

# Evaluation of the prognostic value of platelet to lymphocyte ratio in patients with hepatocellular carcinoma

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**Background:** Hepatocellular carcinoma (HCC) is increasingly common, potentially fatal cancer type globally. Platelet-lymphocyte ratio (PLR) as a biomarker for systemic inflammation has recently been recognized as a valuable prognostic marker in multiple cancer types. The aim of the present study was to assess the prognostic value of PLR in HCC patients and determine the optimal cut-off value for risk stratification.

**Methods:** We retrospectively analyzed patients with diagnosis of HCC (screened by ICD-9 code, confirmed with radiographic examination and/or biopsy) at a large public hospital during 15 years (Jan 2000 through July 2015). PLR, among other serology laboratory values were collected at diagnosis of HCC. Its association with overall survival was evaluated with Cox proportional hazard model.

**Results:** Among 270 patients with HCC, 57 (21.1%) patients died within an average follow-up of 11.9 months. PLR at diagnosis was significantly different between survivors and deceased (128.9 vs. 186.7;  $P=0.003$ ). In multivariate analysis, aspartate transaminase (AST) (HR 2.022,  $P<0.001$ ) and PLR (HR 1.768,  $P=0.004$ ) independently predicted mortality. The optimal cut-off value for PLR was determined to be 220 by receiver-operating characteristics curve, and high PLR group had significantly higher mortality (HR 3.42,  $P<0.001$ ).

**Conclusions:** Our results indicated that elevated PLR at diagnosis above 220 predicted poor prognosis in HCC patients. PLR is a low-cost and convenient tool, which may serve as a useful prognostic marker for HCC.

**Keywords:** Hepatocellular carcinoma (HCC); platelet-lymphocyte ratio (PLR)

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## Introduction

Hepatocellular carcinoma (HCC) is currently the fifth most frequently diagnosed cancer in adult male and seventh in female globally, leading to 25,000 to one million deaths per annum (1-3). As the worldwide epidemics of obesity continues, the incidence of HCC increases with that of non-alcoholic fatty liver disease, and in contrast to the declining mortality rate seen among other cancer types, death rate

of HCC is still on the rise (4-6). As tumor metastasis and recurrence remain the major cause of mortality, there is urgent need for identification of reliable and precise biomarkers to predict prognosis and guide individualized treatment in HCC patients (7,8).

Currently, an accumulating evidence suggests that systemic inflammation suppresses innate anti-tumor immune system, thus facilitates the initiation, progression and metastasis of cancer (7-12). Inflammatory biomarkers

such as platelet-lymphocyte ratio (PLR), neutrophil-lymphocyte ratio (NLR), C-reactive protein have been proven as valuable prognostic factors in multiple gastrointestinal cancers including pancreatic ductal adenocarcinoma, colorectal cancer and gastric cancer (7,9-11,13-16). In HCC however, the results were still conflicting regarding the prognostic value of PLR to predict overall survival and the optimal cut-off of PLR remains unclear (11,17-20).

The present study aims to evaluate the clinical significance of PLR to predict mortality in patients of HCC.

## Method

### Study subjects

We retrospectively reviewed the electronic medical records of patients who presented to John H. Stroger Hospital of Cook County, Chicago IL from January 01, 2000 through July 31, 2015.

We identified potential patients using ICD-9 code (=155) and/or ICD-10 code (= C22) for malignant neoplasm of liver and intrahepatic biliary duct. We confirmed the diagnosis if they had histopathology-proven or radiographically proven HCC by triple-phase enhanced computed tomography and/or magnetic resonance imaging of the abdomen (intense enhancement during arterial phase followed by “washout pattern” during delayed phase). We excluded patients <18 years of age, if they had incomplete data as outlined in *Data Collection* section, or had incomplete follow-up of less than 1 month in our institution.

The present study was approved by the Institutional Review Board of Cook County Health & Hospitals System, Chicago. The database was set up and maintained by the Department of Medicine, Cook County Health & Hospitals System (21).

### Data collection

Eligible patients were censored if there was discontinuation of follow up. We abstracted demographic variables including age, gender, past medical history (hypertension, diabetes), body mass index (BMI) at diagnosis; tumor-related risk factors including etiology of liver disease, Child-Pugh score, number of intra-hepatic lesions, extra-hepatic metastasis, Barcelona staging of HCC20; treatment variables including chemotherapy with sorafenib, curative treatment (liver transplant, resection, radio-frequency

ablation); laboratory values at diagnosis including neutrophil, lymphocyte, hemoglobin, platelet, INR, albumin, aspartate aminotransferase, total bilirubin.

VTE was diagnosed based on radiographic exams including compression ultrasonography, contrast enhanced computed tomography, and pulmonary angiogram. There was no systematic VTE screening. Portal vein thrombosis was not included given limitations on objective differentiation between tumor invasion and true thrombosis. Blinded event adjudication was conducted for all outcome data by three physicians; in case of discrepancy there was a majority vote to adjudicate.

### Statistical analysis

Descriptive data was summarized to characterize the distribution of variables. We used the Kolmogorov-Smirnov and Shapiro-Wilk tests to evaluate if continuous variables were normally distributed. We used Student's *t*-test to compare normally distributed continuous variables; we used Wilcoxon's rank-sum test to compare non-parametric continuous variables; Chi-square test or Fisher's exact test were used to compare categorical variables.

We plotted the bar graph to demonstrate difference of PLR between prognosis groups. Univariate analysis was performed for each laboratory value to predict mortality in Cox regression model. Variables with significance of <0.20 were included in multivariate analysis to identify independent risk factors for mortality. Multivariate analysis was then performed for PLR and epidemiologic factors significantly associated with mortality as demonstrated by prior literature (22,23). Receiver operating characteristics (ROC) curve was plotted for PLR to predict mortality and identify cut-off value by optimized Youden's index. Kaplan-Meier curve was then plotted for survival curves of different PLR groups.

Statistical analysis was performed with Stata version 13 (Stata Corp., College Station, Tex). P value of less than 0.05 indicated statistical significance in analysis.

## Results

### Patient characteristics

Among the 308 patients identified by initial screening, 270 patients were eventually included for analysis (34 patients were excluded as they had biopsy-proven cholangiocarcinoma or metastatic adenocarcinoma,

**Table 1** Epidemiologic characteristics of patients with hepatocellular carcinoma, John H. Stroger Hospital of Cook County

Variables	Cohort (N=270)		Alive (N=213)		Deceased (N=57)		**P value
	Mean/N	SD/%	Mean/N	SD/%	Mean/N	SD/%	
<sup>†</sup> Age (years)	58.5	8.9	58.6	9.4	58.2	7.4	0.760
* $\geq 65$ (years)	59	21.9	50	23.4	9	15.8	0.212
*Gender							0.028
Female	50	18.5	46	21.6	5	8.8	
Male	220	81.4	167	78.4	52	91.2	
*Past medical history							
Diabetes	89	32.9	77	36.2	12	21.1	0.031
Hypertension	126	6.7	103	48.3	23	40.4	0.282
Cirrhosis	229	84.8	180	84.5	49	85.9	0.785
*Barcelona stage							0.002
0, A, B	115	42.6	101	47.4	14	24.6	
C, D	155	57.4	112	52.6	43	75.4	
*VTE	16	5.9	9	4.2	7	12.3	0.022
*Chemotherapy	91	33.7	64	30.0	27	47.3	0.014
*Curative treatment	31	11.5	26	12.2	5	8.80	0.470

<sup>†</sup>, normally distributed continuous variable, presented as mean value and standard deviation; \*, categorical variables, presented as number and percentage of patients; \*\*, P value obtained with Student's *t*-test for continuous values, Chi-square test or Fisher's exact test for categorical variables. N, number; SD, standard deviation.

4 patients were excluded with a follow-up period less than 1 month) (Table 1). The mean age at diagnosis of HCC was 58.5 years for the cohort, 81.4% of patients were male. There were 155 (57.4%) patients who had advanced HCC with Barcelona C or D at diagnosis. A total of 33.7% patients underwent chemotherapy with sorafenib and 11.5% patients underwent curative treatment including surgical resection, radio-frequency ablation or liver transplant. We identified 16 cases of venous thromboembolism within a mean follow up period of 11.9 months, representing a 2-year cumulative incidence of 5.93%. Comparison between groups of survivor and deceased revealed that mortality was significantly higher in male patients, diabetics, patients with advanced HCC, patients who had VTE, and patients who underwent chemotherapy.

#### Association between laboratory values and mortality

Direct comparison of laboratory values collected at diagnosis of HCC between groups revealed that survivors

had significantly lower INR, aspartate transaminase (AST), bilirubin, PLR, and higher albumin (Table 2). This finding was anticipated as survivors were expected to have relatively preserved hepatic synthetic function and less hepatocellular inflammation and damage.

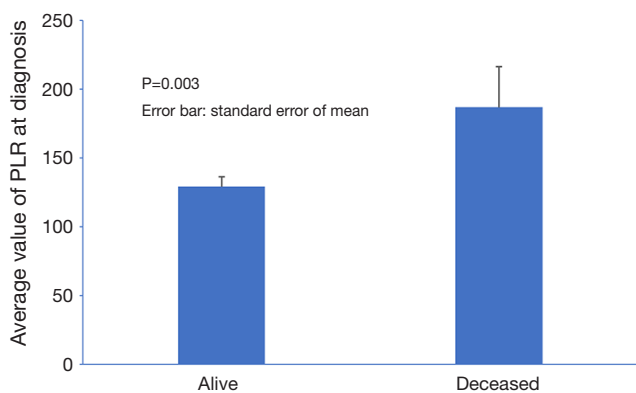
PLR, of note, was significantly lower in survivors ( $P=0.003$ ) as demonstrated in Figure 1. In univariate analysis, hemoglobin, neutrophil count, INR, albumin, AST, bilirubin and PLR were significantly associated with mortality. However, the association remained significant in multivariate analysis only for AST (HR 2.022,  $P<0.001$ ), and PLR (HR 1.768,  $P=0.004$ ). Lower albumin did not reach statistically significant association with mortality (HR 0.655,  $P=0.053$ ) (Table 3).

We then performed multivariate analysis for mortality on PLR, AST and epidemiologic factors predictive of mortality as demonstrated in previous literature, including male gender, advanced HCC, and occurrence of VTE (22,23). All variables remained significantly predictive of mortality (PLR: HR 1.56,  $P=0.028$ ; AST: HR 1.92,  $P<0.001$ ) (Table 4).

**Table 2** Laboratory values at diagnosis of hepatocellular carcinoma

Variables	Cohort	Alive	Deceased	**P value
†Hgb (g/dL)	12.3	12.4	11.9	0.273
*Neutrophil count (10 <sup>9</sup> /L)	4.46	4.23	5.30	0.152
*Lymphocyte count (10 <sup>9</sup> /L)	1.52	1.53	1.50	0.464
*Platelet count (10 <sup>9</sup> /L)	164.7	163.4	169.4	0.189
*INR	1.30	1.24	1.50	0.011
†Albumin (g/dL)	3.18	3.25	2.91	0.008
*AST (unit/L)	125.3	112.1	174.6	0.003
*Bilirubin (mg/dL)	2.36	2.14	3.18	0.047
*PLR	141.1	128.9	186.7	0.003

†, parametric continuous variable; \*, non-parametric continuous variable; \*\*, P value obtained with Student's *t*-test for parametric continuous variables, Wilcoxon's rank-sum test for non-parametric continuous variables. Hgb, hemoglobin; INR, international normalized ratio; AST, aspartate transaminase; PLR, platelet-lymphocyte ratio.

**Figure 1** Bar graph of platelet-lymphocyte ratio (PLR) in alive and deceased group.

### Utility of PLR in prediction of mortality

We plotted ROC curve of PLR for prediction of mortality (Figure 2) and identified the cut-off point of 218, with corresponding sensitivity and specificity of 24.6% and 89.7% respectively. We dichotomized the data based on this cut-off value of PLR into two groups and plotted Kaplan-Meier survival curve (Figure 3) which revealed high PLR group had significantly higher mortality rate (HR 3.42,  $P < 0.001$ ).

### Discussion

In this cohort of 270 patients with HCC, 57 patients

**Table 3** Univariate and multivariate analysis of laboratory values for mortality prediction

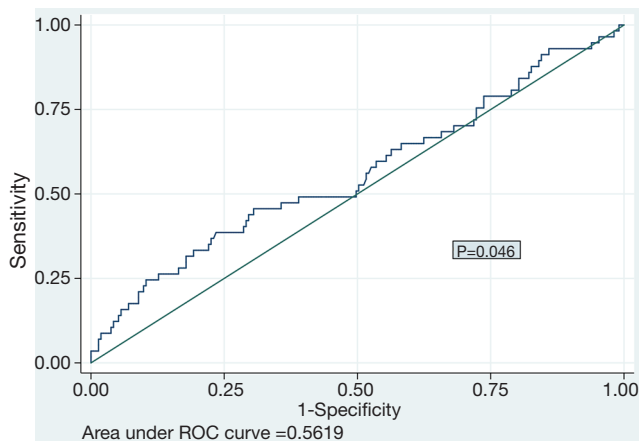
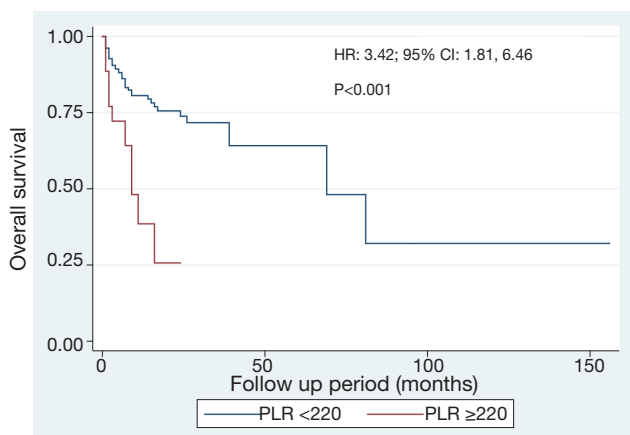
Variables	Univariate analysis		Multivariate analysis	
	Hazard ratio	P value	Hazard ratio	P value
Hgb (g/dL)	0.854	0.012	0.937	0.336
Neutrophil count (10 <sup>9</sup> /L)	1.711	0.024	1.148	0.573
Lymphocyte count (10 <sup>9</sup> /L)	0.795	0.329	–	–
Platelet count (10 <sup>9</sup> /L)	1.305	0.245	–	–
INR	4.717	<0.001	1.378	0.517
Albumin (g/dL)	0.487	<0.001	0.655	0.053
AST (unit/L)	2.257	<0.001	2.022	<0.001
Bilirubin (mg/dL)	1.627	0.001	1.091	0.605
PLR	1.860	0.002	1.768	0.004

Hgb, hemoglobin; INR, international normalized ratio; AST, aspartate transaminase; PLR, platelet-lymphocyte ratio.

**Table 4** Multivariate analysis of epidemiologic and laboratory values for prediction of mortality

Variables	Hazard ratio	P value	95% confidence interval	
VTE	6.49	0.001	2.21	19.1
Gender	3.06	0.022	1.17	7.98
Advanced HCC stage	2.61	0.007	1.29	5.22
PLR	1.56	0.028	1.05	2.33
AST	1.92	<0.001	1.37	2.69

VTE, venous thromboembolism; HCC, hepatocellular carcinoma; PLR, platelet-lymphocyte ratio; AST, aspartate transaminase.

**Figure 2** Receiver-operating characteristics curve of platelet-lymphocyte ratio (PLR) for prediction of mortality.**Figure 3** Kaplan-Meier curve demonstrating survival of different platelet-lymphocyte ratio (PLR) groups.

died within an average follow-up period of 11.9 months. Comparison of laboratory values at diagnosis between survivors and deceased patients revealed significant differences in the levels of INR, albumin, AST, bilirubin and PLR. Higher AST and PLR could independently predict mortality as demonstrated in multivariate analysis. The optimal cut-off point for PLR to predict mortality in HCC patients was determined to be 218 by ROC analysis, and after dichotomization, patients of high PLR group had significantly poor overall survival.

Our results were in line with a growing body of evidence supporting the utility of systemic inflammatory markers (e.g., PLR, NLR, C-reactive protein) to predict prognosis in patients of various cancer types including HCC (7-21). Yang *et al.* analyzed 778 HCC patients undergoing curative liver resection, concluding that PLR quintiles were significantly associated with poor survival in cirrhotic patients or patients with positive hepatitis B surface antigen (11). Similarly, Shirai *et al.* reviewed 131 patients of pancreatic ductal adenocarcinoma who underwent pancreatic resection and reported perioperative PLR independently predicted disease-free survival and overall survival (10). Fuentes *et al.* reported in their cohort of 112 patients with gastric cancer, that patients stratified as high risk by PLR had worse overall survival (22.6 vs. 42.8 months) (13). In the meta-analysis of patients with colorectal cancer, Huang *et al.* included 17 studies and concluded that elevated PLR was associated with poor overall survival, disease-free survival, as well as higher cancer stage and poor differentiation (7). Recently, the utility of PLR has also been extensively explored in various non-cancerous populations, including patients with acute coronary syndrome, immunoglobulin-resistant Kawasaki disease, premature ovarian insufficiency and acute pancreatitis (24-27). These associations were also attributed to the role of PLR as a systemic inflammation marker.

The exact underlying mechanism responsible for

the role of PLR in HCC has yet to be elucidated (11). However, it is postulated to be closely related to the cancer-induced systemic inflammatory response, which suppresses recruitment of immunosuppressive cells such as regulatory T cells, leading to tumor progression and metastasis (7,9,28). Thrombocytosis results from megakaryocyte stimulation due to pro-inflammatory mediator secretion from tumor, and promotes tumor progression in several mechanisms (29). Platelet secretes various growth factors including vascular endothelial growth factor, platelet-derived growth factor, which promotes angiogenesis, cell proliferation and metastasis (14-17). In addition, tumor-induced platelet aggregation protects tumor cells from being cleared by innate immune surveillance of T cells (30,31). On the other hand, tumor-infiltrating lymphocytes induces apoptosis of tumor cells and play an important role in anti-tumor response (32,33). The lymphocyte count reflects the responsiveness of the host immune system and is inversely related with tumor proliferation and invasiveness (7).

Several limitations existed for the present study: (I) although the present data is from a relatively large cohort with heterogeneous HCC patients, our study was retrospective in design and limited by the inherent confounders as patients may have been systematically excluded; (II) all laboratory values were collected at initial diagnosis of HCC. A longitudinal follow up of series of PLR at intervals and important time points (e.g., pre-chemotherapy, perioperative) might provide more insights of its prognostic value.

In conclusion, elevated PLR of above 220 predicts poor prognosis in patients with HCC. As a readily available and low-cost test, PLR proves to be a valuable tool for prognosis stratification and individualized treatment. Further prospective studies are required to confirm the findings of the present study and the optimal cut-off value of PLR in HCC population.

### Acknowledgements

None.

### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

*Ethical Statement:* The study was approved by institutional ethics review board of Cook County Health and Hospitals

System [IRB Organization (IORG) number: IORG0000119] and informed consent was taken from all the patients.

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