The Prognostic Role of the Neutrophil to Lymphocyte Ratio at Recurrence in Esophageal Squamous Cell Carcinoma: Challenges and Future Directions

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Esophageal cancer is the eighth most commonly diagnosed malignancy worldwide and is the sixth leading cause of cancer-related mortality.¹ Globally, esophageal squamous cell carcinoma (ESCC) is the most common histologic subtype and has been linked primarily to tobacco use, alcohol intake, and malnutrition.² ESCC is most prevalent in East and Central Asia, where it comprises greater than 90% of esophageal cancers.^{1,2} Despite advances in multimodality treatment over the years, the prognosis of ESCC remains poor with a 5-year overall survival rate of 15–25%.^{3,4}

The prognosis of ESCC patients has been tied to a variety of inflammatory biomarkers across several studies.^{3–13} The systemic inflammatory response plays an integral role in DNA damage, cell proliferation, angiogenesis, and metastasis.^{3–9} Inflammatory biomarkers, such as neutrophil to lymphocyte ratio (NLR), lymphocyte to monocyte ratio (LMR), and platelet to lymphocyte ratio (PLR), have shown to predict survival in ESCC in multiple retrospective studies.^{3–9} The change in NLR (delta NLR) from time of diagnosis also has shown to predict response to neoadjuvant therapy, time to recurrence, and survival.^{3,9} Several meta-analyses also have confirmed the role of NLR as a prognostic biomarker in ESCC.^{10–12} In addition to the NLR, the modified Glasgow Prognostic Score (mGPS),

which combines albumin and C-reactive protein (CRP), has been demonstrated to predict survival in retrospective studies across multiple cancers, including ESCC.¹³

In the current study by Shota et al.¹⁴ authors conducted a single institution, retrospective study of Japanese patients between 2004 and 2019 to evaluate the prognostic role of NLR at the time of recurrence in ESCC patients. A total of 133 patients were included in the analysis. On the multivariate analysis (MVA), the NLR at recurrence were significantly associated with worse overall survival (hazard ratio [HR] 1.061, 95% confidence interval [CI] 1.002–1.125; $p = 0.043$), whereas the mGPS was not. The optimal cutoff value for NLR at recurrence was set at 3.374 and was determined by survival classification and regression tree (CART) analysis. Time-dependent ROC curves demonstrated that the area under the curve (AUC) value of the NLR at recurrence was superior to mGPS at recurrence in all terms.

This publication is unique in that the majority of the aforementioned studies reported on the preoperative and postoperative NLR in ESCC, but not the NLR at time of recurrence. In addition, this variable may be complementary to other parameters used to assess prognosis, such as time to recurrence, number of lymph nodes, and sites of recurrence.

While the results of this study are interesting, some limitations are noteworthy. First, the study was a single-institution, retrospective study restricted to Japanese patients, which lends itself to selection bias and makes it difficult to generalize to other patient populations. Second, the NLR may be affected by several other clinical variables that were not accounted for in the study, including immunosuppression, inflammation, infection, medications (e.g., steroids), and medical conditions (e.g., diabetes, thyroid dysfunction, hypertension, renal/liver failure).¹⁵

Third, the MVA did not include important parameters, such as performance status, smoking status, and medical comorbidities. Furthermore, serial longitudinal evaluation of the NLR over time may be more informative compared with the NLR at recurrence. Independent of this study, the wide applicability of NLR also is challenged by the large variation in cutoff values seen in the literature ranging between 1.7 and 5.¹²

It is important to recognize the evolving role of precision oncology in clinical practice. With the advent of next-generation sequencing (NGS), serial longitudinal assessment of circulating tumor DNA (ctDNA) has been used to monitor response to therapy and to detect early recurrence. Studies have demonstrated that ESCC patients with post-treatment positive-ctDNA have a higher risk of recurrence, tumor progression, decreased progression-free survival, and lower overall survival.^{16,17} In addition, detection of ctDNA during surveillance has shown to precede radiographic evidence of recurrence by approximately 3–6 months.^{16,18} Thus, ctDNA analysis has the potential to serve as a useful prognostic tool in ESCC, albeit, larger prospective studies are needed to confirm this.

In conclusion, Shota et al. demonstrate that the NLR at time of recurrence may serve as a prognostic biomarker in ESCC in a Japanese patient cohort.¹⁴ However, study findings are limited by the retrospective nature of the study, the small and select patient population, the lack of inclusion of other clinical variables in the analysis, and the wide variability in NLR cutoff values seen across studies. Therefore, while the NLR at time of recurrence may play a prognostic role in ESCC, larger, prospective, multi-institutional studies will need to clarify its role in treatment decisions. Lastly, ctDNA analysis may represent a more powerful tool for predicting recurrence and survival in ESCC.

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