



Role of inflammatory indices in management of hepatocellular carcinoma – neutrophil to lymphocyte ratio

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Hepatocellular carcinoma (HCC) is sixth most common cancer and second leading cause of cancer related death globally (1). Liver transplantation and liver resection are curative surgical options. Thermal ablation e.g., radiofrequency ablation (RFA) or microwave ablation (MWA) are also considered curative for tumors less than 3 cm in size. However, many patients are not suitable to receive curative options due to poor hepatic functional reserve or extrahepatic disease. In such patients, liver directed therapies have major role. The two common techniques of liver directed therapies are (A) trans-arterial chemoembolization (TACE) and (B) selective internal radiation therapy (SIRT). TACE uses chemotherapy while SIRT uses Yttrium90 radioisotope. Our group has conducted meta-analysis comparing liver resection with a combination of TACE and RFA and reported that oncologic outcomes are comparable (2). TACE actually improves survival and hence should be considered as ‘curative adjunct’ and in my opinion classifying TACE as ‘palliative therapy’ doesn’t do justice (3). However, not all patients benefit equally from TACE and it is important to learn which patients benefit the most (4).

Carcinogenesis is interlinked with inflammatory response and many researchers have reported the role of systemic inflammation in predicting outcomes of breast cancer, colorectal cancer, esophageal cancer, gastric cancer, HCC, non-small cell lung cancer and pancreatic cancer patients (5-8). Inflammatory markers like C-reactive protein (CRP), serum albumin and various combinations of hematology components are increasingly investigated to define their

roles in predicting outcomes following treatment of HCC. The commonly validated composite hematology indices are platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), prognostic nutritional index (PNI), modified Glasgow prognostic score, aspartate aminotransferase/platelet count ratio index (APRI), lymphocyte-to-monocyte ratio (LMR) and albumin-bilirubin index (ALBI) (1). Inflammation based indices are routinely available, easy to compute, fast, at no additional cost and reliable. Hence there is a proliferation of manuscripts suggesting the role of these indices in prognosis of HCC patients. The current evidence with regards to utility of all indices is too heterogenous and it is difficult to derive any conclusions which impact routine clinical practice. For the purpose of this editorial, I shall discuss about NLR.

NLR is calculated as absolute neutrophil count (number of neutrophils/ μ L) divided by absolute lymphocyte count (number of lymphocytes/ μ L). Lower NLR is associated with improved prognosis in HCC patients managed by liver transplantation, liver resection, TACE and systemic sorafenib therapy (9). With regards to liver transplantation, a meta-analysis including ten studies and 1,687 patients is reported by Sun *et al.* They showed that elevated NLR was significantly associated with poorer overall survival (OS) (HR 2.71, 95% CI: 1.91–3.83) and disease-free survival (DFS) (HR 3.61, 95% CI: 2.23–5.84) (7). As infections and immunosuppression are integral to organ transplantation, it is important that study protocol takes this into account for possible exclusion of such patients. Role of NLR in predicting oncologic outcomes following curative resection

for HCC is widely published. A meta-analysis including 17 studies with patients treated by curative surgery for HCC showed that elevated preoperative NLR was predictive of OS (HR 1.52; 95% CI: 1.37–1.69), recurrence free survival (RFS) (HR 1.64; 95% CI: 1.44–1.87) as well as DFS (HR 1.50; 95% CI: 1.35–1.67) (10). Additionally, preoperative NLR was also associated with tumor vascular invasion (OR 2.08; 95% CI: 1.60–2.70) and large tumor size (OR: 4.07; 95% CI: 2.60–6.37). Authors acknowledged the bias introduced by varied cut off values by different researchers. The cut-off values of NLR varied from 1.505 to 5.0, with majority using >2.81. In another meta-analysis of 24 articles including 6,318 patients, high NLR before treatment predicted a poor OS (HR 1.54, 95% CI: 1.34–1.76, $P < 0.001$) and RFS (HR 1.45, 95% CI: 1.16–1.82, $P = 0.001$).

With regards to role of NLR in HCC patients treated by TACE, retrospective studies as well as a recent meta-analysis are available as evidence base. Huang *et al.* revealed that an elevated NLR was associated with poor OS among patients undergoing TACE and He *et al.* reported that NLR was less useful in patients receiving TACE for unresectable HCC (11,12). The recent meta-analysis included 16 retrospective studies and 4,023 patients from 2011 to 2019 (13). The NLR cut-off values were heterogeneous (range, 1.77 to 5). Authors concluded that elevated preoperative NLR was associated with poor OS in HCC patients treated by TACE (HR 1.81, $P < 0.00001$) and high NLR predicted tumor vascular invasion (OR 1.49, $P = 0.002$). In the subgroup analysis, statistical significance was found respectively in subgroup $NLR = 5.0$ (HR 1.74, 95% CI: 1.44–2.11), $2.5 \leq NLR < 5$ (HR 1.69, 95% CI: 1.50–1.91), and $NLR < 2.5$ (HR 2.06, 95% CI: 1.77–2.40).

In the January 2020 issue of *Annals of Translational Medicine*, Wang *et al.* reported role of NLR in predicting survival of patients with HCC undergoing TACE (14). Wang *et al.* treated 380 HCC patients with Child-Pugh score below 7 points and European Co-operative Oncology Group (ECOG) performance score ≤ 1 with a suspension of lipiodol (2–20 mL) and doxorubicin (10–50 mg) followed by absorbable gelatin sponge particle embolization until stasis within the tumour feeding vessels. They excluded patients with vascular invasion or any prior therapies. Mean tumour diameter was 7.9cm and patients could receive multiple TACE sessions (range, 1–12, median 2 sessions). Authors decided the cut-off value for NLR as 2.4 based on baseline median NLR. Three days following TACE, NLR increased by up to 6.3 and, at one month, NLR returned to baseline levels. The median follow-up duration was

18.3 months (range, 1.1–66.1 months) and median OS was 21.7 months (95% CI: 18.1–25.2 months). They categorized patients into high (NLR >2.4) and low (NLR ≤ 2.4) NLR. The low baseline NLR group showed improved OS compared with the high baseline NLR group (median OS, 27.1 vs. 15.6 months, respectively; $P = 0.004$, Figure 2A). One month after TACE, the median survival time of low NLR patients and high-NLR patients was 26.3 and 18.2 months, respectively ($P = 0.070$). Based on this information, authors divided patients into two groups: Group 1: Normal baseline and one-month post TACE NLR and Group 2: High baseline NLR or increased post TACE NLR at one month. Authors observed significant survival difference between the two groups. Median survival times of patients with normal NLR was 29.1 months (95% CI: 25.4–36.6 months) and those with high or increased NLR was 19.1 months (95% CI: 15.1–22.9 months) ($P = 0.023$). Based on these results, authors concluded that changes of baseline NLR are significantly associated with OS in HCC patients treated with TACE and suggest that patient selection and prognostic prediction may be refined in future.

Based on this information, I shall make an attempt to do a qualitative summary of available evidence and provide some guidance or take-home messages for hepatologists and hepatobiliary surgeons. To begin with, let us understand the role of lymphocytes and neutrophils in carcinogenesis. Lymphocytes play a significant role in cancer immune-surveillance. Lymphocyte depletion reflects an impaired antitumor response and lymphopenia is associated with inferior oncologic outcomes in patients with various gastrointestinal malignancies e.g. adenocarcinoma of pancreas (15,16). Neutrophils facilitate tumorigenesis and angiogenesis, promotes motility of cancer cells and modulates expression of matrix metalloproteases which helps tumour invasion and metastasis (17–19). Neutrophils are the primary source of circulating vascular endothelial growth factor (VEGF) and VEGF is associated with increased risk of recurrence in HCC (20,21). Thus, for prognosis of HCC patients, lymphocytes are ‘good’ and neutrophils are ‘bad’. Hence, elevated neutrophils (high NLR) and depleted lymphocytes (high NLR) are poor prognosticator. The first reference to NLR should be credited to Zahorec (22). They reported that severity of clinical course of 90 surgical oncologic intensive care unit patients was determined by divergence of neutrophil and lymphocyte count i.e. neutrophilia and lymphopenia. They first proposed the term “neutrophil-lymphocyte stress

factor". Since then, NLR has been widely validated.

I wish to emphasize four issues with regards to available evidence about utility of NLR in HCC patients treated by TACE. Firstly; all the studies are retrospective, secondly; the cut off point for NLR is not standardized, thirdly; majority studies don't differentiate if elevated NLR is primarily due to neutrophilia or lymphopenia or both and lastly, not every study measures and report related markers like VEGF. Li *et al.* has performed Newcastle-Ottawa Scale and reported that majority of the included studies had low or very low risk of bias and hence we should not dismiss the available evidence as low quality (13). Further, to conduct a prospective randomized controlled trial may not be feasible until ideal cut-off value of NLR is defined. With regards to varied cut off points of NLR reported by different authors, it appears that some consensus is essential. In my opinion, as NLR is easy to compute retrospectively, authors have preferentially reported the NLR which shows maximal statistical difference in effect size of therapy. Our group has reported about the role of inflammation-based indices and we chose NLR cut off at 2.7 (1). From the recent meta-analysis, I computed the mean NLR of the 16 studies to be around 3. Low NLR is good and hence I decided to examine the studies which report NLR cut-off value of 5. All the studies have directly or indirectly cited previous cut-off value of 5 which could be traced to Zahorec (22). It may not be ideal to use the cut-off value of 5 as Zahorec derived the value from the cohort of critically ill surgical patients in sepsis who are different than HCC patients. Further, as patients with sepsis are likely to have significant neutrophilia that could increase the value of NLR, I believe cut off value for HCC patients should be lower than 5. I propose future researcher could consider to use NLR cut-off value of 3 (approximate estimate). Also, future studies should consider reporting if elevated NLR was due to predominant neutrophilia or lymphopenia. If a research is planned prospectively, VEGF levels could be measured.

Now three most important questions to seek clarity are:

(I) What should be our approach for patients suitable for therapy with curative intent and have high baseline NLR?

Patients suitable for curative intent therapy should receive their therapy according to local protocols. NLR has prognostic role at best and doesn't influence therapeutic clinical decisions in patients who fulfill criteria for liver transplantation or liver resection. Based on the current evidence, it is possible that patients with high baseline NLR should be advised close follow-up to monitor recurrence or considered to be enrolled into clinical research for adjuvant

therapy.

(II) What should we do with patients who are not candidates for curative therapy and have high baseline NLR?

There is no one-size fit all approach. Local resources, technical expertise, reasons of non-resectability and patient choices impact clinical bedside decisions. In a retrospective study reporting 766 HCC patients, we have shown that outcomes of Barcelona Clinic Liver Cancer (BCLC) stage C patients were superior when they received Hong Kong Liver Cancer (HKLC) system guided therapy (23). Thus, patients with good liver functional reserve and suitable co-morbidity profile may be able to receive, tolerate and complete aggressive therapeutic approach and TACE is indeed complimentary in such treatment planning. So, at this point of time, there is not enough evidence to support that patients with high baseline NLR should be denied TACE. Upon completion of current recommended treatment, patients with high baseline NLR could be recommended close surveillance or enrolled into clinical research for systemic therapies including immunotherapy. Indeed, the knowledge of high baseline NLR and its association with poor prognosis is not immaterial as it aids in informed consenting and counselling of patients.

(III) What should we do with patients who have elevated NLR after some form of therapy e.g., surgery or TACE?

I would consider elevated post-treatment NLR as poor prognosticator and exercise caution to recommend further surgical resection or TACE. Patients may be advised high risk of relapse, offered to join ongoing clinical trials or advised best supportive care. I foresee that in majority of such patients, treatment will be guided by presence of liver dysfunction and co-morbidities.

In conclusion, NLR is a widely validated inflammation-based score that is simple, easy to compute and provides information about prognosis of HCC patients with regards to oncologic outcomes. Not only baseline elevated NLR, but also post-treatment elevated NLR i.e. dynamic changes are important clues which can potentially guide clinicians in making bedside decisions. High quality prospective studies are warranted to define the cut-off value of NLR in patients with HCC. In addition, NLR could be integrated with existing staging systems, used in guiding organ allocation for liver transplantation or add value to composite indices that predict liver dysfunction.

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Footnote

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