nutritional index (PNI) (3,4). McMillan systematically reviewed more than 60 studies regarding GPS and mGPS involving over 30,000 patients (5). He stated that the GPS, mGPS, and evidence of a chronic systemic inflammatory response were involved in the prognosis of patients in a variety of clinical cancer

situations, such as patients with operable disease, those receiving chemo/radiotherapy, and patients with inoperable cancer. Two studies compared the prognostic value of the GPS and mGPS with that of other markers including the NLR, PLR, PNI, and prognostic index (6,7). The results showed that the mGPS predicted survival superior to other markers.

The association of the risk of lung, colorectal, and breast cancer with three inflammatory biomarkers (whole blood leukocyte count, fibrinogen, and CRP) in 84,000 individuals from the general population was reported by Allin *et al.* (8). A stepwise elevation in the risk of cancer was observed with increased levels of one, two, and three inflammatory biomarkers compared to that in patients without an elevated biomarker. This result suggested that the use of a combination of two or three biomarkers could predict more precisely the correlation between biomarkers and cancer behaviors, such as initiation and progression, than the use of an individual biomarker.

Miura *et al.* reported a relationship between preoperative serum albumin levels and the prognosis for both overall and recurrence-free survival after evaluating 556 patients with surgically resected non-small cell lung cancer (NSCLC), including all pathological stages (9). The preoperative serum albumin level was a more important prognostic factor for overall and recurrence-free survival in patients with resected NSCLC than neutrophil or lymphocyte counts, the NLR, or the PNI. The authors also evaluated the prognosis of lung cancer patients with normal lung parameters, emphysema, or fibrosis. The results showed that NSCLC patients with pulmonary fibrosis and a low serum albumin level had poor recurrence-free survival, while in patients with emphysema, a low serum albumin level was not a prognostic risk factor.

Coagulation is associated with tumor progression and metastasis in several cancers. Fibrinogen, an essential coagulation cascade protein, can accumulate at tumor sites and plays an important role in tumor progression. Inflammatory mediators such as IL-6 are known to trigger the production of fibrinogen (10). One study reported that a higher preoperative fibrinogen level was associated with tumor development, indicating a poor prognosis in several types of malignancies (11). Although the exact reason for the association between elevated plasma fibrinogen and poor survival of patients with cancer remains unclear, several studies demonstrated that fibrinogen plays a key role in tumor progression. Specifically, fibrinogen promotes the stable adhesion of tumor cells and survival of metastatic emboli after tumor cell intravasation in lung cancer models, and is therefore an important determinant of spontaneous metastatic potential (12,13).

A recent study by Li *et al.* investigated the potential for the albumin-to-fibrinogen ratio (AFR) to be an effective biomarker to predict the survival of patients with lung cancer (14). A total of 412 patients were assessed in this study including 336 with NSCLC (247 patients with stages I–III and 89 patients with stage IV) and 89 with small cell lung cancer (SCLC). Fifty-nine patients underwent surgery alone, 172 underwent surgery with adjuvant chemo/radiotherapy, and 181 underwent chemo/radiotherapy without surgery. They assessed circulating numbers of inflammation-related cells, and concentrations of inflammation-related proteins and their combinations, including types of white blood cells, fibrinogen and albumin levels, and the AFR, NLR, PLR, and monocyte-lymphocyte ratio. A univariate analysis of the Cox regression model for candidate prognostic factors for lung cancer showed significant differences in the three-year overall survival rate based on albumin and fibrinogen levels, and the AFR, NLR, PLR, and monocyte-lymphocyte ratio. A multivariate analysis showed that a low AFR [adjusted hazard ratio (HR) 1.79, P=0.003], low albumin (HR 1.59, P=0.001), high NLR (HR 1.45, P=0.008), high fibrinogen (HR 1.43, P=0.049), and high PLR (HR 1.37, P=0.023) were significantly associated with poor survival of lung cancer patients.

Li *et al.* (14) also performed a stratified analysis by tumor type (NSCLC or SCLC) and TNM stage (stages I–III or IV) and showed that a low AFR had the highest adjusted HR value (HR 2.31) in patients with NSCLC, both in patients with stages I–III (HR 4.47) and stage IV (HR 3.39) cancer. Key findings of the study were that lung cancer patients with high circulating fibrinogen, and low albumin and AFR, were significantly associated with an increased risk of death, especially NSCLC patients in all stages. The adjusted HR of NSCLC patients (both stages I–III and IV patients) with a low AFR was higher than that with other biomarkers (fibrinogen, albumin, NLR, PLR). However, stages I–III NSCLC included patients both negative and positive for lymph node metastasis and with various tumor sizes, which may have affected the analysis.

We hypothesized that the effect of these biomarkers on cancer prognosis could be highly influenced by the number of systemic tumor cells, and were interested in differences of the prediction potential between the early and advanced stage of cancer, especially in patients with

node-negative early stage lung cancer. Another key finding was that combination treatment with surgery and chemo/radiotherapy improved the prognosis of patients with a low AFR in stages II–III lung cancer. This result suggested that the AFR can predict the clinical efficacy of chemo/radiotherapy when combined with surgery.

Finally, Li *et al.* (14) established a prognostic nomogram including the factors of treatment modality, stage, and with and without the AFR. The concordance index of the nomogram with the AFR showed higher accuracy than that without the AFR. This finding may be significant because the nomogram is simple to use in clinical practice in patients with lung cancer.

The impact of various types of individual biomarkers and their combinations for cancer progression and prognosis has been investigated. Furthermore, many kinds of independent prognostic factors were reported for different types of cancers, clinical stages, treatment modalities, study populations and designs, and sample sizes. Although most of these factors are helpful prognostic biomarkers, it is very difficult to determine which one is the most powerful and prominent.

The influence of inflammation and nutritional status, and their interaction, on a cancer will differ depending on the cancer stage, treatment modality, presence of co-morbidities, and other factors. Therefore, it may be necessary to choose biomarkers based on the individual situation. The study performed by Li *et al.* (14) included a heterogeneous group of patients (i.e., NSCLC and SCLC, with or without surgery), which could be a limitation of that study. As mentioned in that study, a prospective cohort with a multiple-central design and large sample size is warranted to validate the role of the AFR in predicting clinical efficacy of these biomarkers.

In conclusion, a simple, economical, and effective biomarker is required in clinical practice for precisely predicting the survival of lung cancer patients. Thus far, the AFR is the most promising candidate to meet these criteria.

Acknowledgements

None.

Footnote

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

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Cite this article as: Hamanaka K, Miura K, Koyama T, Matsuoka S, Takeda T, Yamada K, Hyogotani A. The pretreatment circulating albumin-to-fibrinogen ratio in patients with non-small cell lung cancer: a simple, economical, and effective biomarker. J Thorac Dis 2019;11(Suppl 3):S241-S244. doi: 10.21037/jtd.2019.01.83