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# The Relationship Between Blood Neutrophil to Lymphocyte Ratio and Tumor Size, Tumor Number, Macrovascular Invasion in Patients with Hepatocellular Carcinoma

## Hepatosellüler Karsinomalı Hastalarda Kan Nötrofil Lenfosit Oranı ile Tümör Boyutu, Tümör Sayısı ve Makrovasküler İnvazyon Arasındaki İlişki

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## ABSTRACT

**Aim:** We aimed to show the relationship between blood neutrophil to lymphocyte ratio that is systemic inflammatory marker and tumor size, tumor number, macrovascular invasion at the time of diagnosis in patients with hepatocellular carcinoma.
**Methods:** A total 48 patients diagnosed with hepatocellular carcinoma were included in our study. The patients were divided into two groups according to the median neutrophil to lymphocyte ratio.
**Results:** A total of 48 patients (11 female, 37 male) were included in our study. The mean age of the patients were 67.18±9.51 years-old. The median neutrophil to lym-phocyte ratio was 3.17. There were significant association between neutrophil to lym-phocyte ratio > 3.17 and macrovascular invasion, the tumor number> 3, the tumor size> 5 cm, Child-Turcot-Pugh score, Model for End-stage Liver Disease-Sodium score, C-reactive protein and blood sodium level (p: 0.005, p: 0.009, p< 0.001, p: 0.003, p:0.008, p: 0.035 and p < 0.001, respectively). Multiple logistic lineer regres-sion analysis showed that NLR> 3.17 was an independent predictor of tumor size> 5 cm and hyponatremia in patients with hepatocellular carcinoma (p: 0.010, p: 0.012, respectively).
**Conclusions:** The value of blood neutrophil to lymphocyte ratio at the time of diag-nosis in patients with hepatocellular carcinoma was a good predictor of tumor size and grade of disease.

Key words: Neutrophil to lymphocyte ratio, Tumor size, Hepatocellular carcinoma

## ÖZ

**Amaç:** Hepatosellüler Karsinomu olan hastalarda tanı anındaki tümör boyutu, tümör sayısı ve makrovasküler invazyon ile kan nötrofil lenfosit oranı arasındaki ilişkiyi gös-termeyi amaçladık.
**Hastalar ve Method:** Çalışmaya toplam 48 hepatosellüler karsinomalı hasta dahil edildi. Hastalar ortalama nötrofil lenfosit oranına göre ikiye bölündü.
**Bulgular:** Toplam 48 hastanın 11'i kadın, 37'si erkek idi. Hastaların ortalama yaşı 67,18±9,51 idi. Ortalama nötrofil lenfosit oranı 3,17 idi. Nötrofil lenfosit oranı (NLR)>3,17 olan hastalarda makrovasküler invazyon, tümör sayısının>3, tümör boyutu>5 cm, Child-Turcot-Pugh skor, Model for End-stage Liver Disease- Sodyum skor, C-reaktif protein and kan sodyum seviyesi ile arasında istatistiksel olarak an-lamlı birliktelik izlendi (p: 0.005, p: 0.009, p< 0.001, p: 0.003, p:0.008, p: 0.035 ve p < 0.001, sırasıyla). Multiple lojistik lineer regresyon analizİ; hepatosellüler karsinomlu hastalarda NLR> 3.17 olması tumor boyutu> 5 cm and hiponatreminin bağımsız bir belirteci olduğunu gösterdi (p: 0.010, p: 0.012, sırasıyla).
**Sonuç:** Hepatosellüler karsinomalı hastalarda tanı anındaki kan nötrofil lenfosit oranının değeri, tümör boyutunun ve hastalık evresinin iyi bir belirtecidir.

Anahtar kelimeler: Nötrofil lenfosit oranı, Tümör boyutu, Hepatosellüler karsinoma

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## INTRODUCTION

Hepatocellular carcinoma (HCC) is a primary malignant tumor of the liver. HCC is the third most common cause of cancer-related deaths worldwide [1]. HCC often develops in patients with chronic liver disease. Chronic liver disease is assessed using routine imaging and alpha-fetoprotein (AFP) levels. Different classifications have been proposed for the diagnosis and stages of HCC, as follows: the Barcelona Clinic liver cancer (BCLC) classification [2], the tumor node metastasis (TNM) classification, the functional liver reserve score, and the Child-Turcot-Pugh scores. There are many factors to consider when determining HCC treatment including tumor numbers, tumor size, and macrovascular invasion, which are evaluated using radiological imaging prior to treatment. Curative hepatic resection, radiofrequency ablation (RFA), and liver transplantation (LT) are primary treatment methods [3]. When HCC is diagnosed at an advanced stage, transarterial embolization (TAE)/transarterial chemoembolization (TACE) and multiple tyrosine kinase inhibitors, such as sorafenib, are alternative treatment options [4]. Despite this, the prognosis of HCC after treatment is not always as positive as anticipated. Consequently, these classifications may not always reflect the true stage of the disease.

Recent studies have shown a relationship between the HCC prognosis and a systemic inflammatory response [5]. The presence of a tumor elicits a systemic inflammatory response, and this is associated with the prognosis [6,7]. Previous studies have demonstrated the neutrophil-to-lymphocyte ratio (NLR) to be a good prognostic predictor of different HCC treatment options such as resection, RFA, LT, TACE and sorafenib [8,9]. The NLR is used as a systemic inflammatory response marker[ 8]. We aimed to demonstrate the relationship between the NLR at the time of HCC diagnosis and tumor size, tumor number, macrovascular invasion, and capsule involvement.

## METHODS

A total of 60 HCC patients were evaluated between January 2009 and December 2011 at a university-affiliated hospital retrospectively. The study protocol was approved by the ethics committee of Necmettin Erbakan University (2012/92). HCC patients diagnosed according to the American Association for the Study of Liver Disease (AASLD) [10] criteria at inpatient and outpatient clinics at our university-affiliated hospital were included in this study. Patients were excluded from the study if they demonstrated any of the following complications: sepsis, active infection, and active bleeding, or if they were undergoing steroid therapy. A total of 12 patients were excluded from this study due to sepsis (n=2), active infection (n=5), active bleeding (n=1), and incomplete data (n=4). Finally, a total of 48 patients were included in this study. The etiologies for HCC were as follows: viral hepatitis (n=35, 27 patients with chronic hepatitis B, and 8 patients with chronic hepatitis C), autoimmune hepatitis (n=1), and cryptogenic cirrhosis (n=12). All demographic, clinical, and laboratory data were recorded, including CTP and MELD-Na results, according to the United Network for Organ Sharing Formula [11], and the NLRs were calculated. An autoanalyzer (Abbott Cell-Dyn Ruby Analyzer) was used for blood parameters by using peripheral blood samples with EDTA. We calculated the NLR as the ratio of neutrophil-to-lymphocytes in the complete blood count.

The median NLR value was calculated according to all the patient values. The patients were divided into two groups, according to whether their NLR was below or above the median NLR value. The variables were tumor size >5 cm, tumor number >3, macrovascular involvement, capsule involvement, AFP, CRP, serum sodium, CTP score and MELD-Na score. We examined the relationship between the NLR at the time of HCC diagnosis and tumor size, tumor number, macrovascular invasion, and capsule involvement.

Statistical Analysis: Descriptive statistics were expressed as mean ± standard deviation or median (minimum to maximum) for continuous numerical variables, while categorical variables were expressed as number of patients and percentages (%).

Univariate logistic regression analysis was used to evaluate the significance of factors that might be effective in differentiating groups with an NLR ≤3.17 and an NLR >3.17. The effects of factors considered to be the most determinative in distinguishing the groups were investigated using mul-

tiple logistic regression analysis. Variables identified as p<0.01 as a result of univariate statistical analyses were included in the logistic regression models as candidate risk factors. Additionally, the odds ratio (OR), 95% confidence intervals (CI), and Wald statistics for each variable were calculated.

Analyses of the data were performed using the IBM SPSS Statistics 17.0 (IBM Corporation, Armonk, NY, USA) program. The results were considered statistically significant when the p-value was <0.05.

## RESULTS

A total of 11 women and 37 men participated in this study, and the mean age was 67.18±9.51 years. Of these 48 patients, there were 35 patients with viral hepatitis (27 patients with chronic hepatitis B, 8 patients with chronic hepatitis C), 1 patient with autoimmune hepatitis, and 12 patients with cryptogenic cirrhosis.

Demographic and laboratory parameters in all patients are presented in Table-1. Clinical parameters are presented in Table-2. There were no statistically significant differences between the NLR groups above and below 3.17 considering age, sex, and AFP (p=0.309, p=0.732, and p=0.096, respectively) (Table-3). The presence of macrovascular invasion significantly increased by 7-fold the likelihood of an NLR above 3.17 (p=0.005, 95% CI: 1.822-26.887).

Although the NLR was >3.17 in all of those with capsule involvement, no significant association was found between the NLR and capsule involvement (p>0.05). The OR and 95% CIs for capsule involvement were not calculated because there were no patients with capsule involvement and an NLR ≤3.17.

When the number of tumors was 3 or more, the likelihood of an NLR >3.17 was 5.959-times higher than for patients with 3 or fewer tumors, which was significant (p=0.009, 95% CI: 1.546-22.580).

The likelihood of an NLR >3.17 was 22-times higher in patients with a tumor size >5 cm (p<0.001, 95% CI: 4.109-117.804). As the CRP level, CTP score, and MELD-Na score increased, the likelihood of an NLR >3.17 also increased significantly (p=0.035, p=0.003, and p=0.008, respectively).

If the serum sodium level decreased, the likelihood of an NLR >3.17 significantly increased (p=0.001, OR: 0.649, 95% CI: 0.507-0.829).

**Table 1. Demographic and Laboratory Findings in All Patients.**

| Parameters | N | Mean± SD |
|---|---|---|
| Age (years) | 48 | 67.18± 9.51 |
| Duration of disease (years) | 48 | 5.84± 4.2 |
| AFP (ng/ml) | 48 | 1228.0± 451.78 |
| Haemoglobin (g/dl) | 48 | 11.8± 1.98 |
| Neutrophil count ($\times10^3$/ml) | 48 | 4225.7± 2009.02 |
| Lymphocyte count ($\times10^3$/ml) | 48 | 1256.3± 464.54 |
| Platelet count ($\times10^3$/ml) | 48 | 169783.3± 8598.25 |
| CRP (mg/l) | 48 | 37.3± 32.80 |
| INR | 48 | 1.3± 0.18 |
| Albumin (g/dl) | 48 | 3.2± 0.50 |
| Creatinine (mg/dl) | 48 | 1.31± 1.01 |
| AST (U/L) | 48 | 73.9± 53.18 |
| ALT (U/L) | 48 | 67.77± 56.66 |
| ALP (U/L) | 48 | 126.1± 71.75 |
| GGT (U/L) | 48 | 93.4± 75.85 |
| Total Bilirubin (mg/dl) | 48 | 2.37± 1.8 |
| Serum Na (mEq/l) | 48 | 135.6± 3.87 |
| NLR | 48 | 3.6± 2.06 |
| CTP score | 48 | 6.6± 1.18 |
| MELD- Na score | 48 | 12.3± 4.81 |

AFP. Alpha fetoprotein; CRP, C-reactive protein; INR, international normalized ratio; AST, Aspartat amino transferase; ALT, Alanina amino transferase; ALP,alkaline phosphatase; GGT,gama glutamyl transferase; Na, Sodium, CTP, Child–Turcotte–Pugh; MELD, Model for End-Stage Liver Disease; NLR, neutrophil-to-lymphocyte ratio;

According to the prospective stepwise logistic regression model, the factors determining the NLR according to the current results were tumor size and serum sodium level (Table-4). Regardless of other factors, a tumor size >5 cm increased the likelihood of an NLR >3.17 by 11.018 fold, which was significant (p=0.010, 95% CI: 1.764-68.831). In addition, if the NLR value was >3.17, the sodium value decreased significantly. (p=0.012, OR: 0.702, 95% CI: 0.534-0.924).

**Table 2. Clinic Features of All Cases.**

| | Numbers of cases | Percentages (%) |
|---|---|---|
| Gender | | |
| Female | 11 | 22.9 |
| Male | 37 | 77.1 |
| Accompanying diseases | | |
| DM | 5 | 10.4 |
| HT | 9 | 18.7 |
| CAD | 2 | 4.2 |
| Causes of CLD | | |
| CHB | 27 | 56.2 |
| CHC | 8 | 16.7 |
| Autoimmune Hepatitis | 1 | 2.1 |
| Cryptogenic | 12 | 25.0 |
| Ascites | 21 | 43.7 |
| Hepatic Ensephalopathy | 1 | 2.1 |
| Endoscopic varices | 31 | 64.6 |
| Grade of varices | | |
| 0 | 17 | 35.4 |
| 1 | 11 | 22.9 |
| 2 | 15 | 31.2 |
| 3 | 5 | 10.4 |
| Macrovascular invasion | 18 | 37.5 |
| Capsule involvement | 4 | 8.3 |
| Tumor number > 3 | 17 | 35.4 |
| Tumor size > 5 cm | 30 | 62.5 |
| Treatments for HCC | | |
| RFA | 8 | 16.6 |
| TACE | 19 | 39.5 |
| Resection | 1 | 0.2 |
| Palliative | 16 | 33.3 |
| Another (sorafenib) | 4 | 8.3 |
| NLR | | |
| <= 3.17 | 24 | 50.0 |
| > 3.17 | 24 | 50.0 |
| Total | 48 | 100.0 |

DM, Diabetes mellitus; HT, hypertension; CAD, chronic artery disease; CLD, chronic liver disease; CHB, chronic hepatitis B; CHC, Chronic hepatitis C; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; LT, liver transplantation; NLR, neutrophil to ymphocyte ratio

**Table 3. Examination of Univariate Logistic Regression Analysis and Univariate Effects of Factors That Might be Predictive of NLR> 3.17**

| | NLR≤3.17 (n=24) | NLR>3.17 (n=24) | p-value | Odds ratio (95% Confidence Interval) |
|---|---|---|---|---|
| Age (years) | 65.8±10.2 | 68.7±9.2 | 0.309 | 1.033 (0.971-1.098) |
| Male factor | 18 (75.0%) | 19 (79.2%) | 0.732 | 1.267 (0.328-4.889) |
| AFP (ng/ml) | 29.5 (2.5-478) | 300 (2.6-36000) | 0.096 | 1.003 (0.999-1.006) |
| Macrovascular invasion | 4 (16.7%) | 14 (58.3%) | 0.005 | 7.000 (1.822-26.887) |
| Capsule involvement | 0 (0.0%) | 4 (16.7%) | 0.109 | NA |
| Tumor number > 3 | 4 (16.7%) | 13 (54.2%) | 0.009 | 5.909 (1.546-22.580) |
| Tumor size > 5 cm | 8 (33.3%) | 22 (91.7%) | <0.001 | 22.000 (4.109-117.804) |
| Haemoglobin (g/dl) | 12.1±2.0 | 11.5±1.9 | 0.336 | 0.864 (0.642-1.163) |
| Platelet count (×103/ml) | 127 (49-270) | 148.5 (6.2-1106) | 0.325 | 1.000 (1.000-1.000) |
| Duration of disease (years) | 3 (0.25-13) | 2 (0.25-30) | 0.575 | 1.038 (0.911-1.182) |
| CRP (mg/l) | 16.5 (5.3-126) | 35.5 (8-124) | 0.035 | 1.024 (1.002-1.047) |
| INR | 1.2±0.2 | 1.3±0.2 | 0.229 | 7.830 (0.273-224.635) |
| Albumin (g/dl) | 3.4±0.5 | 3.0±0.4 | 0.029 | 0.229 (0.061-0.861) |
| Creatinine (mg/dl) | 0.8 (0.5-1.3) | 1.0 (0.7-9.9) | 0.021 | 41.225 (1.752-970.118) |
| AST (U/L) | 52 (21-172) | 67 (17-312) | 0.249 | 1.007 (0.995-1.020) |
| ALT (U/L) | 38 (16-258) | 51 (7-361) | 0.501 | 1.003 (0.994-1.012) |
| GGT (U/L) | 71 (24-427) | 79 (25-213) | 0.837 | 0.999 (0.992-1.007) |
| Total Bilirubin (mg/dl) | 1.1 (0.6-2.8) | 1.2 (0.6-13.9) | 0.300 | 1.423 (0.730-2.773) |
| CTP score | 6 (5-9) | 7 (6-10) | 0.003 | 2.997 (1.448-6.205) |
| MELD- Na score | 10 (6-17) | 14.5 (7-25) | 0.008 | 1.249 (1.058-1.475) |
| Na (mEq/l) | 140 (132-142) | 133.5 (128-136) | <0.001 | 0.649 (0.507-0.829) |

AFP. Alpha fetoprotein; CRP, C-reactive protein; INR, international normalized ratio; AST, Aspartat amino transferase; ALT, Alanina amino transferase; GGT,gama glutamyl transferase; Na, Sodium, CTP, Child–Turcotte–Pugh; MELD, Model for End-Stage Liver Disease; NLR, neutrophil-to-lymphocyte ratio; NA: Not available

Table 4. The Effects of All Possible Risk Factors Thought to be Predictive of NLR> 3.17 with Multiple Prospective Logistic Regression Analysis

| | Odds ratio | 95% Confidence Interval for Exp (B) | | Wald |
|---|---|---|---|---|
| Tumor size > 5 cm | 11.018 | 1.764 | 68.831 | 6.589 |
| Na | 0.702 | 0.534 | 0.924 | 6.381 |

Na: sodium. Multiple Cox regression analysis with the forward conditional stepwise method.

## DISCUSSION

In our study, the NLR was significantly predictive of tumor size independent of MELD-Na and CTP (p=0.010). All previous studies concerning the NLR and HCC have reported on the prognosis following various HCC treatments [8,9]. Treatment decisions are based on HCC staging. Our study suggests that the NLR may be more useful in determining HCC staging than the current staging systems, such as the BCLC, as they do not always predict HCC staging accurately. If the NLR was >3.17 in the HCC patients, we considered the prognosis as poor, and we decided on a higher stage of HCC in patients who had otherwise been classified at a lower stage according to other current staging systems. Including the NLR in addition to the current liver transplantation criteria may provide a more accurate indication and prognosis for HCC patients.

One study has shown that a combination of an NLR and tumor size were effective tools for assessing prognosis in hepatitis B-associated HCC [12].

One meta-analysis has shown that an increased NLR or platelet-to-lymphocyte ratio (PLR) indicated poor outcomes for HCC patients, and suggested that the NLR and PLR could be considered reliable and inexpensive biomarkers for clinical decision-making concerning HCC treatment [13].

He et al. reported that the pre-treatment NLR, the tumor diameter, and the pre-treatment alpha-fetoprotein (AFP) levels were independent predictors of overall survival for HCC patients who had been treated with TACE [14]. Our study suggested that the NLR was related to tumor size but not to AFP levels.

Decision-making for treatment of HCC is very important and the BCLC system, one of the current prognostic staging systems, includes 5 major parameters such as tumor size, tumor number, Child-Turcot-Pugh score, physical status, and tumor metastasis to inform and support treatment decisions. Portal vein thrombosis, tumor size, and alpha-fetoprotein are other prognostic variables [15].

There are several alternative staging systems, including the Cancer of the Liver Italian Program (CLIP) system [16], the Hong Kong Liver Cancer (HKLC) system [17], and the Japan Integrated Scoring (JIS) system [18].

More recently, systemic inflammatory markers have shown an association with HCC prognosis. The NLR is a readily available inexpensive marker used to assess systemic inflammatory changes. The NLR reflects the potential balance between neutrophil-associated pro-tumor inflammation and lymphocyte-dependent anti-tumor immune function [19-22].

Another study suggested that Ishak stage 0-5 patients with a high NLR were associated with a poor outcome, independent of tumor size, and reported that only NLR correlated with PD-L1 expression in the center of the tumor, but not in non-neoplastic liver tumors [23]. The results of our study support a high NLR as an important indicator of tumor size and hyponatremia. As a result, NLR may reflect the real tumor size, including the non-detected microdots with imaging.

Oh et al. reported that CRP and NLR were important prognostic biomarkers for HCC [24]. We have shown a significant relationship between the NLR and CRP in our study. However, NLR >3.17 was an independent determinant of tumor size.

Yoshizumi et al. identified independent risk factors for after living-donor LT tumor recurrence including tumor size, tumor number, and an NLR of 4 or more [25]. In our study, we also observed that NLR >3.17 was an independent indicator of tumor size.

In this study, if the tumor size was <5 cm in the case of imaging measurements in patients with NLR>3.17, it could not be predicted the real tumor size. Although the patients with HCC have lower stage as staging systems, we should consider the

true status of the patients when NLR was higher than 3.17 at the same patients.

All previous studies concerned the NLR and its effect on survival in patients with HCC who received various treatments. However, our study is associated with the predictive ability of NLR on pretreatment assessment of HCC.

Our study had some limitations. First, this was a retrospective study. Second, there was no control group. Third, our study had a small number of patients. In future, prospective studies that include higher patient numbers are required to better elucidate the predictive ability of pretreatment assessment.

In conclusion, NLR may be considered a component of the staging system in the future. NLR also may be used to assist in the selection of treatment options for HCC.

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