Editorial

Is the prognostic nutritional index (PNI) a useful predictive marker for postoperative complications after lung surgery?

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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: Okada S, Shimada J, Teramukai S, *et al.* Risk Stratification According to the Prognostic Nutritional Index for Predicting Postoperative Complications After Lung Cancer Surgery. Ann Surg Oncol 2018;25:1254-61.

Submitted Aug 17, 2018. Accepted for publication Dec 25, 2018.
doi: 10.21037/jtd.2018.12.124
View this article at: http://dx.doi.org/10.21037/jtd.2018.12.124

An article entitled "Risk Stratification According to the Prognostic Nutritional Index for Predicting Postoperative Complications After Lung Cancer Surgery" was published in *Annals of Surgical Oncology* in May 2018. This article described a retrospective study of the clinical significance of the prognostic nutritional index (PNI) as an indicator for postoperative complications following lung cancer surgery. The authors concluded that PNI is a useful predictive marker for postoperative complications after lung cancer resection.

It is well known that lung cancer has the greatest mortality of all malignant tumors, despite all the prevailing preventive and therapeutic approaches to this condition (1). How to improve the survival and reduce the morbidity rate still remains an urgent issue for the patients who undergo lung cancer surgery. A number of clinicopathological factors, including gender, age, Eastern Cooperative Oncology Group (ECOG) score, tumor size, lymph node metastasis status, smoking status, and serum carcinoembryonic antigen (CEA) level have been reported to show strong prognostic significance for operable lung cancer (2-4). Other researchers have found that an elevated neutrophil count is related to a poor prognosis in lung cancer patients, and that an elevated serum albumin level is associated with improved survival among patients with lung cancer (5,6).

The concept of PNI was proposed for the first time in 1980 (7). Initially, the PNI was used to predict the prognosis of digestive system tumors, such as esophageal, gastric and pancreatic carcinomas (8,9). The PNI tool considers the combined effects of hypoalbuminemia and lymphocytopenia. Of these, hypoalbuminemia is the most common and troublesome postoperative complication. In some studies, about 20% to 40% of patients showed an acute, prolonged, and profound drop in serum albumin after surgery (10,11). The laws of physiology suggest that hypoalbuminemia reflects some combination of decreased albumin production, and acute dilution, along with the increased loss or shift of albumin from the vessels (12). Albumin may also be lost through the kidneys, epidermis or gastrointestinal tract (13). In addition, hypoalbuminemia is not only an undernourished condition but also a systemic inflammatory response since the synthesis of serum albumin can be suppressed by malnutrition and inflammation, which will lead to an increased susceptibility to infectious complications after lung cancer surgery. Lymphocytopenia, or lymphopenia, is the condition of having an abnormally low level of lymphocytes in the blood, and may be present as part of a pancytopenia, when the total numbers of all types of blood cells are reduced in patients with lower PNI since lymphocytes are a white blood cell with important functions in the immune system. The lymphocytopenia will also affect a systemic inflammatory response and has a role in influencing the postoperative outcomes with possibly increased infectious complications. So far, there are few publications about preoperative lymphocytopenia, and more basic and clinical research is needed to confirm the findings in the future.

Recently, a new theory has posited that hypoalbuminemia is associated with the small intestine. The small intestine is an effective structure for absorbing diverse types of food and nutrition, but this situation changes during surgery. Under the trauma or bleeding of surgery, maintenance of the vital organs becomes the priority of physiological responses and eating is dispensable. The autonomic nervous system sacrifices perfusion to the small intestine in favor of the heart and brain. It may take a long time to return to normal function after surgery. The small intestine might malfunction and switch from being a remarkable absorptive surface to becoming a counterproductive excretory surface. That is, blood continues to flow through the splanchnic circulation, but with capillary exchange occurring in the opposite direction: nutrients leak from the plasma down their concentration gradient into the lumen of the intestine (14). In fact, this theory is related to hypoalbuminemia after surgery, and it is totally different from the PNI, which we are referring to here as a pre-treatment nutritional risk stratification tool. Generally, not only is the effect of preoperative hypoalbuminemia on the postoperative outcomes problematic, but perioperative hypoalbuminemia after surgery is of concern as well. Therefore, we mentioned this theory related to hypoalbuminemia associated with the small intestine as a reminder of its potential for causing surgery trauma.

In recent years, there have been many studies exploring the relationship between the PNI and the prognosis of patients with lung cancer. Qiu *et al.* performed a retrospective review of 1,416 patients undergoing radical surgery for non-small cell lung cancer (NSCLC) between January 2006 and December 2011. Using the Kaplan-Meier method and multivariate analysis, they evaluated the relationship between PNI and survival of those patients, and found the rates of 1-, 3-, and 5-year survival in patients with a PNI of less than 52 were significantly less favorable than those in patients with a PNI of 52 or higher (15). Kos *et al.* retrospectively reviewed 138 NSCLC patients and found that there was a shorter median overall survival (OS) in the low PNI group compared to the high PNI group [7.0 months with 95% confidence interval (CI), 3.5–10.5 *vs.* 33.0 months with 95% CI, 15.5–50.4] ($P<0.0001$) (16). In the case of elderly lung cancer patients (≥75 years old), similar results have been obtained. Watanabe *et al.* found that there was a significantly different 5-year cancer-specific survival (CSS) rate in the patients with a PNI ≥45 and <45 (76.2% *vs.* 47.8%, $P=0.0166$). Furthermore, they also found that the patients with a high PNI ≥45 have a higher 5-year OS rate compared to the patients with a low PNI <45 (61.9% *vs.* 39.8%, $P=0.0275$) (17). All these studies considered together indicate that the PNI is an independent survival predictor for patients with NSCLC. In addition, PNI has also been used to assess the outcomes of patients with small-cell lung cancer (SCLC) undergoing chemotherapy. Minami *et al.* reviewed 97 SCLC patients in stage IIIB or IV who underwent chemotherapy based on a platinum combination. The results indicated that a higher PNI may be useful as a prognostic factor for a longer OS [hazard ratio (HR) 0.50, 95% CI, 0.31–0.78, $P<0.01$] (18). Furthermore, Okada *et al.* proved that there was a dramatic association between a low PNI score and postoperative complications, regardless of the surgery pattern. They demonstrated that the significance of the PNI as a postoperative complication predictor in patients with NSCLC is similar to that in other initial malignancies (19).

All of the above studies reveal PNI to be an effective and independent predictor of prognosis in patients with lung cancer. However, these studies including Dr. Okada's study have a considerable number of limitations, which must be addressed. Firstly, all above studies were retrospective studies, displaying design and potential selection bias, and also suffering from potential publication bias. Publication bias may exist in situations where the published studies are mostly positive results, and other negative studies with valuable data were neglected due to being unpublished. Second, most of these existing studies were undertaken at single centers with a small-scale sample (i.e., <200 subjects). Although the Okada *et al.* study had a larger sample size of 515, it was still nevertheless a single-center study with incomplete reliability. Furthermore, it is important to note that a fixed cut-off value for the PNI has not yet been widely established in these studies. Therefore, we expect more multicenter, prospective, large-scale studies will be undertaken to obtain a more in-depth and objective evaluation of the scientific significance and value of the PNI in the future.

Acknowledgements

Funding: This work was financially supported by grants from the National Natural Science Foundation of China (No. 81773207), the Science and Technology Support Key Program of Tianjin (17YFZCSY00840), the Tianjin Key Project of Natural Science Foundation (16JCZDJC34200, 16PTSYJC00160) and the Special Program of Talents Development for High Level Innovation and Entrepreneurship Team in Tianjin. The funders had no role in study design, data collection and analysis, decision to publish, or in the preparation of the manuscript.

Footnote

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

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(English Language Editor: John Ayric Gray, AME Publishing Company)

Cite this article as: Li X, Chen J. Is the prognostic nutritional index (PNI) a useful predictive marker for postoperative complications after lung surgery? J Thorac Dis 2019;11(Suppl 3):S334-S336. doi: 10.21037/jtd.2018.12.124

