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Neutrophil-to-lymphocyte ratio as an index of treatment response to trans-arterial chemoembolization in hepatocellular carcinoma

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ABSTRACT

Aim: We evaluated the response to Trans-arterial chemoembolization (TACE) in hepatocellular carcinoma (HCC) patients according to modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria. We determined the prognostic value of the neutrophil-to-lymphocyte ratio (NLR).

Background: TACE is the most commonly used method to treat patients with large, unresectable tumors or as bridge therapy in patients with HCC before liver transplantation.

Methods: In this cross-sectional study, patients with a diagnosis of HCC who were referred for TACE were studied. The response rate to TACE treatment was assessed based on dynamic MRI 28 days after treatment according to mRECIST criteria. The NLR value was calculated, and its prognostic value was evaluated to predict the response to treatment.

Results: Forty patients with HCC who underwent TACE were included. The response to TACE treatment included a complete response (CR) in 6 patients (15%), partial response (PR) in 16 patients (40%), and stable disease (SD) in 18 patients (45%). No progressive disease (PD) was found. Responders (CR and PR) were 22 patients (55%). The mean NLR after treatment in the non-responders was significantly higher than in the responders (4.2 vs. 2.4, P-value = 0.026). NLR values greater than 2.6 after treatment had a sensitivity of 70.6% and a specificity of 77.3% in diagnosing non-responders, with an Area Under the Curve (AUC) of 0.73 [95% confidence interval 0.58-0.89], P-value = 0.011.

Conclusion: Non-responders observed higher levels of NLR after treatment than responders. As a moderate prognostic factor, an NLR level of more than 2.6 after treatment could discriminate against non-responders.

Keywords: Hepatocellular carcinoma, Therapeutic chemoembolization, Liver transplantation

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Introduction

With over 906,000 new cases and 830,000 deaths from cancer globally in 2020, primary liver cancer ranks as the third most prevalent cause of cancer-related deaths worldwide and the sixth most commonly diagnosed disease (1). Men have incidence and mortality rates that are two to three times higher than those of women. Hepatocellular carcinoma (HCC) accounts for 75%–85% of primary liver cancer (1, 2).

Despite treatment strategies and technology improvements, its prognosis has remained poor (3). Trans-arterial chemoembolization (TACE) is largely used for HCCs in their early stages. Thus, unresectable large-size tumors or multifocal tumors without invasion of the portal vein can be managed with TACE (4). Also, it is widely

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recommended as a 'bridge' therapy for patients on the transplantation list. Although it has improved the survival of patients, there are still variable prognoses among HCC patients undergoing TACE (5, 6).

Many factors have been implemented to assess the survival and prognosis of patients undergoing TACE, such as those related to the tumor, such as vascularity and portal invasion, Child-Pugh score, C-reactive protein, CT vascularization, and blood cell ratios (7-10). Also, scoring systems have been created for this purpose, like the modified Response Evaluation Criteria in Solid Tumors (mRECIST) index systems, which use the density and regression of tumors from imaging modalities (11, 12).

In patients with HCC, inflammatory cytokines induce a systemic immune response (13). The neutrophil-to-lymphocyte ratio (NLR) has been reported to be a prognostic tool in many disorders, such as ovarian cancer, colorectal cancer, and HCC (10, 14, 15). However, NLR's prognostic ability for HCC is still controversial. The majority of earlier research demonstrated that NLR is an independent predictor of overall survival (OS) (16), while Sullivan et al. discovered no connection between NLR and lower OS (17). Also, another study showed that an increased NLR rather than a decreased NLR for patients after TACE suggested a better outcome (18). Hence, this study aimed to investigate the prognostic value of NLR as a tumor biology marker in HCC patients undergoing TACE.

Methods

Study design and population

This is a retrospective cross-sectional study on HCC patients who underwent TACE therapy in Imam Khomeini Hospital Complex's liver transplantation unit during 2019 and 2020.

Data collection tools and methods

Radiologic features of the tumor were assessed from a dynamic MRI of the liver one week before TACE and another one 28 days after the procedure. For some patients, TACE was performed in two sessions. Measures are reported for the last session in such cases. Response to treatment was evaluated by an expert radiologist based on mRECIST criteria. According to the mRECIST criteria (12), a complete response (CR) was defined as the absence of intratumoral arterial contrast enhancement in all the lesions.

Similarly, a partial response (PR) was defined as a more than 30% reduction in the sum of the diameters of viable lesions with arterial phase enhancement. Progressive disease (PD) was considered if there was more than a 20% increase in the sum of the diameters of viable lesions with arterial phase enhancement. Patients not fitting any of these categories were considered to have stable disease (SD). Complete or partial responses were classified as the 'responders' group, while all others were classified as the 'non-responders' group. Demographic information, clinical and drug histories, and laboratory reports were also collected. Neutrophil and lymphocyte counts were extracted from the complete blood count with differential (CBC diff), and NLR was calculated accordingly.

Data Analysis Methods

Qualitative variables were reported with their count and percentage. The normal distribution of quantitative values was evaluated with histograms and the Shapiro-Wilk normality test. Mean and standard deviation (SD) were used for summarizing variables with a normal distribution. Median and interquartile range (IQR) were utilized for variables with a non-normal distribution. Independent and paired samples Student's t-tests, analysis of variance (ANOVA), and Chi-square test (χ^2) were performed accordingly for comparison. Mean difference (MD) and standard error (SE) were used for reporting paired-samples analysis. Receiver Operating Characteristic (ROC) curve analysis and the Area Under the Curve (AUC with a 95% confidence interval (CI)) were employed for prognostication and sensitivity analysis. An AUC higher than 0.7 was considered a good prognostic and discriminating tool. In the next step, we used a productive function [sensitivity × specificity] for statistically significant ROC curves and coordinates to search for the highest-yielding number and its respective NLR as the best cut-off point (19). An alpha level of <0.05 was considered significant. Statistical analyses were performed using R statistical package v4.0.3 [R Foundation for Statistical Computing, Vienna, Austria] and SPSS v24 [IBM SPSS Statistics, Armonk, NY]. There was no missing data.

Ethical considerations

This study was approved by the Tehran University of Medical Sciences ethics committee (IR.TUMS.IKHC.REC.1397.245).

Results

In total, forty patients with HCC were included in the study. The mean (SD) age of participants was 62.3 (9.8) years, and 28 (70.0%) were male (Table 1). Eleven (27.5%) patients received TACE twice. The median (IQR) tumor size was 39.5 (29.7) millimeters, with positive skewness before TACE. Most patients were bicytopenic or pancytopenic before TACE based on laboratory results. White blood cell (WBC) changes before and after TACE were insignificant. The mean NLR was 2.3 (1.0) before TACE and 3.2 (2.6) after TACE, representing a significant increase (MD [SE] = -0.9 [0.4], P-value = 0.036) (Table 1).

Considering mRECIST criteria, 6 patients revealed CR, 16 patients PR, 18 patients SD, and no one showed PD. As a result, 22 (55%) patients were in the responders group. The mean age of non-responders (68.7 [9.3]) was significantly higher than that of responders (57.0 [6.5], P-value < 0.001). Lymphocyte counts were significantly different between responders and non-responders after TACE, i.e., in the non-responders group, it was 878.8 (448.2), which was lower than in the responders (1269.3 [442.2], P-value = 0.010) group. In contrast, neutrophil counts of non-responders (2720.6 [457.1]) were higher than those of responders (2396.1 [470.2], P-value = 0.037). Post-TACE NLR calculation revealed almost twice the difference, with 4.2 (2.9) for non-responders and 2.4 (2.0) for responders (P-value = 0.026). Such variations were not observed in pre-TACE and other measurements (Table 2).

ROC curve analysis revealed that NLR calculation before the TACE procedure had no discriminating or prognostic ability (AUC = 0.38 [95% CI 0.20–0.57], P-value = 0.221), as opposed to post-TACE calculation (AUC = 0.73 [95% CI 0.58–0.89], P-value = 0.011). The results indicate that higher NLR measurements after TACE were related to non-response based on mRECIST categories. Post-hoc analysis of a significant ROC curve disclosed a cut-off of 2.6 with 70.6% sensitivity and 77.3% specificity.

Table 1. Baseline characteristics and WBC data of participants

	Before TACE	After TACE	P-value
Age (mean (SD))	62.3 (9.8)	-	
Gender (Males count (percent))	28 (70.0%)	-	
WBC	3671.5 (521.1)	3708 (472.3)	0.698
Neutrophil	2468.1 (480.2)	2537.6 (486.5)	0.438
Lymphocyte	1203.4 (356.7)	1099.1 (480.7)	0.267
NLR	2.3 (1.0)	3.2 (2.6)	0.036

Table 2. Baseline characteristics and WBC data of responders and non-responders groups

	Responders	Non-responders	P-value
Age (mean (SD))	57.0 (6.5)	68.7 (9.3)	<0.001
Gender (Males count (percent))	16 (72.7)	23 (66.7)	0.738
Lab data before TACE			
WBC (mean (SD))	3680.6 (436.5)	3685.4 (619.0)	0.977
Neutrophil	2508.2 (453.6)	2428.6 (509.2)	0.604
Lymphocyte	1172.3 (273.7)	1256.8 (438.3)	0.604
Hemoglobin	10.4 (1.3)	10.4 (1.3)	0.901
Platelet (103)	95.5 (9.5)	99.8 (9.8)	0.173
NLR	2.3 (0.9)	2.2 (1.2)	0.792
Lab data post-TACE			
WBC (mean (SD))	3731.4 (433.2)	3679.4 (531.0)	0.738
Neutrophil	2396.1 (470.2)	2720.6 (457.1)	0.037
Lymphocyte	1269.3 (442.2)	878.8 (448.2)	0.010
NLR	2.4 (2.0)	4.2 (2.9)	0.026

Discussion

The HCC rate has been increasing in recent years as populations are aging, chronic liver disorders are becoming more prevalent, and communities are transitioning from communicable to non-communicable diseases (20-22). Furthermore, advancements in technology and diagnostic tools have led to earlier cancer diagnoses (23). Although this has resulted in the early detection of hepatic masses, a significant portion of tumors still present with invasion of the portal vein and other structures (24). Total resection of the tumor is not feasible in these cases, so adjuvants are used to reduce tumor size and invasion before surgical intervention. TACE is among the most common methods for treating patients with large, unresectable HCC tumors. Additionally, this method is widely used for bridge therapy in HCC transplant candidates.

The main finding of this study is that NLR calculation 28 days after TACE is a moderate prognosticator of poor response to treatment, with an NLR value of 2.6 being the optimal value for distinguishing good and poor outcomes, with 70.6% sensitivity and 77.3% specificity. Given its low cost, availability, simplicity, accuracy, and prognostic power, NLR could be added to HCC staging systems for better evaluation. No other cell count showed such discriminatory power, and pre-TACE analysis of NLR was not useful.

TACE does not completely eradicate tumors. Several published meta-analyses indicate that neoadjuvant TACE does not improve HCC prognosis (25, 26). A large systematic review and meta-analysis of 12,372 patients revealed a 52.5% success rate for TACE, with a mean survival duration of 19.4 months and a five-year survival rate of 32.4% (27). In our study, 55% of patients responded to TACE, a proportion similar to previous studies.

Finding prognostically useful indicators is crucial for guiding clinical decisions about adjuvant or neoadjuvant therapy options. The mRECIST criteria are valid sets that comprehensively assess tumor necrosis using dynamic magnetic imaging (12). In a study of 245 patients receiving TACE treatment, the survival rate was much worse in non-responders (SD + PD) (28). Similarly, mRECIST scores were found to correlate with survival (29). Jun et al. demonstrated that a high blood CRP level is significantly linked to a 10-month mortality rate in patients with large HCC undergoing TACE (8). Hasdemir et al. showed that the vascularization pattern of the largest HCC lesion can be used as an index for survival prognosis under TACE treatment (9).

NLR's prognostic ability for HCC remains controversial, prompting this study. We found that NLR correlates with mRECIST categories and can be used as an adjunct. However, other studies have reported different findings. Most earlier research demonstrated that NLR is an independent predictor of overall survival (OS) (16), while Sullivan et al. found no connection between NLR and lower OS (17). Another study suggested an increased NLR rather than a decreased NLR after TACE indicated a better outcome (18). While some studies mention that pre-TACE NLR is associated with treatment response, this was not detectable in our sample (30, 31). Increased lymphocytes are an anti-tumoral response to malignant cells. However, a higher neutrophil count and increased NLR indicate a suppressed immune system that permits angiogenesis and invasion of tumor cells (32-34). A study on NLR’s dynamic change after TACE showed that NLR increased for the first three months and then significantly decreased to lower values (35). Controversial findings may relate to the timing of sample collection, and a dynamic assessment of NLR might be more informative (35, 36). Hong et al. showed that high NLR correlated with vascular invasion (≥1.6) and can be considered a predictive factor of long-term survival in patients with resectable HCC who are candidates for neoadjuvant TACE (37).

The exact pathophysiology for the correlation between elevated NLR and poor survival in patients with different cancers is not determined. The body's systemic inflammatory reaction to tumor growth may create an environment conducive to tumor advancement (38). For instance, increased neutrophils produce cytokines such as vascular endothelial growth factor, interleukin-18, and matrix metalloproteinases, hindering the anti-tumor response of natural killer cells and activated T cells, contributing to tumor progression (39, 40). At the same time, decreased lymphocytes could weaken the host's anti-tumor response. Consequently, a high NLR may indicate a tumor microenvironment that promotes tumor progression.

Being limited to one center's patients and the referral nature of our center may have influenced our results and the homogeneity of the sample. Moreover, short follow-up, cross-sectional assessment, and potential biases were among the limitations of this work.

Additional research is required to validate these results. Larger, well-designed prospective studies with follow-up data, dynamic NLR evaluation, and confounding factor modifications may yield more accurate prognostic results. Additionally, we advise research to evaluate various indicators that may be therapeutically helpful in more accurately predicting survival. Moreover, NLR could be combined with current staging methods.

Conclusion

TACE has become a fundamental part of HCC treatment. Efforts should be made in clinical and scientific centers to understand tumor behavior and associated factors for invasive approaches to reduce undesired outcomes and select the best-responding patients during pre-operative sessions. A combination of neutrophil and lymphocyte counts can adjunct mRECIST in post-TACE procedures. Baseline NLR and follow-up crude counts of blood cells have not shown promising results. Although NLR can be used in selected cases, its trend and serial measurement are more informative. Larger studies with follow-up data and adjustments for confounding contributors may yield more accurate results with predictive features.

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Conflict of interests

The authors declare that they have no competing interests.

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