Preoperative inflammatory markers of NLR and PLR as an indicator of poor prognosis in resectable HCC

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Background: Recently, many studies have demonstrated that chronic inflammation plays a predominant role in cancer cells propagation, angiogenesis and immunosuppression. Cancer-related inflammation (CRI) has been shown to be correlated with poor cancer outcome. Our study aim to evaluate the prognostic value of the neutrophil-to lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in HCC patients who underwent liver resection. Methods: Between 2012 and 2015, 239 patients with HCC who received liver resection at XiangYa Hospital Central South University were included in this study. The values of simple inflammatory markers including NLR and PLR in predicting the long-term outcomes of these patients were evaluated using Kaplan-Meier curves and Cox regression models. Results: The cutoff value of NLR and PLR were 2.92, 128.1. In multivariate Cox regression analysis, high NLR (≥ 2.92) and high PLR (≥ 128.1) were independent risk factors predicting poorer outcomes in HCC patients. However, high NLR and high PLR were prognostic factors in tumor size and tumor number. Conclusions: In this study, we identified that high NLR (≥ 2.92) and high PLR (≥ 128.1) are useful prognostic factors to predict outcomes in patients with HCC patients who underwent liver resection.

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Abstract

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Methods: Between 2012 and 2015, 239 patients with HCC who received liver resection at XiangYa Hospital Central South University were included in this study. The values of simple inflammatory markers including NLR and PLR in predicting the long-term outcomes of these patients were evaluated using Kaplan-Meier curves and Cox regression models.

Results: The cutoff value of NLR and PLR were 2.92, 128.1. In multivariate Cox regression analysis, high NLR ($\geqslant$ 2.92) and high PLR ($\geqslant$ 128.1) were independent risk factors predicting poorer outcomes in HCC patients. However, high NLR and high PLR were prognostic factors in tumor size and tumor number.

31 Conclusions: In this study, we identified that high NLR (≥ 2.92) and high PLR (≥128.1) are
32 useful prognostic factors to predict outcomes in patients with HCC patients who underwent liver
33 resection.

Introduction

Hepatocellular carcinoma (HCC) is the most common cancer and third leading cause of cancer-related death worldwide[1]. Hepatitis infection plays a leading role in HCC occurrence and progression[2]. Owing to the high percentage of hepatitis B virus (HBV) and aflatoxin infection, China alone accounts for approximately half of all HCC cases and HCC is a major medical burden in our country. Hepatectomy and liver transplantation are considered as the curative treatment for HCC patients[3, 4], and, despite improved diagnosis and advances in surgical techniques, the clinical outcome of HCC still poor[5].

Recently, many studies have demonstrated that chronic inflammation plays a predominant role in cancer cells propagation, angiogenesis and immunosuppression[6]. Cancer-related inflammation (CRI) has been shown to be correlated with poor cancer outcome[7, 8]. The inflammation caused by EB virus infection is related to nasopharyngeal cancer, hepatitis virus infection leads to HCC, and Helicobacter pylori infection leads to gastric cancer. CRI helps cancer cells to acquire malignant biological behaviors, including proliferation, infiltration, angiogenesis, and metastasis. The nuclear factor κb (NF-κB)[9] and transcription activator 3 (STAT3)[10] pathways are well known in CRI. Chemokines, including TNF[11], CXCL8[12], and IL-6[13], also play an important role in the pathophysiological process of tumor formation. CRI parameters, including C-reactive protein (CRP)[6], platelet-to-lymphocyte ratio (PLR)[14], and neutrophil-lymphocyte ratio (NLR)[15], are widely used in cancer patients to guide treatment and predict prognosis. These biomarkers are more readily available and non-invasive.

However, the power of NLR and PLR to predict the outcomes of patients with HCC after liver resection is under debate. Our study was designed to combine the preoperative inflammatory maker NLR and PLR to evaluate the prognosis in patients with HCC who underwent curative resection.

Materials & Methods

Study population

Our study included 239 patients with HCC who underwent liver resection between 20012 and 2015 at XiangYa Hospital, Central South University, China. HCCs were confirmed by postoperative pathology. Patients with any one of the following items were excluded from this study: (1) the patients who underwent splenectomy; (2) recurrence HCC; (3) ruptured HCC; (4) infections during the perioperative period; (5) combined with autoimmune diseases; (6) preoperative antitumor treatments; and (7) preoperative application of interferon, interleukin and other similar drugs. This study was approved by the ethics committee of XiangYa Hospital Central South University(No.201709984) and with the patients' informed consent.

Follow-up and definitions

Blood routine, liver function, serum alpha-fetoprotein (AFP), and hepatitis B surface antigen (HBsAg) were tested in all patients. Abdomen ultrasonography, computed tomography (CT) or magnetic resonance imaging (MRI) and chest radiography were performed for all patients. NLR was neutrophil count to lymphocyte count, PLR was platelet count to lymphocyte count. Recurrence was diagnosed by imagings(CT or MRI) and AFP. An AFP level >20 ng/mL was defined as being high[16]. The cutoff values of NLR and PLR were determined by receiver operating characteristic curves(ROC) according to overall survival of patients. The seventh edition of the American Joint Committee on Cancer tumor-node metastasis (TNM) staging system and Barcelona Clinic Liver Cancer were applied to rank the HCC stage.

Statistical analysis

Statistical analyses were performed using Prism software (GraphPad Prism Software, La Jolla, CA) and SPSS 21.0 (SPSS Company, Chicago, IL) for Windows. Quantitative values were analysised by *t* tests. Categorical variables were compared using the chi-square test or Fisher's exact test. Recurrence-free survival (RFS) and overall survival(OS) were evaluated using the Kaplan-Meier method and the log-rank test. Prognostic factors of RFS and OS were analyzed by univariate and multivariate analyses[17]. $P < 0.05$ was considered statistically significant.

Results

Assessment of the Cut-off value of NLR, PLR and LMR

According to the ROC curve, the ideal cutoff values for preoperative NLR, PLR were 2.92, 128.1, respectively. The ROC area under the curve for NLR, PLR was 0.63 (95% CI for the area between 0.56 to 0.71), 0.67 (95% CI for the area between 0.55 to 0.72) respectively. The cutoff values of NLR, PLR presented correspond to sensitivity values of 51%, 81%, and specificity values of 78%, 42%, respectively (Figure 1).

The relationship of clinical and pathologic characteristics with preoperative NLR and PLR in patients with HCC

A total of 239 patients met the enrollment conditions, including 200 (83.68%) males and 39 (16.32%) females and were enrolled in the present study. As presented in Table 1, the mean age was (50.14±11.98) years. The mean tumor size was (5.88±3.59) cm and 56 (23.43%) patients had multiple tumors. A high preoperative AFP was observed in 155 (64.85%) patients. HBV surface antigen was positive in 202 (84.5%) patients, 71 (29.7%) patients had tumor encapsulation, and 174 (72.8%) patients had liver cirrhosis that was confirmed by pathology.

As shown in Table 1, the relationship between preoperative NLR, PLR and clinical and pathologic characteristics was investigated. The high-NLR group included 104 (43.51%) patients (NLR>2.92) and 135 (56.49%) patients were identified as the low-NLR (NLR≤2.92) group. 87 (36.4%) patients were identified as the high-PLR group (PLR>128.1), and 152 (63.6%) patients were identified as the low-PLR group (PLR≤128.1).

Preoperative NLR level and PLR level were closely correlated with the tumor size, TNM stage and BCLC stage (P<0.05). The PLR was also correlated with age, platelet count, prothrombin time (PT), AFP, and satellite nodules (P<0.05). No obvious correlations with gender, HBsAg, hospital stay, liver cirrhosis, serum albumin, total bilirubin (TBil), glutamic-pyruvic transaminase (ALT), or glutamic-oxaloacetic transaminase (AST) were observed (P>0.05).

The correlation between NLR, PLR and postoperative RFS and OS in HCC patients who underwent liver resection

Kaplan-Meier survival analysis showed that the NLR>2.92 group was associated with a shorter recurrence-free survival (RFS) (Figure 2A) and overall survival (OS) (Figure 2C). The HCC patients in the PLR>128.1 group were also associated with a shorter RFS (Figure 2B) and OS (Figure 2D).

From the univariate analysis in Table 2, we found that tumor size (HR 1.30, 95% CI 1.08-1.56), NLR (HR 2.85, 95% CI 1.63-4.93), PLR (HR 1.013, 95% CI 1.00-1.02), BCLC stage (HR 3.005, 95% CI 1.39-6.50), and satellite nodules (HR 4.27, 95% CI 2.55-7.14) were correlated with RFS in HCC patients who underwent liver resection ($P<0.05$). The platelet count (HR 1.01, 95% CI 1.00-1.01), AST (HR 1.02, 95% CI 1.00-1.03), tumor size (HR 1.42, 95% CI 1.23-1.63), NLR (HR 1.48, 95% CI 1.15-1.88), PLR (HR 1.007, 95% CI 1.001-1.013), TNM stage (HR 19.42, 95% CI 2.61-144.3), BCLC stage (HR 2.43, 95% CI 0.99-5.98) , satellite nodules (HR 4.42, 95% CI 2.66-7.33), and tumor number (HR 2.78, 95% CI 1.18-6.54) were correlated with OS ($P<0.05$). Gender, HBsAg, hospital stay, liver cirrhosis, serum albumin, total bilirubin (TBil), ALT and so on had no statistically significant association with RFS or OS ($P>0.05$).

In the multivariate analysis, we found that NLR (HR 1.16, 95% CI 1.06-1.26), PLR (HR 1.004, 95% CI 1.001-1.006) were independent risk factors for RFS in HCC patients. The NLR (HR 1.14, 95% CI 1.04-1.25), PLR (HR 1.004, 95% CI 1.001-1.007) were independent risk factors for OS in HCC patients.

Combined NLR and PLR to analysis the HCC patients' RFS and OS who underwent hepatectomy

In the previous results, we found that high NLR and high PLR are independent risk factors for RFS and OS after hepatectomy in HCC patients. We combined NLR with PLR to investigate whether the prediction of RFS and OS was more accurate. We defined NLR≤2.92 as NLR_{-low}, NLR>2.92 as NLR_{-high}, PLR≤128.1 as PLR_{-low}, PLR>128.1 as PLR_{-high}. We found that patients with simultaneously high NLR and PLR had the worst RFS (median 12 months) and OS (median 18 months), while patients with simultaneously low NLR and PLR had the best RFS (median 14.5 months) and OS (median 23 months). The NLR_{-low} and PLR_{-low} group had the best outcome and their RFS and OS were superior to other groups. The worst group was NLR_{-high} combined

with PLR_{-high}. The results showed that patients with simultaneously high NLR and high PLR were more prone to metastasis and had the worst OS (Figure 3).

The relationship between NLR, PLR, tumor size, and satellite nodules

According to multivariate analysis, we found that tumor size was an independent risk factor for poor outcomes in HCC patients who underwent liver resection. Is there any correlation between tumor size and NLR and PLR? We analyzed the relationship between NLR, PLR and tumor size. We divided the tumor size into three groups: ≤3 cm group, between 3-10 cm group, and ≥10 cm group. We found the NLR and PLR were higher in groups with larger tumor size (P<0.05) (Figure 4).

The mean NLRs in the tumor≤3cm group, 3-10 cm group and ≥10 cm group were (2.32 ± 0.15), (3.23 ± 0.17), and (4.03 ± 0.38), respectively(Figure 4A); the mean PLRs were (90.21 ± 6.44), (128.5 ± 5.4), (157 ± 13.41), respectively(Figure 4B). We hypothesized that with high neutrophil and platelet counts, the cancer cells can release various chemokines, and promote tumor growth. At the same time, the number of lymphocytes decreased, and the tumor cells escaped from the immune surveillance; the immune system could not play its normal anti-tumor effect. As a result, the HCC tumor growth progresses, and tumor size is larger.

We further analyzed the relationship between NLR, PLR and BCLC stage. We found that the advantaged BCLC stage had higher NLR and PLR values. The mean NLR values of BCLC O, A, B, C stage were (1.70 ± 0.14), (2.93 ± 0.13), (3.05 ± 0.26), and (4.82 ± 0.65) (Figure 5A), respectively. The mean PLR values of BCLC O, A, B, C stage were (81.93 ± 10.68), (122.1 ± 5.61), (122.5 ± 8.91), (149.2 ± 16.13) (Figure 5B).

Discussion

Many researchers have demonstrated that inflammation contributes to the pathogenesis and progression of cancer[18]. The presence of systemic inflammation is associated with poor survival in many types of tumors, and anti-inflammatory agents have been associated with cancer prevention and treatment[19]. Inflammation can promote cancer development through multiple mechanisms, which include gene mutation, cancer cells proliferation and angiogenesis[7]. Among the various inflammatory markers, NLR and PLR were been shown to have predict effection in various cancers, including HCC[20], esophageal carcinoma[21], renal carcinoma[22], and lung cancer[23]. Lu,S et al[20] had studied the NLRhave study the NLR in the early and intermediate stage HCC, and in our research, we had found the NLR and PLR can predict the prognosis of HCC patients who underwent liver research, and the stage was include early, intermediate and advantage stage HCC, we all have similar result.

In solid tumors, inflammation often appears before the tissue malignant transformation. The occurrence and development of systemic immune responses provide an appropriate microenvironment for cancer metastasis and recurrence. In China, most HCC patients have hepatitis infection; the inflammatory status plays an important role in promoting the development of HCC. NLR and PLR, as sensitive indexes of the body's inflammation system, can reflect the inflammatory state and predict the prognosis of the tumor.

Neutrophil can strength tumor biological behaviour and get the ability of growth and metastasis. The higher neutrophil can upregulate the expression of growth factors, kinds of chemokines, which play an important rloe in tumor development and progression. Platelets play a leading role in tumor progression. Platelets can secrete inflammatory factors, including TGF-β and VEGF, which can accelerate the differentiation and proliferation of tumor cells. Moreover, platelets release platelet derived factors, platelet reactive protein, etc., which play an important role in tumor adhesion, and angiogenesis to (1) prepare the microenvironment for tumor metastasis: the platelets secrete angiogenic factor, growth factor and prepare a suitable metastasis microenvironment for the cancer cell; (2) Shield the cancer cell: the platelets can adhere to the tumor. On the one hand, platelets can protect the cancer cells from blood flow mechanical force. On the other hand, platelets can provide a shield for cancer cells that allows them to escape immune surveillance.

Many studies have confirmed that lymphocytes are the most important cells in tumor killing; relative or absolute reduction of lymphocytes, the antitumor effect is also decreased. PD-1 and CTLA–4 inhibitors are the most important immune drugs[24, 25]. They can reduce tumor cell and T lymphocyte cell interaction by inhibiting the cancer cell surface expression of PD-1 and CTAL-4. The HCC patient's decreased immunity, especially the abnormality of the tumor immune microenvironment, leads to the failure of the lymphocyte immune response and the cancer cells escape from immune surveillance. In turn, immune tolerance or immune escape occurs, and then the tumors are more likely to progress or metastasize. In our study, we found that patients with higher NLR and PLR had worse RFS and OS prognosis. On the one hand, the increase of neutrophil and platelet counts promotes tumorigenesis; on the other hand, the decrease in the number of lymphocytes leads to the patient's immune decrease and lead to tumor progression.

In our study, we found that the tumor size was correlated with the NLR and PLR; the larger the tumor size, the higher the NLR and PLR. We hypothesize that (1) as neutrophil and platelet counts increase, they secrete many kinds of growth factors and inflammatory factors, which promote the growth of tumor cells and stromal cells. The inflammatory factors also impact the tumor microenvironment and promote tumor growth. (2) Larger tumor size means higher tumor burden. The lymphocytes are obviously deceased and the effect on tumor cells killing is also weaker, thereby promoting the development of the tumor. The tumor size is one of the prognostic predictor for HCC patients, but the tumor size was more difficult to get than the NLR, PLR. And tumor size cannot provide an accurate prediction in HCC, because NLR and PLR can reflect whether HCC patients are associated with cirrhosis and hypersplenism. If the tumor is small, but the liver cirrhosis and hypersplenism are obvious, the prognosis of HCC patients will be poor.

We also found that the BCLC stage was correlated with high NLR and high PLR. The advantage BCLC stages have higher PLR and NLR. Multiple tumors and/or vascular invasion in HCC patients may lead to a stronger inflammatory response and weaker immune response. The higher neutrophil and platelet count mean a stronger inflammatory response. Lower lymphocyte counts mean the immune response is decreased, and the cancer cells are more likely to metastasize.

This study has some limitations. First, the number of patients in our study is small and the patients were retrospectively studied in a single center. Therefore, we could not avoid selection bias when collecting information on patients with HCC. Second, the NLR and PLR were assessed by single measurements at the time of admission for the initial diagnosis.

Conclusion

In conclusion, our study showed that NLR and PLR are useful prognostic factors to predict outcomes in patients with HCC who underwent live resection. This finding can assist in guiding the clinical management of HCC patients.

Acknowledgements

We gratefully acknowledge all the authors' works for this paper and all the patients in our study.

Reference

[1] Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D and Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015; 136: E359-386.

[2] Bruix J, Reig M and Sherman M. Evidence-Based Diagnosis, Staging, and Treatment of Patients With Hepatocellular Carcinoma. Gastroenterology 2016; 150: 835-853.

[3] Roayaie S, Jibara G, Tabrizian P, Park JW, Yang J, Yan L, Schwartz M, Han G, Izzo F, Chen M, Blanc JF, Johnson P, Kudo M, Roberts LR and Sherman M. The role of hepatic resection in the treatment of hepatocellular cancer. Hepatology 2015; 62: 440-451.

[4] Zhou L, Huang Y, Li J and Wang Z. The mTOR pathway is associated with the poor prognosis of human hepatocellular carcinoma. Med Oncol 2010; 27: 255-261.

[5] Villanueva A, Hoshida Y, Battiston C, Tovar V, Sia D, Alsinet C, Cornella H, Liberzon A, Kobayashi M, Kumada H, Thung SN, Bruix J, Newell P, April C, Fan JB, Roayaie S, Mazzaferro V, Schwartz ME and Llovet JM. Combining clinical, pathology, and gene expression data to predict recurrence of hepatocellular carcinoma. Gastroenterology 2011; 140: 1501-1512 e1502.

[6] Chaturvedi AK, Caporaso NE, Katki HA, Wong HL, Chatterjee N, Pine SR, Chanock SJ, Goedert JJ and Engels EA. C-reactive protein and risk of lung cancer. J Clin Oncol 2010; 28: 2719-2726.

[7] Elinav E, Nowarski R, Thaiss CA, Hu B, Jin C and Flavell RA. Inflammation-induced cancer: crosstalk between tumours, immune cells and microorganisms. Nat Rev Cancer 2013; 13: 759-771.

[8] Antonioli L, Blandizzi C, Pacher P and Hasko G. Immunity, inflammation and cancer: a leading role for adenosine. Nat Rev Cancer 2013; 13: 842-857.

[9] Ratnam NM, Peterson JM, Talbert EE, Ladner KJ, Rajasekera PV, Schmidt CR, Dillhoff ME, Swanson BJ, Haverick E, Kladney RD, Williams TM, Leone GW, Wang DJ and Guttridge DC. NF-kappaB regulates

GDF-15 to suppress macrophage surveillance during early tumor development. J Clin Invest 2017; 127: 3796-3809.

[10] Izumi K, Fang LY, Mizokami A, Namiki M, Li L, Lin WJ and Chang C. Targeting the androgen receptor with siRNA promotes prostate cancer metastasis through enhanced macrophage recruitment via CCL2/CCR2-induced STAT3 activation. EMBO Mol Med 2013; 5: 1383-1401.

[11] Balkwill F. Tumour necrosis factor and cancer. Nat Rev Cancer 2009; 9: 361-371.

[12] Manfroi B, McKee T, Mayol JF, Tabruyn S, Moret S, Villiers C, Righini C, Dyer M, Callanan M, Schneider P, Tzankov A, Matthes T, Sturm N and Huard B. CXCL-8/IL8 Produced by Diffuse Large B-cell Lymphomas Recruits Neutrophils Expressing a Proliferation-Inducing Ligand APRIL. Cancer Res 2017; 77: 1097-1107.

[13] He G, Dhar D, Nakagawa H, Font-Burgada J, Ogata H, Jiang Y, Shalapour S, Seki E, Yost SE, Jepsen K, Frazer KA, Harismendy O, Hatziapostolou M, Iliopoulos D, Suetsugu A, Hoffman RM, Tateishi R, Koike K and Karin M. Identification of liver cancer progenitors whose malignant progression depends on autocrine IL-6 signaling. Cell 2013; 155: 384-396.

[14] Dalpiaz O, Krieger D, Ehrlich GC, Pohlmann K, Stojakovic T, Pummer K, Zigeuner R, Pichler M and Hutterer GC. Validation of the Preoperative Platelet-to-Lymphocyte Ratio as a Prognostic Factor in a European Cohort of Patients with Upper Tract Urothelial Carcinoma. Urol Int 2017; 98: 320-327.

[15] McNamara MG, Templeton AJ, Maganti M, Walter T, Horgan AM, McKeever L, Min T, Amir E and Knox JJ. Neutrophil/lymphocyte ratio as a prognostic factor in biliary tract cancer. Eur J Cancer 2014; 50: 1581-1589.

[16] Tao YM, Huang JL, Zeng S, Zhang S, Fan XG, Wang ZM, Yang HX, Yuan XH, Wang P, Wu F, Luo J, Zeng DY and Shen H. BTB/POZ domain-containing protein 7: epithelial-mesenchymal transition promoter and prognostic biomarker of hepatocellular carcinoma. Hepatology 2013; 57: 2326-2337.

[17] Hu K, Wang ZM, Li JN, Zhang S, Xiao ZF and Tao YM. CLEC1B Expression and PD-L1 Expression Predict Clinical Outcome in Hepatocellular Carcinoma with Tumor Hemorrhage. Transl Oncol 2018; 11: 552-558.

[18] Sanford DE, Belt BA, Panni RZ, Mayer A, Deshpande AD, Carpenter D, Mitchem JB, Plambeck-Suess SM, Worley LA, Goetz BD, Wang-Gillam A, Eberlein TJ, Denardo DG, Goedegebuure SP and Linehan DC. Inflammatory monocyte mobilization decreases patient survival in pancreatic cancer: a role for targeting the CCL2/CCR2 axis. Clin Cancer Res 2013; 19: 3404-3415.

[19] Pribluda A, Elyada E, Wiener Z, Hamza H, Goldstein RE, Biton M, Burstain I, Morgenstern Y, Brachya G, Billauer H, Biton S, Snir-Alkalay I, Vucic D, Schlereth K, Mernberger M, Stiewe T, Oren M, Alitalo K, Pikarsky E and Ben-Neriah Y. A senescence-inflammatory switch from cancer-inhibitory to cancer-promoting mechanism. Cancer Cell 2013; 24: 242-256.

[20] Lu SD, Wang YY, Peng NF, Peng YC, Zhong JH, Qin HG, Xiang BD, You XM, Ma L and Li LQ. Preoperative Ratio of Neutrophils to Lymphocytes Predicts Postresection Survival in Selected Patients With Early or Intermediate Stage Hepatocellular Carcinoma. Medicine (Baltimore) 2016; 95: e2722.

[21] Feng JF, Huang Y and Chen QX. Preoperative platelet lymphocyte ratio (PLR) is superior to neutrophil lymphocyte ratio (NLR) as a predictive factor in patients with esophageal squamous cell carcinoma. World J Surg Oncol 2014; 12: 58.

[22] Hu H, Yao X, Xie X, Wu X, Zheng C, Xia W and Ma S. Prognostic value of preoperative NLR, dNLR, PLR and CRP in surgical renal cell carcinoma patients. World J Urol 2017; 35: 261-270.

[23] Sanchez-Salcedo P, de-Torres JP, Martinez-Urbistondo D, Gonzalez-Gutierrez J, Berto J, Campo A, Alcaide AB and Zulueta JJ. The neutrophil to lymphocyte and platelet to lymphocyte ratios as biomarkers for lung cancer development. Lung Cancer 2016; 97: 28-34.

[24] Rizvi NA, Hellmann MD, Snyder A, Kvistborg P, Makarov V, Havel JJ, Lee W, Yuan J, Wong P, Ho TS, Miller ML, Rekhtman N, Moreira AL, Ibrahim F, Bruggeman C, Gasmi B, Zappasodi R, Maeda Y, Sander C, Garon EB, Merghoub T, Wolchok JD, Schumacher TN and Chan TA. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science 2015; 348: 124-128.

[25] Wei SC, Levine JH, Cogdill AP, Zhao Y, Anang NAS, Andrews MC, Sharma P, Wang J, Wargo JA, Pe'er D and Allison JP. Distinct Cellular Mechanisms Underlie Anti-CTLA-4 and Anti-PD-1 Checkpoint Blockade. Cell 2017; 170: 1120-1133 e1117.

Figure legends:

Figure 1. The ROC curve of the NLR, PLR, and LMR in HCC patients. Panels A, B, and C correspond to the NLR, PLR, and LMR ROC curves, respectively.

Figure 2. Kaplan-Meier survival analysis indicates that patients with NLR>2.92 have a shorter RFS and OS (A and C), PLR>128.1 have a shorter RFS and OS (B and D).

Figure 3. Effect of combined NLR and PLR on RFS and OS in HCC patients who underwent hepatectomy.

Figure 4. Analysis of the relationship between NLR, PLR and tumor size.

Figure 5. Analysis of the relationship between NLR, PLR and BCLC stage.

Figure 1

Figure 1. The ROC curve of the NLR,PLR

The ROC curve of the NLR, PLR in HCC patients. Figure1- A, Figure1-B correspond to the NLR, PLR ROC curves.

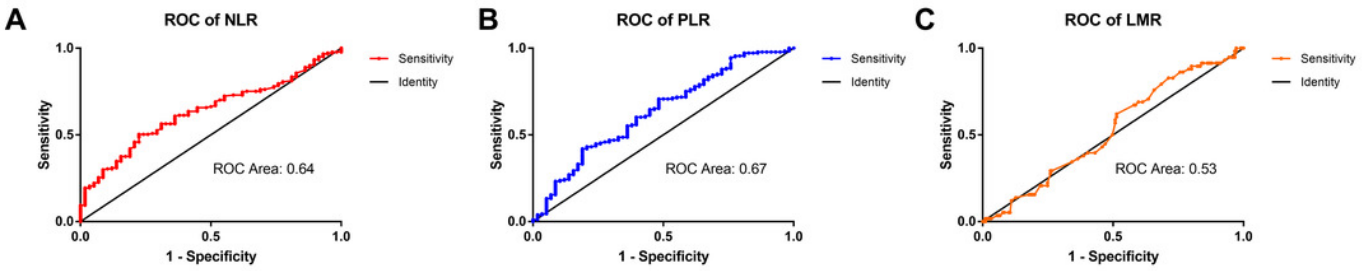

Figure 2

Figure 2

Kaplan-Meier survival analysis indicates that patients with NLR>2.92 have a shorter RFS and OS (A and C) , PLR>128.1 have a shorter RFS and OS (B and D).

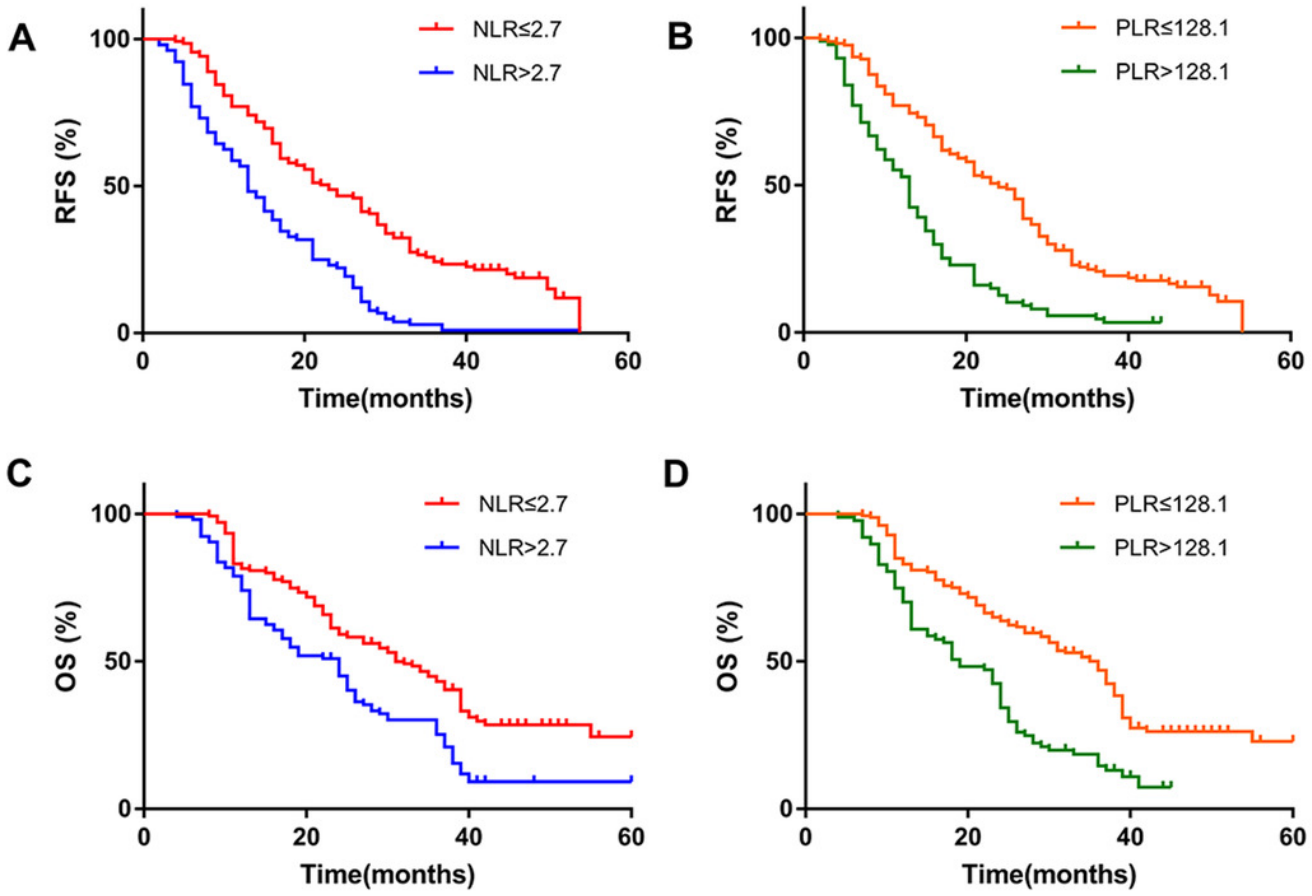

Figure 3

Figure 3

Effect of combined NLR and PLR on RFS and OS in HCC patients who underwent hepatectomy.

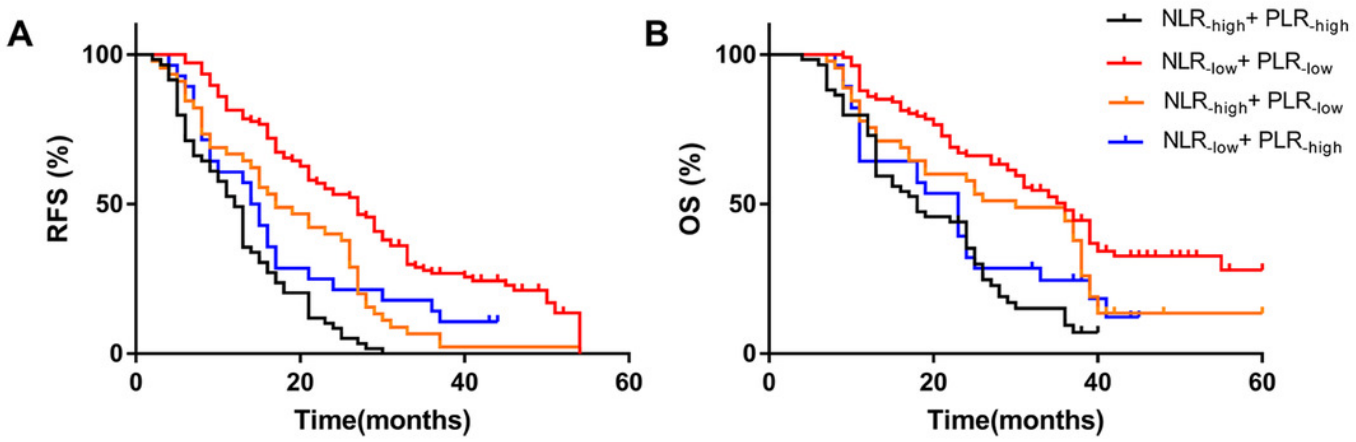

Figure 4

Figure 4

Analysis of the relationship between NLR, PLR and tumor size.

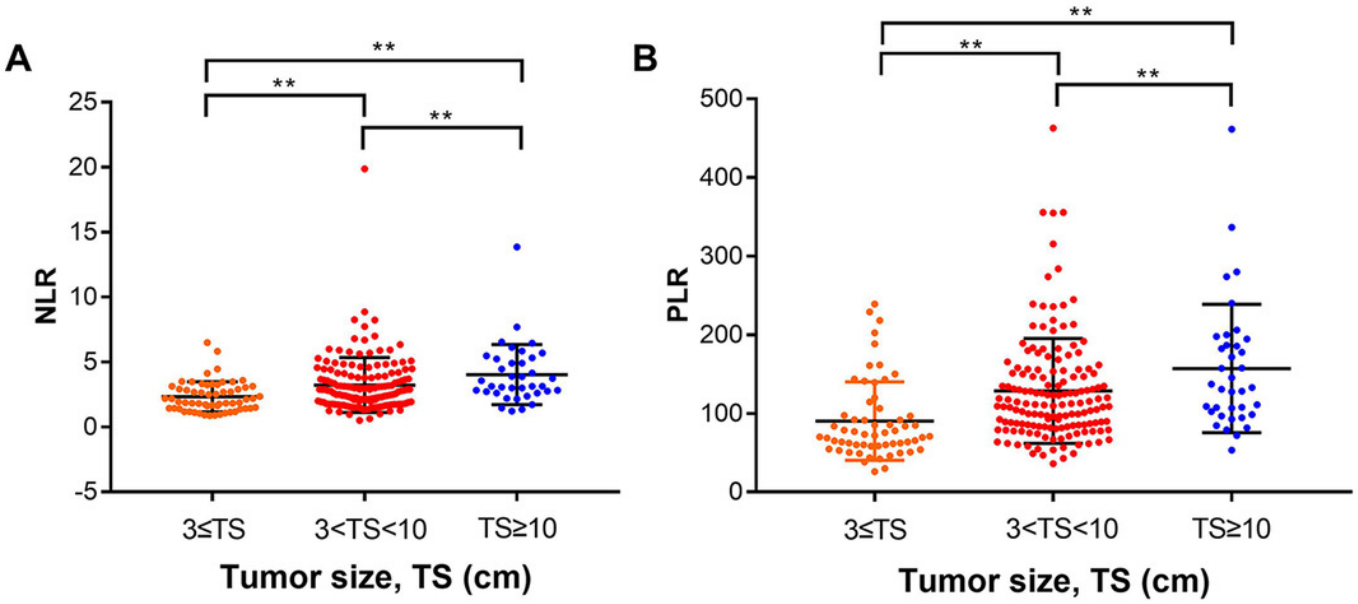

Figure 5

Figure 5

Analysis of the relationship between NLR, PLR and BCLC stage

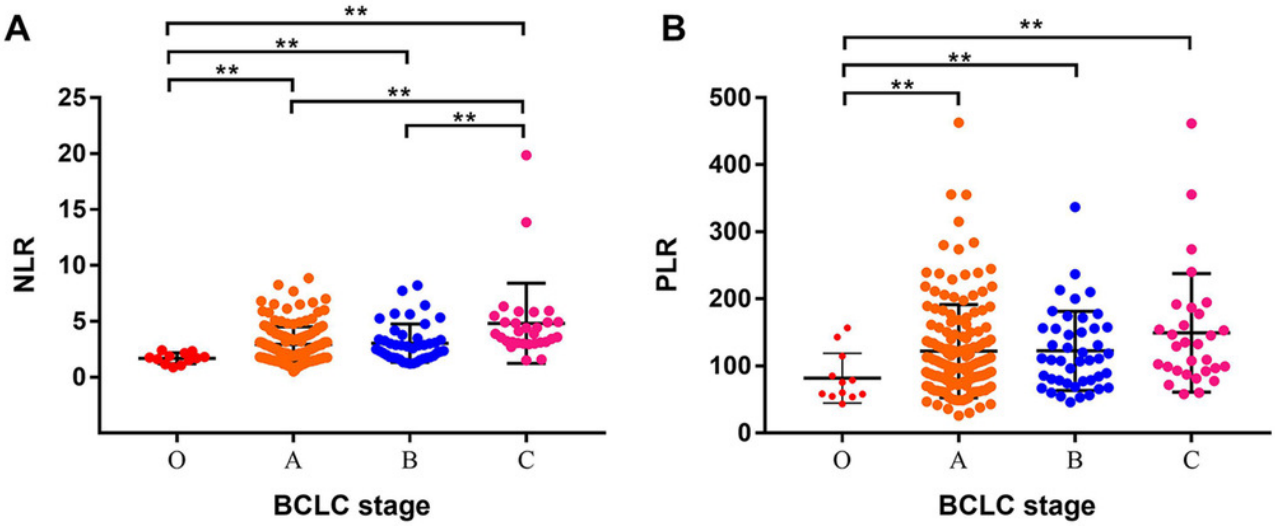

Table 1(on next page)

Table 1. HCCPatients (n=239) Categorized by NLR, PLR and Their Clinical Pathologic Characteristics.

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Clinical character		NLR			PLR		
		≤2.92 (n = 135)	>2.92(n = 104)	*P*-value	≤128.1(n =152)	>128(n = 87)	*P*-value
Age, years		49.0±12.47	51.28±11.33	0.34	48.82±11.21	52.54±13.01	0.02
Serum albumin, g/L		41.36 ±0.38	41.49±0.5	0.59	41.82±0.39	40.97±0.49	0.18
Tumor size, cm		5.01±0.26	6.99±0.36	0.00	5.18±0.25	7.17±0.39	0.00
Platelet，10^9/L		156.0±6.92	167.7±6.89	0.25	133.4±4.43	209.7±9.03	0.00
TBil, μmol/L		14.2±0.63	16.24±1.52	0.18	14.56±0.57	16.02±1.82	0.35
ALT, U/L		41.06±2.77	44.91±3.19	0.36	41.66±2.39	44.62±3.95	0.49
AST, U/L		44.51±2.72	50.18±3.05	0.17	44.18±2.14	52.28±4.12	0.06
PT, s		13.22±0.10	13.33±0.10	0.57	13.38±0.09	13.06±0.09	0.02
Gender	Male	115	85	0.49	132	68	0.10
□	Female	20	19		20	19	
HBsAg	Negative	23	14	0.48	19	18	0.10
	Positive	112	90		133	69	
AFP, ng/mL	≤20	50	34	0.49	45	39	0.02
□	>20	85	70		107	48	
Liver cirrhosis	No	33	32	0.31	41	24	0.92
□	Yes	102	72		111	63	
Tumor encapsulation	No	96	72	0.78	110	58	0.37
□	Yes	39	32		42	29	
Tumor number	Single	105	77	0.54	119	63	0.35
□	Multiple	30	27		33	24	
Satellite nodules	No	125	96	0.98	146	75	0.01
□	Yes	10	8		6	12	
Edmondson grade	I–II	103	83	0.53	116	70	0.52
□	III–IV	32	21		36	17	
BCLC stage	0	11	0	0.00	10	1	0.04
	A	93	60		101	52	
□	B	28	17		27	18	
□	C	3	27		14	16	
TNM stage	I	95	48	0.00	102	41	0.01
□	II	30	19		27	22	
□	III	10	37		23	24	

Characteristics.

NLR, neutrophil-to-lymphocyte ratio; HBsAg, hepatitis B surface antigen; AFP, α-fetoprotein; TNM, tumor-node-metastasis; TBil, total bilirubin; PT, Prothrombin time; CTP, Child-Turcotte-Pugh; BCLC stage: The Barcelona Clinic

5 Liver Cancer staging; ALT, glutamic-pyruvic transaminase; AST, glutamic oxalacetic transaminase.

Table 2(on next page)

Table 2. Univariate and multivariate analyses ofprognostic factors with RFS and OS in patients with HCC (n =239)

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Table 2. Univariate and multivariate analyses of prognostic factors with RFS and OS in patients with HCC (n =239).

Clinicopathologic variable	RFS	□	OS	□
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Univariate analysis				
Gender (male vs. female)	2.40(0.54-10.64)	0.25	1.93(0.77-4.89)	0.16
Age, years (>60 vs. ≤60)	1.00(0.97-1.04)	0.86	0.98 (0.96-1.00)	0.21
Serum albumin, g/L (≤35 vs. >35)	1.00 (0.88-1.04)	0.28	0.99(0.93-1.05)	0.73
Platelet,10^9/L (≤160 vs. >160)	1.00(0.99-1.008)	0.50	1.01(1.001-1.01)	0.02
TBil, μmol/L (≤17.1 vs. >17.1)	1.02(0.97-1.05)	0.83	1.01(0.98-1.05)	0.52
ALT, U/L (≤50 vs. >50)	1.01(0.99-103)	0.40	1.01(0.98-1.03)	0.09
AST, U/L (≤40 vs. >40)	1.01(0.99-1.03)	0.29	1.02(1.00-1.03)	0.05
PT, s (≤13.2 vs. >13.2)	0.89(0.60-1.31)	0.54	0.82(0.61-1.08)	0.16
AFP, ng/mL (>20 vs. ≤20)	2.18(0.95-5.03)	0.07	1.72(0.94-3.15)	0.08
HBV (presence vs. absence)	4.86(0.64-37.04)	0.13	1.19(0.54-2.63)	0.67
NLR (>2.92 vs. ≤2.92)	2.85(1.63-4.93)	<0.01	1.48(1.16-1.88)	<0.01
PLR (>128.1 vs. ≤128.1)	1.01(1.00-1.02)	0.012	1.01(1.00-1.013)	0.014
BCLC stage (C vs. 0/A/B)	3.01(1.39-6.50)	<0.01	2.43(0.98-5.98)	<0.01
TNM stage (II/III vs. I)	6.57(0.87-49.8)	0.01	19.42(2.61-144.3)	<0.01
Tumor number (multiple vs. single)	2.48(0.71-8.56)	0.15	2.78(1.18-6.54)	0.02
Edmondson grade (III/IV vs. I/II)	1.56(0.51-4.76)	0.44	1.12(0.54-2.32)	0.75
Tumor size, cm (>5 vs. ≤5)	1.30(1.08-1.57)	<0.01	1.42(1.23-1.63)	<0.01
Satellite nodules (presence vs. absence)	4.27(2.55-7.14)	<0.01	4.42(2.66-7.33)	<0.01
Tumor encapsulation (none vs. complete)	1.34(0.53-3.62)	0.51	1.45(0.73-2.85)	0.29
Liver cirrhosis (presence vs. absence)	1.30(0.53-3.17)	0.57	1.03(0.53-1.99)	0.94
Hospital stay, d	1.02(0.88-1.19)	0.75	1.04(0.94-1.16)	0.45
Multivariate analysis				
Platelet,10^9/L (≤160 vs. >160)	NA		0.99(0.99-1.00)	0.46
AST, U/L (≤40 vs. >40)	NA		1.00 (0.99-1.01)	0.42
AFP, ng/mL (>20 vs. ≤20)	1.39(1.05-1.88)	0.03	1.37(1.01-1.86)	0.04
Tumor size, cm (>5 vs. ≤5)	1.10(1.05-1.15)	0.01	1.10(1.05-1.16)	0.01
NLR (>2.92 vs. ≤2.92)	1.16(1.06-1.26)	<0.01	1.14(1.04-1.25)	<0.01
PLR (>128.1 vs. ≤128.1)	1.01(1.00-1.01)	<0.01	1.00 (1.00-1.01)	<0.01
TNM (II/III vs. I)	1.40(0.77-2.53)	0.27	1.39(0.76-2.55)	0.28
Tumor number (multiple vs. single)	1.34(0.92-1.96)	0.13	1.33(0.91-1.95)	0.15
Satellite nodules (presence vs. absence)	3.03(1.62-5.65)	0.00	2.98(1.59-5.57)	0.00

NLR, neutrophil-to-lymphocyte ratio; HBsAg, hepatitis B surface antigen; AFP, α-fetoprotein; TNM, tumor-node-metastasis; TBil, total bilirubin; PT, Prothrombin time; CTP, Child-Turcotte-Pugh; BCLC stage: The Barcelona Clinic Liver Cancer staging; ALT, glutamic-pyruvic transaminase; AST, glutamic oxalacetic transaminase.