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

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Background: Many recent studies have demonstrated the predominant role chronic inflammation plays in cancer cell propagation, angiogenesis and immunosuppression. Cancer-related inflammation (CRI) has been shown to correlate with poor cancer prognosis. Our study aimed to evaluate the prognostic value of the neutrophil-to lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in patients with hepatocellularcarcinoma (HCC) who have undergone liver resection.

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

Results: The cutoff values of the NLR and PLR were 2.92 and 128.1, respectively. In multivariate Cox regression analysis, high NLR (≥ 2.92) and high PLR (≥ 128.1) were independent risk factors predicting poorer outcomes in patients with HCC. 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 in predicting outcomes in patients with HCC who underwent liver resection.

1 **Preoperative inflammatory markers of NLR and PLR as an indicators of poor**

2 **prognosis in resectable HCC**

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17 **Abstract**

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20 inflammation (CRI) has been shown to correlate with poor cancer prognosis. Our study aimed to

21 evaluate the prognostic value of the neutrophil-to lymphocyte ratio (NLR) and platelet-to-

22 lymphocyte ratio (PLR) in patients with hepatocellular carcinoma (HCC) who have undergone

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28 Results: The cutoff values of the NLR and PLR were 2.92 and 128.1, respectively. In multivariate

29 Cox regression analysis, high NLR ($\geq$ 2.92) and high PLR ($\geq$ 128.1) were independent risk

30 factors predicting poorer outcomes in patients with HCC. However, high NLR and high PLR

31 were prognostic factors in tumor size and tumor number.

32 Conclusions: In this study, we identified that high NLR (≥ 2.92) and high PLR (≥ 128.1) are

33 useful prognostic factors in predicting outcomes in patients with HCC who underwent liver

34 resection.

Introduction

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

Recently, many studies have demonstrated that chronic inflammation plays a predominant role in cancer cell propagation, angiogenesis and immunosuppression [6]. Cancer-related inflammation (CRI) has been shown to correlate with poor cancer prognosis [7, 8]. 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 ability of the NLR and PLR to predict the prognosis of patients with HCC after liver resection is under debate. Our study was designed to combine the preoperative inflammatory markers NLR and PLR to evaluate the prognosis of patients with HCC who underwent curative resection.

61 **Materials & Methods**

62 Study population

63 Our study included 239 patients with HCC who underwent liver resection between 2012 and

64 2015 at XiangYa Hospital, Central South University, China. HCC was confirmed using

65 postoperative pathology. Patients with any one of the following items were excluded from this

66 study: (1) had undergone splenectomy; (2) recurrence of HCC; (3) ruptured HCC; (4) infections

67 during the perioperative period; (5) other autoimmune diseases; (6) preoperative antitumor

68 treatments; and (7) preoperative application of interferon, interleukin or other similar drugs. This

69 study was approved by the ethics committee of XiangYa Hospital Central South University (No.

70 201709984) and with the patients' informed consent.

71

72 Follow-up and definitions

73 Blood routine, liver function, serum alpha-fetoprotein (AFP), and hepatitis B surface antigen

74 (HBsAg) were tested in all patients. Abdomen ultrasonography, computed tomography (CT) or

75 magnetic resonance imaging (MRI), and chest radiography were performed for all patients. NLR

76 measured neutrophil count to lymphocyte count, and PLR measured platelet count to lymphocyte

77 count. Recurrence was diagnosed using imaging (CT or MRI) and AFP. An AFP level >20

78 ng/mL was defined as being high [16]. The cutoff values of NLR and PLR were determined

79 using receiver operating characteristic curves (ROC) according to the overall survival of patients.

80 The seventh edition of the American Joint Committee on Cancer tumor-node metastasis (TNM)

81 staging system and Barcelona Clinic Liver Cancer were applied to rank the HCC stage.

82

83 Statistical analysis

84 Statistical analyses were performed using Prism software (GraphPad Prism Software, La Jolla,

85 CA) and SPSS 21.0 (SPSS Company, Chicago, IL) for Windows. Quantitative values were

86 analyzed using *t* tests. Categorical variables were compared using the chi-square test or Fisher's

87 exact test. Recurrence-free survival (RFS) and overall survival (OS) were evaluated using the

88 Kaplan-Meier method and the log-rank test. Prognostic factors of RFS and OS were analyzed

89 using univariate and multivariate analyses [17]. $P < 0.05$ was considered statistically significant.

90

91   **Results**

92   **Assessment of the cut-off value of NLR, PLR and LMR**

93   According to the ROC curve, the ideal cutoff values for preoperative NLR and PLR were 2.92

94   and 128.1, respectively. The ROC areas under the curve for the NLR and PLR were 0.63 (95%

95   CI for the area between 0.56 to 0.71) and 0.67 (95% CI for the area between 0.55 to 0.72),

96   respectively. The cutoff values of the NLR and PLR presented correspond to sensitivity values of

97   51% and 81%, and specificity values of 78% and 42%, respectively (Figure 1).

98

99   **The relationship of clinical and pathologic characteristics with preoperative NLR and PLR**

100 **in patients with HCC**

101 A total of 239 patients met the enrollment conditions, including 200 (83.68%) males and 39

102 (16.32%) females, and were enrolled in the present study. As presented in Table 1, the mean age

103 was (50.14±11.98) years. The mean tumor size was (5.88±3.59) cm and 56 (23.43%) patients

104 had multiple tumors. A high preoperative AFP was observed in 155 (64.85%) patients. HBV

105 surface antigen was positive in 202 (84.5%) patients, 71 (29.7%) patients had tumor

106 encapsulation, and 174 (72.8%) patients had liver cirrhosis that was confirmed by pathology.

107

108 As shown in Table 1, the relationships between preoperative NLR and PLR, and between clinical

109 and pathologic characteristics were investigated. The high-NLR group included 104 (43.51%)

110 patients (NLR>2.92) and 135 (56.49%) patients were identified as being in the low-NLR

111 (NLR≤2.92) group. Eighty-seven (36.4%) patients were identified as being in the high-PLR

112 group (PLR>128.1), and 152 (63.6%) patients were identified as being in the low-PLR group

113 (PLR≤128.1).

114

115 Preoperative NLR level and PLR level were closely correlated with tumor size, TNM stage and

116 BCLC stage ($P<0.05$). The PLR also correlated with age, platelet count, prothrombin time (PT),

117 AFP, and satellite nodules ($P<0.05$). No obvious correlations with gender, HBsAg, hospital stay,

118 liver cirrhosis, serum albumin, total bilirubin (TBil), glutamic-pyruvic transaminase (ALT), or

119 glutamic-oxaloacetic transaminase (AST) were observed ($P>0.05$).

120

121 **The correlation between NLR, PLR and postoperative RFS and OS in patients with HCC**

122 **who underwent liver resection**

123   Kaplan-Meier survival analysis showed that the NLR>2.92 group was associated with a shorter

124   recurrence-free survival (RFS) (Figure 2A) and overall survival (OS) (Figure 2C). The patients

125   with HCC in the PLR>128.1 group were also associated with a shorter RFS (Figure 2B) and OS

126   (Figure 2D).

127

128   From the univariate analysis in Table 2, we found that tumor size (HR 1.30, 95% CI 1.08-1.56),

129   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,

130   95% CI 1.39-6.50), and satellite nodules (HR 4.27, 95% CI 2.55-7.14) correlated with RFS in

131   patients with HCC who underwent liver resection ($P<0.05$). The platelet count (HR 1.01, 95% CI

132   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

133   (HR 1.48, 95% CI 1.15-1.88), PLR (HR 1.007, 95% CI 1.001-1.013), TNM stage (HR 19.42,

134   95% CI 2.61-144.3), BCLC stage (HR 2.43, 95% CI 0.99-5.98), satellite nodules (HR 4.42, 95%

135   CI 2.66-7.33), and tumor number (HR 2.78, 95% CI 1.18-6.54) correlated with OS ($P<0.05$).

136   Gender, HBsAg, hospital stay, liver cirrhosis, serum albumin, total bilirubin (TBil), ALT and so

137   on had no statistically significant association with RFS or OS (P＞0.05).

138

139   In the multivariate analysis, we found that NLR (HR 1.16, 95% CI 1.06-1.26) and PLR (HR

140   1.004, 95% CI 1.001-1.006) were independent risk factors for RFS in patients with HCC. NLR

141   (HR 1.14, 95% CI 1.04-1.25) and PLR (HR 1.004, 95% CI 1.001-1.007) were independent risk

142   factors for OS in patients with HCC.

143

144   **Combined NLR and PLR to analyze RFS and OS in patients with HCC who underwent**

145   **hepatectomy**

146   In the previous results, we found that high NLR and high PLR are independent risk factors for

147   RFS and OS after hepatectomy in patients with HCC. We combined NLR with PLR to

148   investigate whether the prediction of RFS and OS was more accurate. We defined NLR≤2.92 as

149   NLR_{-low}, NLR>2.92 as NLR_{-high}, PLR≤128.1 as PLR_{-low}, and PLR>128.1 as PLR_{-high}. We found

150   that patients with simultaneously high NLR and PLR had the worst RFS (median 12 months) and

151   OS (median 18 months), while patients with simultaneously low NLR and PLR had the best RFS

152   (median 14.5 months) and OS (median 23 months). The NLR_{-low} and PLR_{-low} groups had the best

153   outcome and their RFS and OS were superior to other groups. The worst group was the NLR_{-high}

154   group combined with the PLR$_{-high}$ group. The results showed that patients with simultaneously

155   high NLR and high PLR were more prone to metastasis and had the worst OS (Figure 3).

156

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

158   Using multivariate analysis, we found that tumor size was an independent risk factor for poor

159   prognosis in patients with HCC who underwent liver resection. To see if there is any correlation,

160   we analyzed the relationship between NLR, PLR and tumor size. We divided the tumors into

161   three groups by size: ≤3 cm group, between 3-10 cm group, and ≥10 cm group. We found the

162   NLR and PLR were higher in groups with larger tumor size ($P<0.05$) (Figure 4).

163   The mean NLRs in the tumor≤3cm group, 3-10 cm group and ≥10 cm group were (2.32 ± 0.15),

164   (3.23 ± 0.17), and (4.03 ± 0.38), respectively (Figure 4A); the mean PLRs were (90.21 ± 6.44),

165   (128.5 ± 5.4), (157 ± 13.41), respectively (Figure 4B). We hypothesized that with high

166   neutrophil and platelet counts, cancer cells can release various chemokines and promote tumor

167   growth. At the same time, the number of lymphocytes decreased, and tumor cells escaped from

168   the immune surveillance, as the immune system could not activate its normal anti-tumor effect.

169   As a result, the HCC tumor growth progresses, increasing the tumor size.

170

171   We further analyzed the relationship between NLR, PLR and BCLC stage. We found that the

172   advantaged BCLC stage had higher NLR and PLR values. The mean NLR values of BCLC 0, A,

173   B, and C stages were (1.70 ± 0.14), (2.93 ± 0.13), (3.05 ± 0.26), and (4.82 ± 0.65) (Figure 5A),

174   respectively. The mean PLR values of BCLC0, A, B, and C stages were (81.93 ± 10.68), (122.1 ± 5.61)

175   ± 5.61), (122.5 ± 8.91), and (149.2 ± 16.13), respectively (Figure 5B).

176

177

178 **Discussion**

179 Many researchers have demonstrated that inflammation contributes to the pathogenesis and

180 progression of cancer [18]. The presence of systemic inflammation is associated with poor

181 survival in many types of tumors, and anti-inflammatory agents have been associated with cancer

182 prevention and treatment [19]. Inflammation can promote cancer development through multiple

183 mechanisms, including gene mutation, cancer cell proliferation and angiogenesis [7]. NLR and

184 PLR have been shown to have the ability to predict the prognosis in various cancers, including

185 HCC [20], esophageal carcinoma [21], renal carcinoma [22], and lung cancer [23]. Lu et al [20]

186 have studied the NLR in early and intermediate stage HCC, and in our research, we found the

187 NLR and PLR can predict the prognosis of patients with HCC who underwent liver research. The

188 stages included were early, intermediate and advanced stage HCC, all showing similar results.

189

190 In solid tumors, inflammation often appears before the tissue malignant transformation. The

191 occurrence and development of systemic immune responses provide an appropriate

192 microenvironment for cancer metastasis and recurrence. In China, most patients with HCC have

193 hepatitis infection, the inflammatory status playing an important role in promoting the

194 development of HCC. The NLR and PLR, sensitive indexes of the body's inflammation system,

195 can reflect the inflammatory state and predict the prognosis of the tumor.

196

197 Neutrophil can strengthen the biological behavior of the tumor, causing it to grow and

198 metastasize. Higher neutrophil levels can upregulate the expression of growth factors, such as the

199 types of chemokines, which play an important role in tumor development and progression.

200 Platelets play a leading role in tumor progression. Platelets can secrete inflammatory factors,

201 including TGF-β and VEGF, which can accelerate the differentiation and proliferation of tumor

202 cells. Moreover, platelets release platelet derived factors, such as platelet reactive protein, etc.,

203 which play an important role in tumor adhesion, and angiogenesis to (1) prepare the

204 microenvironment for tumor metastasis by secreting angiogenic factor and growth factor; and (2)

205 shield the cancer cell so the platelets can adhere to the tumor. Platelets can protect cancer cells

206 from the mechanical force of blood flow, and can also provide a shield for cancer cells that

207 allows them to escape immune surveillance.

208

209   Many studies have confirmed that lymphocytes are the most important cells in tumor killing.
210   When there is a relative or absolute reduction of lymphocytes, the antitumor effect is also
211   decreased. PD-1 and CTLA–4 inhibitors are the most important immunity drugs [24, 25]. They
212   can reduce tumor cell and T lymphocyte cell interaction by inhibiting the cancer cell surface
213   expression of PD-1 and CTAL-4. The patient's decreased immunity, specifically the abnormality
214   of the tumor immune microenvironment, leads to the failure of the lymphocyte immune
215   response, and the cancer cells escape from immune surveillance. When immune tolerance or
216   immune escape occurs, tumors are more likely to progress or metastasize. In our study, we found
217   that patients with higher NLR and PLR had worse RFS and OS prognosis. On one hand, the
218   increase of neutrophil and platelet counts promotes tumorigenesis; on the other hand, the
219   decrease in the number of lymphocytes leads to the patient's immunity decline, leading to tumor
220   progression.
221
222   In our study, we found that tumor size correlated with the NLR and PLR; the larger the tumor
223   size, the higher the NLR and PLR. We hypothesize that (1) as neutrophil and platelet counts
224   increase, they secrete many kinds of growth factors and inflammatory factors, which promote the
225   growth of tumor cells and stromal cells and impact the tumor microenvironment and promote
226   tumor growth; and (2) larger tumor size means higher tumor burden. The number of lymphocytes
227   obviously decreased, and the effect of tumor cells killing is also weakened, thereby promoting
228   the development of the tumor. Tumor size is one of the prognostic predictors for patients with
229   HCC, but tumor size was more difficult to measure than the NLR and PLR. Additionally, tumor
230   size cannot provide an accurate prediction of HCC, because the NLR and PLR can reflect
231   whether patients with HCC are associated with cirrhosis and hypersplenism. If the tumor is
232   small, but liver cirrhosis and hypersplenism are obvious, the prognosis of patients with HCC will
233   be poor.
234
235
236   We also found that the BCLC stage correlated with high NLR and high PLR. The advanced
237   BCLC stages had higher PLR and NLR. Multiple tumors and/or vascular invasion in patients
238   with HCC may lead to a stronger inflammatory response and weaker immune response. Higher
239   neutrophil and platelet counts mean a stronger inflammatory response. Lower lymphocyte counts
240   mean the immune response is decreased, and cancer cells are more likely to metastasize.

241

242 This study has some limitations. First, the number of patients in our study is small and the

243 patients were retrospectively studied in a single center. Therefore, we could not avoid selection

244 bias when collecting information on patients with HCC. Second, the NLR and PLR were

245 assessed by single measurements at the time of admission for the initial diagnosis.

246

247 **Conclusion**

248 In conclusion, our study showed that NLR and PLR are useful prognostic factors in predicting

249 outcomes in patients with HCC who underwent live resection. This finding can assist in guiding

250 the clinical management of patients with HCC.

251

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254

255 **Reference**

256 [1] Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D and Bray F.
257 Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int
258 J Cancer 2015; 136: E359-386.

259 [2] Bruix J, Reig M and Sherman M. Evidence-Based Diagnosis, Staging, and Treatment of Patients With
260 Hepatocellular Carcinoma. Gastroenterology 2016; 150: 835-853.

261 [3] Roayaie S, Jibara G, Tabrizian P, Park JW, Yang J, Yan L, Schwartz M, Han G, Izzo F, Chen M, Blanc JF,
262 Johnson P, Kudo M, Roberts LR and Sherman M. The role of hepatic resection in the treatment of
263 hepatocellular cancer. Hepatology 2015; 62: 440-451.

264 [4] Zhou L, Huang Y, Li J and Wang Z. The mTOR pathway is associated with the poor prognosis of human
265 hepatocellular carcinoma. Med Oncol 2010; 27: 255-261.

266 [5] Villanueva A, Hoshida Y, Battiston C, Tovar V, Sia D, Alsinet C, Cornella H, Liberzon A, Kobayashi M,
267 Kumada H, Thung SN, Bruix J, Newell P, April C, Fan JB, Roayaie S, Mazzaferro V, Schwartz ME and
268 Llovet JM. Combining clinical, pathology, and gene expression data to predict recurrence of hepatocellular
269 carcinoma. Gastroenterology 2011; 140: 1501-1512 e1502.

270 [6] Chaturvedi AK, Caporaso NE, Katki HA, Wong HL, Chatterjee N, Pine SR, Chanock SJ, Goedert JJ and
271 Engels EA. C-reactive protein and risk of lung cancer. J Clin Oncol 2010; 28: 2719-2726.

272 [7] Elinav E, Nowarski R, Thaiss CA, Hu B, Jin C and Flavell RA. Inflammation-induced cancer: crosstalk
273 between tumours, immune cells and microorganisms. Nat Rev Cancer 2013; 13: 759-771.

274 [8] Antonioli L, Blandizzi C, Pacher P and Hasko G. Immunity, inflammation and cancer: a leading role for
275 adenosine. Nat Rev Cancer 2013; 13: 842-857.

276 [9]   Ratnam NM, Peterson JM, Talbert EE, Ladner KJ, Rajasekera PV, Schmidt CR, Dillhoff ME, Swanson BJ,
277   Haverick E, Kladney RD, Williams TM, Leone GW, Wang DJ and Guttridge DC. NF-kappaB regulates
278   GDF-15 to suppress macrophage surveillance during early tumor development. J Clin Invest 2017; 127:
279   3796-3809.
280 [10] Izumi K, Fang LY, Mizokami A, Namiki M, Li L, Lin WJ and Chang C. Targeting the androgen receptor
281   with siRNA promotes prostate cancer metastasis through enhanced macrophage recruitment via
282   CCL2/CCR2-induced STAT3 activation. EMBO Mol Med 2013; 5: 1383-1401.
283 [11] Balkwill F. Tumour necrosis factor and cancer. Nat Rev Cancer 2009; 9: 361-371.
284 [12] Manfroi B, McKee T, Mayol JF, Tabruyn S, Moret S, Villiers C, Righini C, Dyer M, Callanan M,
285   Schneider P, Tzankov A, Matthes T, Sturm N and Huard B. CXCL-8/IL8 Produced by Diffuse Large B-cell
286   Lymphomas Recruits Neutrophils Expressing a Proliferation-Inducing Ligand APRIL. Cancer Res 2017;
287   77: 1097-1107.
288 [13] He G, Dhar D, Nakagawa H, Font-Burgada J, Ogata H, Jiang Y, Shalapour S, Seki E, Yost SE, Jepsen K,
289   Frazer KA, Harismendy O, Hatziapostolou M, Iliopoulos D, Suetsugu A, Hoffman RM, Tateishi R, Koike
290   K and Karin M. Identification of liver cancer progenitors whose malignant progression depends on
291   autocrine IL-6 signaling. Cell 2013; 155: 384-396.
292 [14] Dalpiaz O, Krieger D, Ehrlich GC, Pohlmann K, Stojakovic T, Pummer K, Zigeuner R, Pichler M and
293   Hutterer GC. Validation of the Preoperative Platelet-to-Lymphocyte Ratio as a Prognostic Factor in a
294   European Cohort of Patients with Upper Tract Urothelial Carcinoma. Urol Int 2017; 98: 320-327.
295 [15] McNamara MG, Templeton AJ, Maganti M, Walter T, Horgan AM, McKeever L, Min T, Amir E and
296   Knox JJ. Neutrophil/lymphocyte ratio as a prognostic factor in biliary tract cancer. Eur J Cancer 2014; 50:
297   1581-1589.
298 [16] Tao YM, Huang JL, Zeng S, Zhang S, Fan XG, Wang ZM, Yang HX, Yuan XH, Wang P, Wu F, Luo J,
299   Zeng DY and Shen H. BTB/POZ domain-containing protein 7: epithelial-mesenchymal transition promoter
300   and prognostic biomarker of hepatocellular carcinoma. Hepatology 2013; 57: 2326-2337.
301 [17] Hu K, Wang ZM, Li JN, Zhang S, Xiao ZF and Tao YM. CLEC1B Expression and PD-L1 Expression
302   Predict Clinical Outcome in Hepatocellular Carcinoma with Tumor Hemorrhage. Transl Oncol 2018; 11:
303   552-558.
304 [18] Sanford DE, Belt BA, Panni RZ, Mayer A, Deshpande AD, Carpenter D, Mitchem JB, Plambeck-Suess
305   SM, Worley LA, Goetz BD, Wang-Gillam A, Eberlein TJ, Denardo DG, Goedegebuure SP and Linehan
306   DC. Inflammatory monocyte mobilization decreases patient survival in pancreatic cancer: a role for
307   targeting the CCL2/CCR2 axis. Clin Cancer Res 2013; 19: 3404-3415.
308 [19] Pribluda A, Elyada E, Wiener Z, Hamza H, Goldstein RE, Biton M, Burstain I, Morgenstern Y, Brachya G,
309   Billauer H, Biton S, Snir-Alkalay I, Vucic D, Schlereth K, Mernberger M, Stiewe T, Oren M, Alitalo K,
310   Pikarsky E and Ben-Neriah Y. A senescence-inflammatory switch from cancer-inhibitory to cancer-
311   promoting mechanism. Cancer Cell 2013; 24: 242-256.
312 [20] Lu SD, Wang YY, Peng NF, Peng YC, Zhong JH, Qin HG, Xiang BD, You XM, Ma L and Li LQ.
313   Preoperative Ratio of Neutrophils to Lymphocytes Predicts Postresection Survival in Selected Patients
314   With Early or Intermediate Stage Hepatocellular Carcinoma. Medicine (Baltimore) 2016; 95: e2722.

315   [21]   Feng JF, Huang Y and Chen QX. Preoperative platelet lymphocyte ratio (PLR) is superior to neutrophil
316   lymphocyte ratio (NLR) as a predictive factor in patients with esophageal squamous cell carcinoma. World
317   J Surg Oncol 2014; 12: 58.
318   [22]   Hu H, Yao X, Xie X, Wu X, Zheng C, Xia W and Ma S. Prognostic value of preoperative NLR, dNLR,
319   PLR and CRP in surgical renal cell carcinoma patients. World J Urol 2017; 35: 261-270.
320   [23]   Sanchez-Salcedo P, de-Torres JP, Martinez-Urbistondo D, Gonzalez-Gutierrez J, Berto J, Campo A,
321   Alcaide AB and Zulueta JJ. The neutrophil to lymphocyte and platelet to lymphocyte ratios as biomarkers
322   for lung cancer development. Lung Cancer 2016; 97: 28-34.
323   [24]   Rizvi NA, Hellmann MD, Snyder A, Kvistborg P, Makarov V, Havel JJ, Lee W, Yuan J, Wong P, Ho TS,
324   Miller ML, Rekhtman N, Moreira AL, Ibrahim F, Bruggeman C, Gasmi B, Zappasodi R, Maeda Y, Sander
325   C, Garon EB, Merghoub T, Wolchok JD, Schumacher TN and Chan TA. Cancer immunology. Mutational
326   landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science 2015; 348: 124-
327   128.
328   [25]   Wei SC, Levine JH, Cogdill AP, Zhao Y, Anang NAS, Andrews MC, Sharma P, Wang J, Wargo JA, Pe'er
329   D and Allison JP. Distinct Cellular Mechanisms Underlie Anti-CTLA-4 and Anti-PD-1 Checkpoint
330   Blockade. Cell 2017; 170: 1120-1133 e1117.

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334

335 **Figure legends:**

336 Figure 1. The ROC curves of the NLR, PLR, and LMR in patients with HCC. A. The ROC area

337 of NLR was 0.63. B. The ROC area of PLR was 0.67. C The ROC area of LNR was 0.53.

338

339 Figure 2. Kaplan-Meier survival analysis indicates that patients with NLR>2.92 have a shorter

340 RFS and OS (A and C); patients with PLR>128.1 have a shorter RFS and OS (B and D).

341

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

343 underwent hepatectomy. The NLR-high and PLR-high group had the worst RFS (median 12

344 months) and OS (median 18 months), and the NLR-low and PLR-low group had the best RFS

345 (median 14.5 months) and OS (median 23 months).

346

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

348   We divided the tumors into three groups according to size: ≤3 cm group, between 3-10 cm

349   group, and ≥10 cm group. A: The mean NLRs in the tumor≤3cm group, 3-10 cm group and ≥10

350   cm group were (2.32 ± 0.15), (3.23 ± 0.17), and (4.03 ± 0.38), respectively. B: the mean PLRs

351   were (90.21 ± 6.44), (128.5 ± 5.4), and (157 ± 13.41), respectively. **means $P < 0.05$.

352

353   Figure 5. Analysis of the relationship between NLR, PLR and BCLC stage. A:The mean NLR

354   values of the BCLC 0, A, B, and C stages were (1.70 ± 0.14), (2.93 ± 0.13), (3.05 ± 0.26), and

355   (4.82 ± 0.65), respectively. B:The mean PLR values of the BCLC 0, A, B, and C stages were

356   (81.93 ± 10.68), (122.1 ± 5.61), (122.5 ± 8.91), and (149.2 ± 16.13), respectively. **means $P <$

357   0.05.

Figure 1

The ROC curves of the NLR, PLR, and LMR in patients with HCC.

The ROC curves of the NLR, PLR, and LMR in patients with HCC. A. The ROC area of NLR was 0.63. B. The ROC area of PLR was 0.67. C The ROC area of LNR was 0.53.

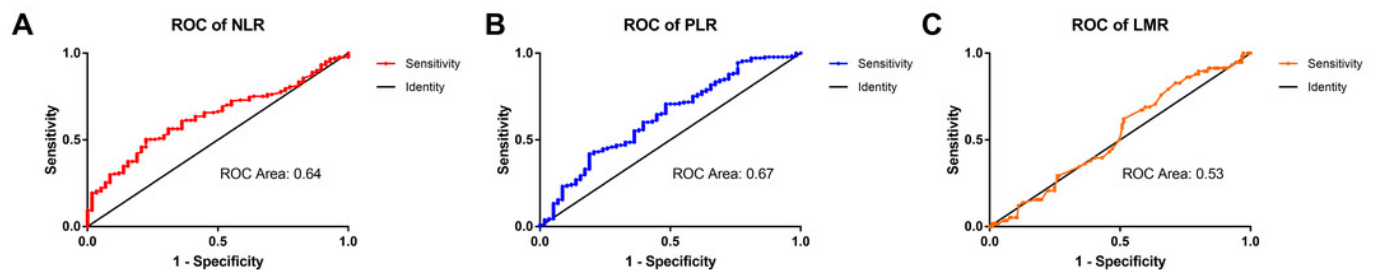



Figure 2

Kaplan-Meiersurvival analysis indicates that patients with NLR>2.92 have a shorter RFSand OS (A and C); patients with PLR>128.1 have a shorter RFS and OS (B andD).

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

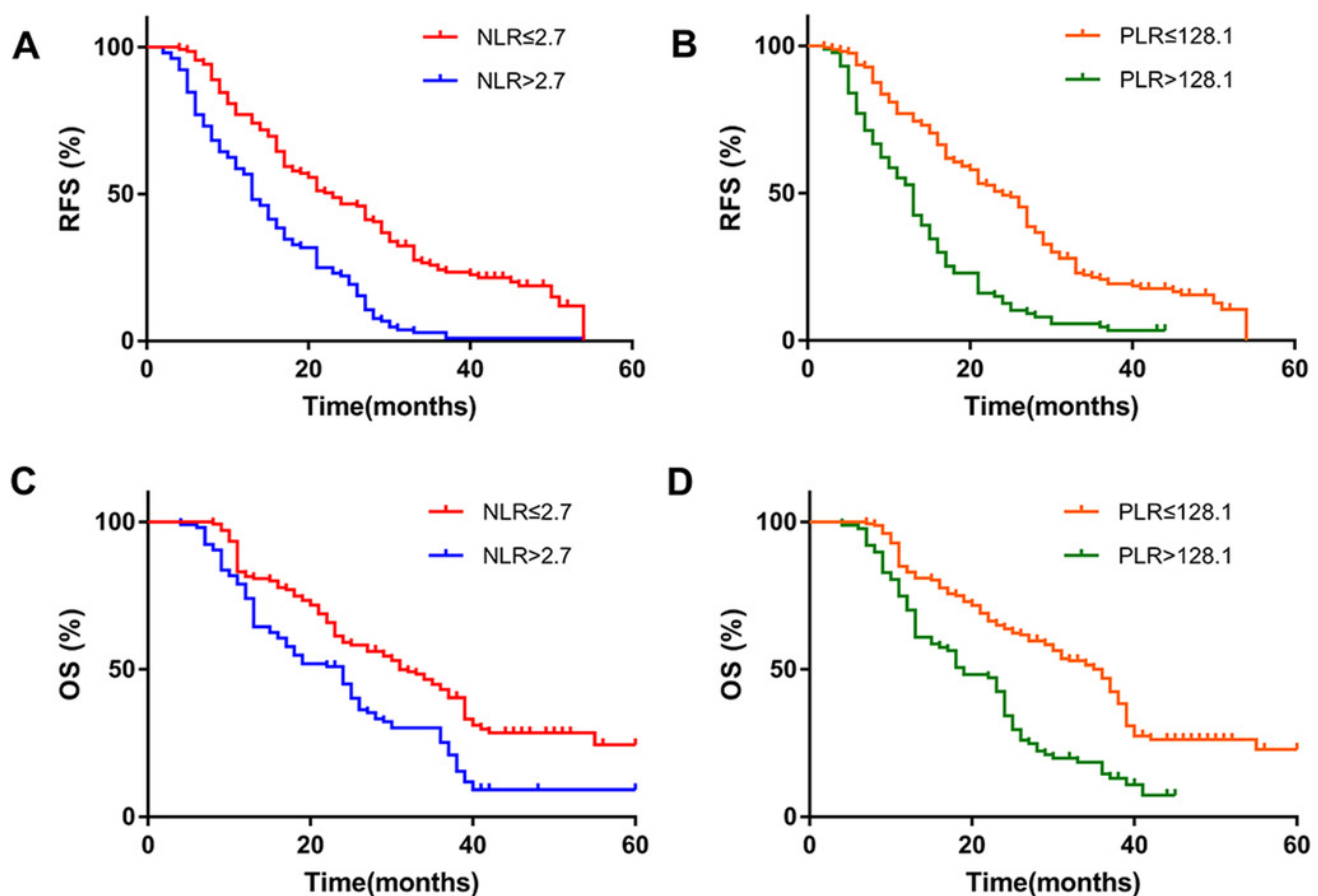



Figure 3

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

The NLR-high and PLR-high group had the worst RFS (median 12 months) and OS (median 18 months), and the NLR-low and PLR-low group had the best RFS (median 14.5 months) and OS (median 23 months).

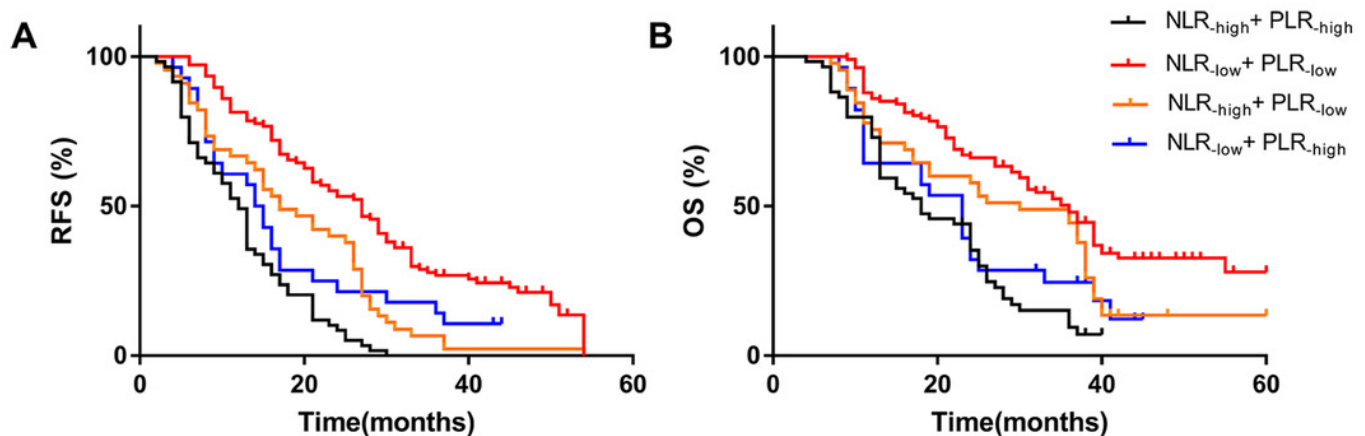



Figure 4

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

We divided the tumors into three groups according to size: ≤ 3 cm group, between 3-10 cm group, and ≥ 10 cm group. A: 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. B: the mean PLRs were (90.21 ± 6.44), (128.5 ± 5.4), and (157 ± 13.41), respectively. ** means $P \leq 0.05$.

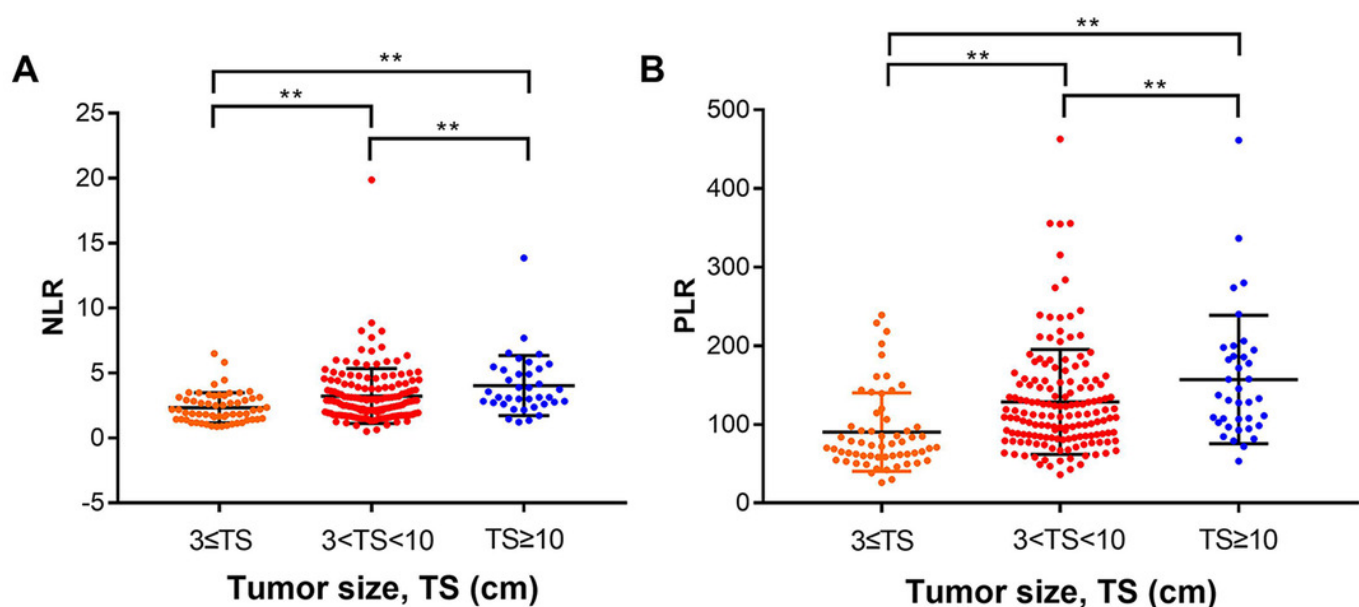
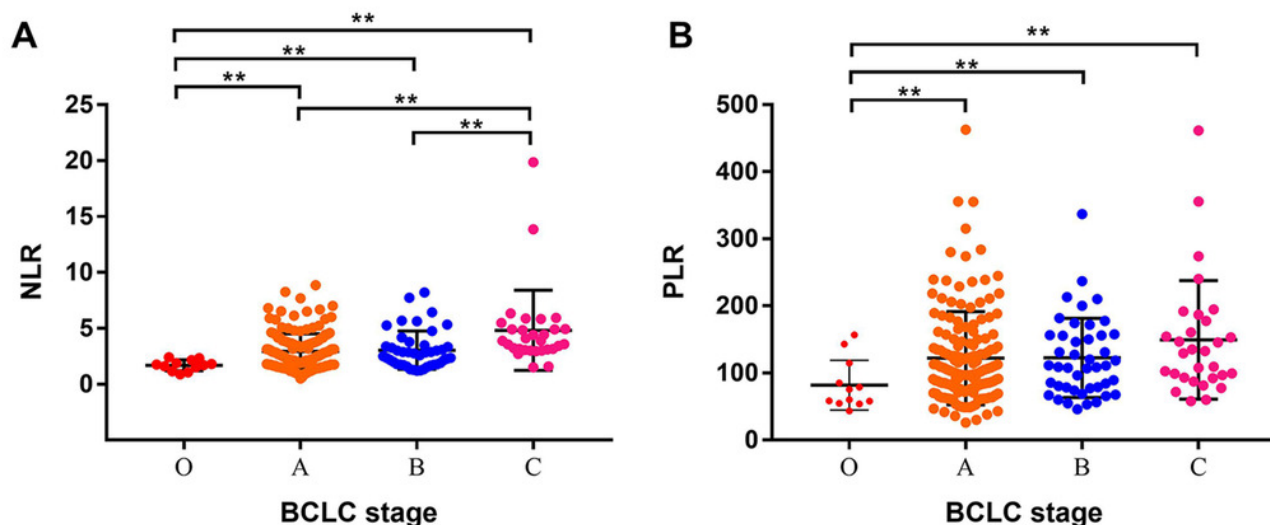



Figure 5

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

Analysis of the relationship between NLR, PLR and BCLC stage. A : The mean NLR values of the BCLC 0, A, B, and C stages were (1.70 ± 0.14), (2.93 ± 0.13), (3.05 ± 0.26), and (4.82 ± 0.65), respectively. B : The mean PLR values of the BCLC 0, A, B, and C stages were (81.93 ± 10.68), (122.1 ± 5.61), (122.5 ± 8.91), and (149.2 ± 16.13), respectively. ** means $P \square 0.05$.

HCC patients (n=239) categorized by NLR, PLR and their clinical pathologic characteristics.

1   **Table 1. HCC Patients (n=239) Categorized by NLR, PLR and Their Clinical Pathologic**

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	

2   **Characteristics.**

3   NLR, neutrophil-to-lymphocyte ratio; HBsAg, hepatitis B surface antigen; AFP, α-fetoprotein; TNM, tumor-node-

4   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.

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

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

3   NLR, neutrophil-to-lymphocyte ratio; HBsAg, hepatitis B surface antigen; AFP, α-fetoprotein; TNM, tumor-node-

4   metastasis; TBil, total bilirubin; PT, Prothrombin time; CTP, Child-Turcotte-Pugh; BCLC stage: The Barcelona

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