Editorial

Neutrophil-to-lymphocyte ratio as a prognostic biomarker in hepatocellular carcinoma after transarterial chemoembolization

Soung Won Jeong^

Division of Gastroenterology and Hepatology, Department of Internal Medicine, Soonchunhyang University Seoul Hospital, Soonchunhyang University College of Medicine, Seoul, Korea

Correspondence to: Soung Won Jeong. Division of Gastroenterology and Hepatology, Department of Internal Medicine, Soonchunhyang University Seoul Hospital, Soonchunhyang University College of Medicine, 59 Daesagwan-ro, Yongsan-gu, Seoul 04401, Korea. Email: jeongsw@schmc.ac.kr.

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Hepatocellular carcinoma (HCC) is the fifth most common cancer globally and the third leading cause of cancer-related deaths, in accordance with the World Health Organization (globacan.iarc.fr).

HCC is an inflammation-related malignancy, mainly associated with hepatitis B or hepatitis C viral infections. Transarterial chemoembolization (TACE) is considered for intermediate-stage HCC that is not eligible for curative treatment options (1,2). Tumor size, number of tumors, α-fetoprotein (AFP) level, Child-Turcotte-Pugh score, vascular invasion and tumor response have been identified as significant factors predicting overall survival (OS) in HCC patients treated with TACE (3-6). However, the identification of robust prognostic markers is required for the precise prediction of response to TACE in HCC patients. Serum parameters are among the most promising biomarkers of HCC recurrence and survival, as they are readily available, and their measurement can be performed rapidly and affordably.

Recently, elevated peripheral neutrophil-lymphocyte ratio (NLR) has been reported as an indicative marker of poor OS in various cancers (7,8). High NLR has also been associated with poor survival in HCC patients undergoing locoregional therapy, including TACE (9-12), resection (13,14) and radiofrequency ablation (RFA) (15,16). A recent study in this journal by Wang *et al.* (17) demonstrated that NLR >2.4 in baseline was an independent prognostic indicator of poor OS. A high NLR one month after TACE has also been related with poor prognosis. The results showed that elevated NLR was associated with large tumor size, high levels of total bilirubin and aspartate transaminase, and low red blood cell counts. These associations might be attributed to the inflammatory responses induced by large tumors, resulting in a high NLR.

Systemic inflammation has been associated with poor prognosis in multiple cancer entities. Inflammatory responses in the tumor microenvironment play important roles in cancer cell proliferation and tumor progression (18,19).

As a marker of systemic inflammation, the NLR has been associated to cancer progression, metastasis, and prognosis in various tumors. Notably, neutrophils, which are the main factor of the inflammatory tumor microenvironment, are closely associated with tumor cell proliferation and survival, as well as tumor angiogenesis, metastasis, and disruption of the acquired immune system (20). Meanwhile, lymphocytes are key players in cancer immune surveillance, suppressing tumor progression (21). Importantly, decreased lymphocyte counts have been associated with impaired anti-tumor immune responses, enabling tumor progression and metastasis (22). Hence, lymphocytes and neutrophils exert opposing functions in inflammatory responses and cancer progression.

^ ORCID: 0000-0003-2855-6011.

There are several issues in this study. First, the baseline NLR cut-off value used in this study was 2.4. However, the baseline NLR cut-off values are different in each study (23). Different NLRs applied to each center make various data and confused for clinical use. Thus, large cohort studies are required to establish the most appropriate NLR cut-off value, which provides good sensitivity and specificity. Second, tumor response after TACE is an important predictor of OS; thus, it is crucial to assess its relationship with other predictive factors. Although this was a retrospective study, the analysis of tumor response could have enabled the determination of the predictive value of NLR. Third, in this study, authors identified the baseline NLR as an independent predictor of poor OS. Although NLR has been suggested as a treatment response marker, it remains unclear whether NLR can distinguish between tumor size and number of lesions. Future studies are required to assess the predictive value of NLR in cohorts stratified according to the tumor size and the number of lesions.

Fourth, various following treatments including hepatic resection, RFA, systemic chemotherapy, radiation, and conservative treatment might be conducted after the TACE, and the effect of these subsequent treatments should be considered as a limitation for the analysis.

Currently, NLR with other combined factors such as plate to lymphocyte ratio (9), aspartate aminotransferase-to-alanine aminotransferase ratio (24), or C-reactive protein to albumin ratio (25), have been identified to promote the survival prediction after TACE. Additionally, prognostic score including NLR was noticeable comparing with the prior scores (12).

In conclusion, baseline NLR and its dynamic changes during therapy can predict OS in HCC patients treated with TACE. NLR may be a simple, available, inexpensive and reliable predictive marker for HCC. Furthermore, the combination of NLR with other predictive factors or the development of a prognostic score using NLR could improve the prognostic prediction. However, the appropriate cut-off value of NLR should be established in a large cohort study.

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