ORIGINAL RESEARCH

Prognostic Significance of Elevated Platelet Count (>200 x 10^9 per L) in BCLC Stages B and C of Hepatocellular Carcinoma: A Retrospective Multicenter Analysis

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Introduction: In hepatocellular carcinoma (HCC) comorbidities related to decreased liver function or to portal hypertension often limit treatment options. Traditionally, low platelet count has been considered a negative prognostic factor in HCC, especially in early stages. However, recent evidence suggests that elevated platelet count may also predict worse outcomes in advanced stages, suggesting a stage-dependent prognostic impact.

Aim: This study evaluated the prognostic role of platelet counts across BCLC stages, adjusted for portal hypertension, to improve individualized patient management.

Methods: In this retrospective, multicenter study, platelet count of 1112 patients with HCC in different tumor stages was analyzed. Various platelet count cutoffs (X to Y × 10^9/L) were tested to identify the optimal prognostic threshold. To isolate the effect of platelet levels from portal hypertension, spleen diameter was incorporated as an adjustment variable in multivariate analyses, with variceal status considered when available (in about two thirds of patients). Using an optimized cut-off, survival analysis was performed using univariate and multivariate Cox proportional hazards models. Bootstrapping was performed for internal validation.

Results: Platelet count outside 84–200 × 10^9/L was associated with poorer survival (HR = 0.66, 95% CI = 0.57–0.78, p < 0.0001). Bootstrapping showed robustness of the final model. Subgroup analysis revealed worse survival in BCLC stages B and C but not stage A for elevated platelet counts (>200 × 10^9/L) in multivariate analysis (including spleen diameter).

Conclusion: Platelet counts showed a stage-dependent prognostic impact in HCC. A platelet count above a cutoff of 200/μL at diagnosis was associated with poorer prognosis. Using this cutoff may improve survival prediction in BCLC B and C patients with potential usage for risk stratification and guidance of treatment decisions. Further external validation is required to confirm these findings and evaluate their clinical applicability.

Keywords: hepatocellular carcinoma, HCC, platelets, survival, cutoff, biomarker, BCLC

Introduction

Hepatocellular carcinoma (HCC) is a common and deadly cancer, frequently arising in patients with chronic liver disease or cirrhosis.[1,2] Treatment is often complicated by portal hypertension-related comorbidities, contributing to end-stage liver disease symptoms such as ascites, kidney failure, variceal bleeding, and thrombocytopenia.[3,4] Platelet count, a critical marker of significant portal hypertension, is effective in predicting postoperative outcomes in BCLC Stage A patients and guiding clinical decisions.[5,6] Despite increasing data on the relevance of platelet count across other BCLC stages its role has to be further refined.

Early studies have shown that in BCLC Stages B and C, the prognostic role of platelet counts exhibits an opposite trend compared to BCLC Stage A.[7,8] Recent evidence complementing these findings by Scheiner et al, showed in a large patient cohort that increased mean platelet volume and low platelet count correlate with improved survival in HCC patients.[9] Similarly, Huo et al reported that elevated platelet counts across all BCLC stages (0-D) are associated with advanced tumor characteristics and predict worse overall survival in HCC patients[10] and Chen et al demonstrated a U-shaped curve associating platelet count with survival in BCLC Stage B patients.[11] These studies highlight the complex role of platelet counts in HCC progression across different BCLC stages. However, the precise role of platelet counts remains unclear and a clinically relevant cutoff for BCLC B and C patients still needs to be established.

Non-invasive methods, such as CT-derived liver and spleen volumes, are increasingly being used for the evaluation of portal hypertension in HCC.[12] Whereas liver stiffness measurements may not reliably assess clinically significant portal hypertension in HCC patients.[13] These imaging approaches underscore the utility of certain Baveno criteria elements, particularly spleen diameter, in the non-invasive assessment of portal hypertension in HCC patients.

Delineating the relationship between platelet count, portal hypertension, and additional underlying factors is important for prognostic assessment, improvement of treatment strategies and new therapeutic approaches in HCC. Our study focuses on evaluating platelet count comprehensively across BCLC stage to validate previous findings and to find better clinically meaningful cutoffs for platelet count at diagnosis of HCC.

Methods

Study Design

Epidemiological data, survival, and recurrence rates were analyzed in a cohort of patients diagnosed with HCC between 2006 and 2022. Consecutive Patients were included with following criteria:[1] age ≥18 years, and[2] a radiological or histological diagnosis of HCC. The study included patients from the University Medical Center Munich, University Clinic Mannheim, and University Clinic Vienna. Data collection and retrospective analysis were conducted in compliance with the Declaration of Helsinki and approved by the local ethics committee (LMU Ethics Committee: 18–604). Patient consent was not required due to the study's retrospective design. To ensure data confidentiality, all patient information was anonymized throughout the study.

Background and Data Collection

We conducted a retrospective analysis of 1112 patients with HCC from three centers: Munich (n = 754), Vienna (n = 250), and Mannheim (n = 108). In total 632 deceased during the study period while 480 were censored. Diagnosis was made either histologically (postoperatively or by puncture) or by imaging and typical contrast enhancement on the basis of progressed liver disease. Most current lab values available at time or shortly before initial treatment (<3 months) were used for the analysis. Macrovascular invasion was diagnosed based on contrast-enhanced imaging (CT and/or MRI) following the standard diagnostic criteria for HCC. Baseline characteristics assessed included age, sex, height, weight, performance status (according to the Eastern Cooperative Oncology Group), presence of cirrhosis, Child-Pugh score, etiology of liver disease, presence of ascites, portal hypertension, spleen diameter, BCLC Stage and laboratory values. Data were extracted, recorded, and entered into a central database by trained personnel. Information on patient survival and disease recurrence was obtained from clinical reports, death certificates issued by local public health departments, and registration offices. Data processing and storage adhered to the Bavarian Law of Cancer Registries.

Exploratory Analysis of Platelet Range for HCC Patients

To find optimal cut-off values we tested the Log rank test with different cut-offs and chose the cut-offs with the lowest p-value as previously described.[14,15] Patients for which lab values were not available according to the requirement (<3 months prior to first treatment) were not considered for subsequent analysis. To determine the optimal platelet range for patients with hepatocellular carcinoma, we considered the lowest (11 × 10^9/L) and highest (1073 × 10^9/L) platelet counts in our cohort. We iteratively tested various platelet ranges from X to Y x 10^9/L including combinations such as 10–12, 12–14, 100–150, 400–700, until all possible range sizes were covered. Patients were categorized as either inside or outside each range. An exhaustive analysis was conducted by plotting survival curves for all platelet ranges and assessing the separation of these curves. For each range, we fitted a survival model, visualized survival curves, and used the Log rank test to evaluate differences in survival probabilities. The p-value from the Log rank test was computed for each range. The range associated with the best survival outcomes allowed the classification of patients into three groups: "normal range", "low platelet counts", and "high platelet counts", which differed from conventional platelet ranges.

Statistical Analysis

Continuous data were summarized using means, medians, minimum and maximum values, and standard deviations, while categorical data were presented as absolute frequencies and relative percentages. Comparisons of patient characteristics were made using analysis of variance (ANOVA) or the Kruskal–Wallis test for continuous data and Chi-square tests for categorical variables. Survival analysis was conducted from the date of diagnosis until death or the last patient contact. Follow-up and survival times were censored as of December 31, 2022. Univariable analysis involved fitting a series of Cox proportional hazards models to assess the relationship between individual variables and survival. Significant variables were identified, and a multivariable Cox regression model was developed to determine independent predictors of survival. Rows with missing values were excluded to ensure robust analysis. Stepwise forward selection was used to refine the model, starting from a null model and progressively adding variables. The final model summarized significant predictors of survival, with a significance level set at 0.05. All analyses were performed using RStudio 2023.09.1+494 "Desert Sunflower" release.

Results

In this retrospective cohort study, we analyzed a total of 1112 patients diagnosed with HCC from all BCLC stages across three European centers. Baseline characteristics are provided in Table 1.

To identify clinically relevant platelet cutoffs, platelet count prognostic potential was examined across BCLC stages. Based on previous observations, we hypothesized that two cutoffs better discriminate survival of HCC patients. To explore the prognostic potential of cutoff pairs, we iteratively tested cutoff pairs that stratified risk of patients in low, medium, and high platelet count groups. A cutoff pair dividing the patients into low (<84/nl), medium (84–200) and high platelet counts (>200/nl) showed the strongest predictive potential (Figure 1A). This cutoff pair showed a significantly better model fit compared to any single cutoff (spp. Table 1). Patients with platelet counts within 84 to 200 x 10^9/L at diagnosis were significantly associated with better survival, whereas platelet counts outside this range were linked to poorer survival (Figure 1B).

As shown in Table 2, low platelet counts were significantly associated with a higher prevalence of cirrhosis (96.1% vs 84.8% and 56.3%, p < 0.001), more advanced liver disease (reflected by higher Child-Pugh scores), as well as higher incidences of metastasis, macroscopic portal vein infiltration, ascites (50.2%), and portal hypertension (90.3%) (p < 0.001). On the other hand, platelet numbers above 200/nl were significantly associated with BCLC C stages.

According to the new platelet cutoffs we performed a multivariate Cox Regression analysis across BCLC stages and for each BCLC stage separately (Table 3 and Figure 2). Spleen diameter was included in the model to adjust for portal hypertension and to adjust for potential confounders. We further included macroscopic portal hypertension or metastasis. The multivariate analysis showed that in BCLC A patients lower platelet counts (<84/nl) were associated to poorer survival whereas in BCLC B and C patients primarily elevated platelet counts (>200/μL) were associated to poorer survival. Due to the incomplete assessment of varice status (available in 868 of the 1112 patients) it was not included in

Table 1 Baseline Characteristics of the HCC Patients Across BCLC Stages

Variable	BCLC A	BCLC B	BCLC C	BCLC D	p-value
n	364	334	355	59	
Age (mean (SD))	65.99 (10.33)	67.65 (10.18)	65.69 (10.74)	62.12 (8.65)	0.001
Female (%)	89 (24.5)	54 (16.2)	56 (15.8)	6 (10.2)	0.003
Height (mean (SD))	1.73 (0.09)	1.73 (0.07)	1.74 (0.09)	1.76 (0.07)	0.044
Weight (mean (SD))	79.21 (16.69)	81.71 (15.52)	80.21 (14.60)	85.36 (16.09)	0.028
BMI (mean (SD))	26.41 (4.50)	27.19 (4.50)	26.39 (4.10)	27.78 (4.44)	0.021
ECOG (%)					<0.001
0	271 (74.7)	186 (55.7)	160 (45.2)	26 (44.1)	
1	74 (20.4)	134 (40.1)	159 (44.9)	23 (39.0)	
2	16 (4.4)	14 (4.2)	33 (9.3)	9 (15.3)	
3	2 (0.6)	0 (0.0)	2 (0.6)	1 (1.7)	
Cirrhosis = 1 (%)	261 (71.7)	274 (82.0)	268 (75.5)	57 (96.6)	<0.001
Childscore (%)					<0.001
1 – Child-Pugh A	287 (78.8)	233 (69.8)	233 (65.6)	2 (3.4)	
2 – Child-Pugh B	67 (18.4)	92 (27.5)	105 (29.6)	3 (5.1)	
3 – Child-Pugh C	10 (2.7)	9 (2.7)	17 (4.8)	54 (91.5)	
Etiology (%)					<0.001
Alcohol	100 (27.5)	132 (39.5)	106 (29.9)	29 (49.2)	
Viral	106 (29.1)	78 (23.4)	102 (28.7)	16 (27.1)	
Other (NASH included)	61 (16.8)	41 (12.3)	39 (11.0)	10 (16.9)	
Unknown	97 (26.6)	83 (24.9)	108 (30.4)	4 (6.8)	
Ascites = 1 (%)	84 (23.1)	94 (28.1)	135 (38.0)	48 (81.4)	<0.001
Portal Vein thrombosis = 1 (%)	19 (5.5)	55 (19.0)	77 (36.7)	9 (52.9)	<0.001
Portal hypertension = 1 (%)	198 (54.4)	222 (66.5)	214 (60.6)	47 (79.7)	<0.001
Macrovascular invasion = 1 (%)	6 (1.7)	21 (6.4)	160 (45.7)	29 (49.2)	<0.001
Metastases = 1 (%)	1 (0.3)	7 (2.1)	140 (40.1)	10 (17.2)	<0.001
Lymph Node involvement = 1 (%)	12 (3.5)	33 (11.6)	79 (38.3)	4 (23.5)	<0.001
Gruppe (%)					<0.001
Spleen-Diameter cranio-caudal (mean (SD))	9.96 (3.75)	10.42 (3.71)	10.80 (3.66)	13.45 (3.68)	<0.001
AFP (ng/mL) (median [IQR])	7.45 [3.80, 72.35]	19.95 [5.20, 189.00]	168.10 [9.55, 4038.50]	108.15 [5.05, 5070.25]	<0.001
Bilirubin (mg/dl) (median [IQR])	0.90 [0.60, 1.30]	1.00 [0.70, 1.50]	1.00 [0.60, 1.51]	3.36 [2.59, 4.23]	<0.001
Alkaline Phosphatase (U/L) (median [IQR])	112.00 [83.00, 151.50]	144.00 [102.00, 202.00]	159.50 [116.00, 243.75]	208.50 [160.00, 295.75]	<0.001

(Continued)

Table 1 (Continued).

| Variable	BCLC A	BCLC B	BCLC C	BCLC D	p-value
INR (median [IQR])	1.10 [1.00, 1.14]	1.17 [1.08, 1.26]	1.10 [1.02, 1.30]	1.40 [1.30, 1.45]	<0.001
Albumin in g/dl (median [IQR])	4.10 [3.50, 4.50]	3.80 [3.40, 4.30]	3.84 [3.34, 4.20]	2.76 [2.59, 3.08]	<0.001
Platelet count (median [IQR])	157.50 [103.25, 220.75]	142.00 [97.00, 206.50]	180.00 [117.00, 260.25]	94.50 [71.25, 159.50]	<0.001

Notes: Values are shown as mean (standard deviation, SD) if normally distributed or median [interquartile range, IQR] if non-normally distributed; categorical data are presented as percentages. Statistical comparisons between BCLC stages used ANOVA for normally distributed variables, Kruskal–Wallis test for non-normally distributed variables, and Chi-square (χ^2) test for categorical variables.
Abbreviations: BMI, Body Mass Index; ECOG, Eastern Cooperative Oncology Group Performance Status; BCLC, Barcelona Clinic Liver Cancer Staging System; Childscore, Child-Pugh Score; NASH, Non-Alcoholic Steatohepatitis; AFP, Alpha-Fetoprotein; INR, International Normalized Ratio.

the previous model. Upon inclusion of varice status the overall model the performance does not improve (Concordance with varices 0.72 versus 0.72 without varices) and the multivariate Cox-Regression analysis results remain nearly unchanged spp Table 2. We also assessed the effect of antiplatelet medication (data available for 593 patients, with 112 receiving treatment); the hazard ratio was 1.14 (p = 0.391), and the concordance index remained 0.72 (spp Table 3). Bootstrapping, performed with 1000 resamples, validated the robustness of the model's coefficient estimates and the predictive accuracy of platelet counts as a prognostic marker (spp Table 4).

Discussion

Low platelets count in HCC has been extensively researched as surrogate of portal hypertension, particularly in patients with early-stage disease (BCLC A and B). Thrombocytopenia is considered in this setting a negative predictor of the outcome of surgical or interventional procedures. In contrast, recent research highlighted an association between lower platelet count and favorable outcome in patients with advanced-stage disease (BCLC C and D) (Scheiner et al, 2018). Chen et al recently underscored the association with poor prognosis of elevated platelet counts for BCLC B patients as well.[16] However, only few studies have linked elevated platelet counts to shorter survival.[7,8,16] The findings of Scheiner et al and Chen et al prompted us to examine the precise role of platelet counts in HCC across different BCLC stages, adjusting for the effects of portal hypertension, a factor not considered in previous studies to validate these observations and to find clinically relevant cutoff values.
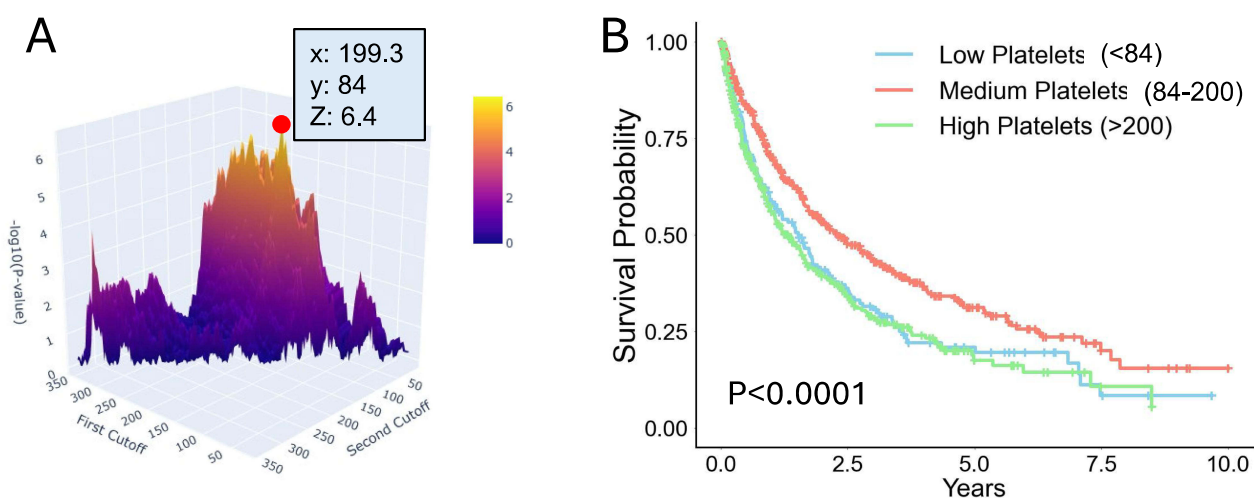
Figure 1 (**A**) Heatmap depicting the statistical significance (z-axis) of various cutoff pairs tested with the Logrank survival test (z-axis), hereby the best survival discrimination was found for an upper cutoff of 200000 platelets/μL and lower cutoff at 84000 platelets/μL (**B**) Kaplan-Meier survival analysis with newly defined platelet count cutoffs, comparing survival probabilities of patients within the new platelet range (84–200 × 10^9/L) vs outside ranges (Logrank, p<0.0001).
Abbreviation: BCLC, Barcelona Clinic Liver Cancer Staging system.

Table 2 Baseline Characteristics of Patients According to the Newly Defined Platelet Ranges

Variable	Low Platelets (<84 x10⁹L) (n=182)	Normal Range (84–200 x10⁹L) (n=545)	High Platelets (>200 x10⁹L) (n=364)	p-value
ECOG (%)				0.311
0	120 (58.0)	314 (60.4)	194 (53.4)	
1	74 (35.7)	171 (32.9)	140 (38.6)	
2	13 (6.3)	31 (6.0)	28 (7.7)	
3	0 (0.0)	4 (0.8)	1 (0.3)	
Height (mean (SD))	1.73 (0.09)	1.74 (0.08)	1.73 (0.08)	0.585
Weight (mean (SD))	81.64 (17.98)	81.83 (15.61)	78.61 (14.20)	0.012
BMI (mean (SD))	27.10 (4.88)	27.05 (4.62)	26.06 (3.68)	0.004
Age (mean (SD))	62.15 (9.60)	66.80 (9.50)	67.70 (11.60)	<0.001
Sex = Female (%)	45 (21.7)	81 (15.6)	73 (20.1)	0.081
Cirrhosis = Y (%)	199 (96.1)	441 (84.8)	205 (56.3)	<0.001
Child-Score (%)				<0.001
1 – Child-Pugh A	80 (38.6)	372 (71.5)	291 (79.9)	
2 – Child-Pugh B	85 (41.1)	112 (21.5)	63 (17.3)	
3 – Child-Pugh C	42 (20.3)	36 (6.9)	10 (2.7)	
Etiology (%)				<0.001
Alcoholic	76 (36.7)	203 (39.0)	83 (22.8)	
Viral	71 (34.3)	142 (27.3)	85 (23.4)	
Other	35 (16.9)	71 (13.7)	41 (11.3)	
Unknown	25 (12.1)	104 (20.0)	155 (42.6)	
Ascites = Y (%)	104 (50.2)	162 (31.2)	91 (25.0)	<0.001
Portal vein thrombosis = Y (%)	35 (22.4)	66 (16.0)	58 (20.4)	0.142
Portal hypertension = Y (%)	187 (90.3)	350 (67.4)	135 (37.2)	<0.001
BCLC Stage (%)				<0.001
A	61 (29.5)	180 (34.6)	117 (32.1)	
B	70 (33.8)	172 (33.1)	85 (23.4)	
C	49 (23.7)	147 (28.3)	152 (41.8)	
D	27 (13.0)	21 (4.0)	10 (2.7)	
Macrovascular invasion = Y (%)	41 (20.0)	94 (18.2)	76 (21.1)	0.549
Metastases = Y (%)	17 (8.3)	63 (12.2)	76 (21.4)	<0.001
Lymph node involvement = Y (%)	16 (10.3)	51 (12.5)	60 (21.4)	0.001
Spleen diameter cranio-caudal (mean (SD))	13.97 (3.52)	10.53 (3.31)	8.49 (3.08)	<0.001

(*Continued*)

Table 2 (Continued).

Variable	Low Platelets (<84 x10⁹L) (n=182)	Normal Range (84–200 x10⁹L) (n=545)	High Platelets (>200 x10⁹L) (n=364)	p-value
AFP (ng/mL) (median [IQR])	20.60 [5.20, 210.95]	14.90 [5.10, 310.50]	77.20 [4.70, 2693.00]	0.002
Bilirubin (mg/dl) (median [IQR])	1.70 [1.15, 2.76]	1.00 [0.70, 1.50]	0.70 [0.50, 1.10]	<0.001
Alkaline phosphatase (U/L) (median [IQR])	135.50 [104.00, 186.00]	136.00 [95.00, 189.00]	150.00 [106.75, 257.25]	<0.001
INR (median [IQR])	1.29 [1.18, 1.40]	1.13 [1.08, 1.30]	1.10 [1.00, 1.20]	<0.001
Albumin in g/dl (median [IQR])	3.40 [2.90, 3.90]	3.90 [3.40, 4.40]	4.00 [3.50, 4.33]	<0.001
Platelet count (median [IQR])	66.00 [52.00, 79.00]	139.00 [112.00, 168.00]	261.00 [226.00, 325.00]	<0.001

Notes: Baseline characteristics of patients according to the newly defined platelet ranges: low (<84,000/μL), normal (84,000–200,000/μL), and high (>200,000/μL). Values are shown as mean (standard deviation, SD) if normally distributed or median [interquartile range, IQR] if non-normally distributed; categorical data are presented as percentages. Statistical comparisons between platelet count groups used ANOVA for normally distributed variables, Kruskal–Wallis test for non-normally distributed variables, and Chi-square (χ^2) test for categorical variables.
Abbreviations: ECOG, Eastern Cooperative Oncology Group Performance Status; BMI, Body Mass Index; BCLC, Barcelona Clinic Liver Cancer Staging System; AFP, Alpha-Fetoprotein; INR, International Normalized Ratio.

Table 3 Multivariate Cox Regression Analysis by BCLC Stages

Variable	All BCLC (n=1112)	BCLC A	BCLC B	BCLC C	BCLC D
ECOG	1.38 (1.21–158), p < 0.0001	1.46 (1.10–1.94), p = 0.010	1.18 (0.92–1.52), p = 0.202	1.49 (1.20–1.86), p < 0.001	1.02 (0.63–1.66), p = 0.920
Age (increase in 5 years)	1.09 (1.05–1.15), p < 0.0001	1.24 (1.11–1.38), p < 0.001	1.04 (0.96–1.12), p = 0.333	1.05 (0.98–1.14), p = 0.165	1.23 (0.99–1.54), p = 0.066
Child-Score	1.20 (1.01–1.40), p=0.0236	1.46 (0.94–2.26), p = 0.093	1.83 (1.34–2.51), p < 0.001	1.27 (0.99–1.63), p = 0.062	1.74 (0.65–4.65), p = 0.272
Ascites	1.68 (1.37–2.05), p < 0.0001	1.13 (0.64–2.00), p = 0.673	1.36 (0.92–2.01), p = 0.125	1.68 (1.22–2.32), p = 0.002	4.06 (1.57–10.47), p = 0.004
BCLC Stage	1.60 (1.42–1.80) p < 0.0001	n.a.	n.a.	n.a.	n.a.
Macrovascular invasion	1.16 (0.94–1.44) p = 0.1766	0.64 (0.15–2.74), p = 0.549	0.86 (0.49–1.52), p = 0.609	1.32 (0.99–1.75), p = 0.055	0.82 (0.40–1.69), p = 0.586
Metastases	1.27 (1.00–1.62), p = 0.0509	3.24 (0.44–23.91), p = 0.249	1.75 (0.70–4.39), p = 0.236	1.29 (0.97–1.72), p = 0.081	2.75 (1.12–6.77), p = 0.028
Spleen Diameter (increase in 5 cm steps)	1.01 (0.99–1.04), p = 0.2690	1.12 (0.84–1.48), p = 0.434	1.06 (0.86–1.30), p = 0.588	1.26 (1.00–1.58), p = 0.046	1.02 (0.69–1.52), p = 0.921
Platelets (increase in 50/nl steps)	1.10 (1.05–1.15), p < 0.0001	1.08 (0.99–1.18), p = 0.070	1.24 (1.12–1.36), p < 0.001	1.07 (1.01–1.14), p = 0.029	1.43 (1.14–1.79), p = 0.002
Group: Low Platelets (<84/nl)	1.18 (0.94–1.49), p = 0.1563	2.17 (1.25–3.76), p = 0.006	1.16 (0.77–1.74), p = 0.471	1.02 (0.66–1.58), p = 0.922	0.93 (0.47–1.84), p = 0.830
Group: High Platelets (>200/nl)	1.65 (1.35–2.02), p < 0.0001	1.57 (0.99–2.48), p = 0.054	1.93 (1.35–2.77), p < 0.001	1.66 (1.20–2.29), p = 0.002	2.55 (0.84–7.69), p = 0.097

Notes: Multivariate Cox regression analysis by BCLC stages. Model variables from the previous model across all stages were included. Hazard ratios (HR) with 95% confidence intervals (CI) and p-values are presented, showing the stage-dependent prognostic significance of platelet counts, specifically the detrimental impact of elevated platelet counts (>200 000/μL) in BCLC B and C stages.
Abbreviations: ECOG, Eastern Cooperative Oncology Group Performance Status; BCLC, Barcelona Clinic Liver Cancer Staging System; HR, Hazard Ratio; CI, Confidence Interval.
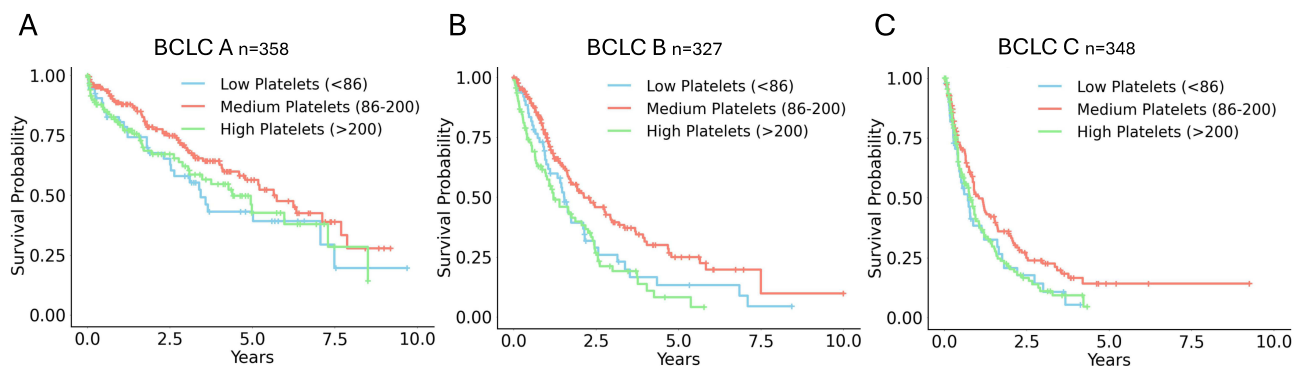
Figure 2 (**A**) Kaplan-Meier survival analysis with the newly defined platelet count cutoffs for BCLC stage A patients (**B**) Kaplan-Meier survival analysis with the newly defined platelet count cutoffs for BCLC stage B patients (**C**) Kaplan-Meier survival analysis with the newly defined platelet count cutoffs for BCLC stage C patients.
Abbreviation: BCLC, Barcelona Clinic Liver Cancer Staging system.

To further investigate this apparently conflicting information on the prognostic role of platelet counts and given that conventional platelet cutoffs did not adequately discriminate the different populations, we tested various cutoff values for discriminatory potential and found better discriminatory potential upon using two cutoff values (spp. Table 1). We identified that platelet counts above a cutoff of 200/nl indicated poorer survival in the patient population. The multi-variate analyses confirmed that elevated platelet counts, according to the new cutoff of 200/μL, were negatively associated with survival in HCC patients. This finding aligns with the results of Pinter et al and Chen et al,[9,16] showing that elevated platelet counts are associated with poorer survival in BCLC B and C stages (Table 3). The new lower cutoff (below 84/μL) closely approximates the commonly used 100/μL cutoff for assessing surgical risk in BCLC A patients hereby validating the study cohort and methodology (Table 3).[5,17,18] A recent meta-analysis further supports our data, demonstrating that while low platelets (<100/nl) predict poorer prognosis in curative-intent HCC patients, elevated platelet counts are associated with worse outcomes in palliative treatment settings (BCLC B and C).[19]

Other prognostic markers, in addition to or in combination with platelet counts, can further support prognostic estimation in HCC. Inflammatory markers like the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are associated with poorer outcomes, especially in HCC with BCLC B stage.[20–24] The aspartate amino-transferase to platelet ratio index (APRI) helps assess liver fibrosis, while C-reactive protein (CRP) reflects systemic inflammation and correlates with advanced disease.[25–27] Lymphocyte-to-monocyte ratio (LMR) and red cell distribution width (RDW) have additionally shown a linkage between hematologic changes to prognosis.[20,28] Additionally, Shi et al demonstrated that integrating platelet counts with CD8+ T cell levels improves prognostic accuracy in HCC patients with portal vein tumor thrombosis (PVTT).[29] Combining these markers with platelet counts could create more comprehensive models for risk assessment and treatment planning in HCC.

Preclinical evidence suggests a complex, potentially detrimental role of platelets in hepatocarcinogenesis. For example, platelet-derived GPIbα, which plays a crucial role in platelet adhesion to blood vessels, has been shown to be critical for HCC development in a model of non-alcoholic steatohepatitis.[30] Additionally, platelet releasates have been found to enhance the proliferative response of HCC cells.[31] Other in vitro findings reinforce the importance of platelets in HCC pathogenesis,[32] indicating that platelets themselves may play a harmful role. Padickakudy et al reported that platelet-derived serotonin promotes tumor angiogenesis with elevated serotonin levels predisposing patients to early HCC recurrence, collectively linking platelet-driven hypercoagulability to venous thromboembolic events and poorer prognosis.[33] Further studies are needed to delineate the impact of platelets on HCC progression to advance biomarker discovery and therapeutic targeting.

Despite its multicentric nature, our study has several limitations. Platelet counts were not adjusted for inflammatory markers such as C-reactive protein (CRP) or leukocyte numbers, which could influence the results. Additionally, the absence of a validation cohort means that these findings require further confirmation through subsequent studies. Therapy-related variables (eg, sorafenib, SIRT) could further refine prognosis and survival outcomes. Data collection protocols across centers

may introduce variability and could impact reliability and standardization. Further the study design is retrospective and missing information (ie variceal status) or inconsistencies could affect the reliability of the conclusions.

The impact of platelet count was adjusted for surrogate markers of portal hypertension and comprehensively analyzed across different BCLC stages. This study revealed a stage-dependent association of elevated platelet counts with poor HCC prognosis and suggests a new platelet cutoff (200/μL) for assessing prognosis in BCLC B and C patients, which could enhance risk stratification and guide therapeutic decision-making.

Disclosure

Alexander B Philipp and Enrico N De Toni are co-senior authors for this study. Najib Ben Khaled reports meeting attendance fees and travel reimbursements from Eisai; lecture honorarium from Falk Foundation, AstraZeneca; consultant for Ipsen, Roche; research support from Genentech, outside the submitted work. Florian P Reiter has received honoraria for lectures, consulting activities and travel support from the Falk Foundation, AbbVie, Gilead, Ipsen, AstraZeneca, Roche, and Novartis. Daniel Roessler reports personal fees from Ipsen, Bayer, and Falk, outside the submitted work. Bernhard Scheiner reports grants, personal fees for speaker honoraria from Eisai, travel supports from Ipsen, Gilead, AbbVie, Roche; speaker honoraria, consulting fee and travel supports from AstraZeneca, outside the submitted work. Matthias Pinter reports grants, personal fees from AstraZeneca, Bayer, BMS, Eisai, Roche, Ipsen, Eli Lilly, MSD, outside the submitted work. Max Seidensticker reports grants from Astra Zeneca, Boston Scientific, SIRTEX Medical; personal fees for lectures from Cook Medical, Siemens Healthineers, Balt, outside the submitted work. Alexander Philipp reports grants and/or personal fees from AstraZeneca, Roche, MSD, Falk Foundation, Ipsen, Pfizer, outside the submitted work. Enrico De Toni is an employee of Boehringer-Ingelheim; he reports personal fees from AstraZeneca, Bayer, BMS, EISAI, Lilly, MSD, Pfizer, IPSEN, Terumo, Roche; travel grants from Arqule, AstraZeneca, BMS, Bayer, Eli Lilly, IPSEN and Roche. The authors report no other conflicts of interest in this work.

References

1. Flemming JA, Yang JD, Vittinghoff E, Kim WR, Terrault NA. Risk prediction of hepatocellular carcinoma in patients with cirrhosis: the ADRESS-HCC risk model. *Cancer*. 2014;120(22):3485–3493. doi:10.1002/cncr.28832
2. Tsochatzis EA, Bosch J, Burroughs AK. Liver cirrhosis. *Lancet*. 2014;383(9930):1749–1761. doi:10.1016/S0140-6736(14)60121-5
3. Choi GH, Park JY, Hwang HK, et al. Predictive factors for long-term survival in patients with clinically significant portal hypertension following resection of hepatocellular carcinoma. *Liver Int*. 2011;31(4):485–493. doi:10.1111/j.1478-3231.2010.02436.x
4. Cillo U, Bassanello M, Vitale A, et al. The critical issue of hepatocellular carcinoma prognostic classification: which is the best tool available? *J Hepatol*. 2004;40(1):124–131. doi:10.1016/j.jhep.2003.09.027
5. Maithel SK, Kneuertz PJ, Kooby DA, et al. Importance of low preoperative platelet count in selecting patients for resection of hepatocellular carcinoma: a multi-institutional analysis. *J Am Coll Surg*. 2011;212(4):638–648. doi:10.1016/j.jamcollsurg.2011.01.004
6. Pang Q, Qu K, Zhang JY, et al. The prognostic value of platelet count in patients with hepatocellular carcinoma: a systematic review and meta-analysis. *Medicine*. 2015;94(37):e1431. doi:10.1097/MD.0000000000001431
7. Brau N, Fox RK, Xiao P, et al. Presentation and outcome of hepatocellular carcinoma in HIV-infected patients: a U.S.-Canadian multicenter study. *J Hepatol*. 2007;47(4):527–537. doi:10.1016/j.jhep.2007.06.010
8. Nouso K, Ito Y, Kuwaki K, et al. Prognostic factors and treatment effects for hepatocellular carcinoma in child C cirrhosis. *Br J Cancer*. 2008;98(7):1161–1165. doi:10.1038/sj.bjc.6604282
9. Scheiner B, Kirstein M, Popp S, et al. Association of platelet count and mean platelet volume with overall survival in patients with cirrhosis and unresectable hepatocellular carcinoma. *Liver Cancer*. 2019;8(3):203–217. doi:10.1159/000489833
10. Liu PH, Hsu CY, Su CW, et al. Thrombocytosis is associated with worse survival in patients with hepatocellular carcinoma. *Liver Int*. 2020;40(10):2522–2534. doi:10.1111/liv.14560
11. Lu L, Zhang Y, Zheng P, et al. Elevated platelet count is associated with poor survival after transarterial chemoembolization treatment in patients with hepatocellular carcinoma: a cohort study. *J Hepatocell Carcinoma*. 2020;7:191–199. doi:10.2147/JHC.S274349
12. Romero-Cristobal M, Clemente-Sanchez A, Ramon E, et al. CT-derived liver and spleen volume accurately diagnose clinically significant portal hypertension in patients with hepatocellular carcinoma. *JHEP Rep*. 2023;5(3):100645. doi:10.1016/j.jhepr.2022.100645
13. Allaire M, Campion B, Demory A, et al. Baveno VI and VII criteria are not suitable for screening for large varices or clinically significant portal hypertension in patients with hepatocellular carcinoma. *Aliment Pharmacol Ther*. 2023;58(3):346–356. doi:10.1111/apt.17599
14. Chen Y, Huang J, He X, et al. A novel approach to determine two optimal cut-points of a continuous predictor with a U-shaped relationship to hazard ratio in survival data: simulation and application. *BMC Med Res Methodol*. 2019;19(1):96. doi:10.1186/s12874-019-0738-4
15. Chang C, Hsieh MK, Chang WY, Chiang AJ, Chen J. Determining the optimal number and location of cutoff points with application to data of cervical cancer. *PLoS One*. 2017;12(4):e0176231. doi:10.1371/journal.pone.0176231
16. Lu L, Su Z, Zheng P, et al. Association between platelet count and hepatocellular carcinoma overall survival: a large retrospective cohort study. *BMJ Open*. 2020;10(11):e038172. doi:10.1136/bmjopen-2020-038172

17. Schrecker C, Waidmann O, El Youzouri H, et al. Low platelet count predicts reduced survival in potentially resectable hepatocellular carcinoma. *Curr Oncol*. 2022;29(3):1475–1487. doi:10.3390/curroncol29030124

18. Amano H, Tashiro H, Oshita A, et al. Significance of platelet count in the outcomes of hepatectomized patients with hepatocellular carcinoma exceeding the Milan criteria. *J Gastrointest Surg*. 2011;15(7):1173–1181. doi:10.1007/s11605-011-1538-2

19. Kraj L, Chmiel P, Gryziak M, Grabowska-Derlatka L, Szymanski L, Wysokinska E. Impact of thrombocytopenia on survival in patients with hepatocellular carcinoma: updated meta-analysis and systematic review. *Cancers*. 2024;16(7):1293. doi:10.3390/cancers16071293

20. Shen Y, Wang H, Chen X, Li W, Chen J. Prognostic significance of lymphocyte-to-monocyte ratio and platelet-to-lymphocyte ratio in patients with hepatocellular carcinoma undergoing transcatheter arterial chemoembolization and radiofrequency ablation. *Onco Targets Ther*. 2019;12:7129–7137. doi:10.2147/OTT.S217935

21. Xu C, Wu F, Du L, Dong Y, Lin S. Significant association between high neutrophil-lymphocyte ratio and poor prognosis in patients with hepatocellular carcinoma: a systematic review and meta-analysis. *Front Immunol*. 2023;14:1211399. doi:10.3389/fimmu.2023.1211399

22. Li DZ, Guo J, Song QK, Hu XJ, Bao XL, Lu J. Prognostic prediction of the platelet-to-lymphocyte ratio in hepatocellular carcinoma: a systematic review and meta-analysis. *Transl Cancer Res*. 2022;11(11):4037–4050. doi:10.21037/tcr-22-1197

23. Yang Y, Wang MC, Tian T, et al. a high preoperative platelet-lymphocyte ratio is a negative predictor of survival after liver resection for hepatitis B virus-related hepatocellular carcinoma: a retrospective study. *Front Oncol*. 2020;10:576205. doi:10.3389/fonc.2020.576205

24. Ocal O, Kimm MA, Hoang TPT, et al. Predictive value of platelet-to-lymphocyte and neutrophil-to-lymphocyte ratio in HCC treated with sorafenib and radioembolization. *JHEP Rep*. 2024;6(4):100995. doi:10.1016/j.jhepr.2023.100995

25. Allenson K, Roife D, Kao LS, Ko TC, Wray CJ. Estimation of hepatocellular carcinoma mortality using aspartate aminotransferase to platelet ratio index. *J Gastrointest Oncol*. 2020;11(2):291–297. doi:10.21037/jgo.2018.11.01

26. Carr BI, Akkiz H, Guerra V, et al. C-reactive protein and hepatocellular carcinoma: analysis of its relationships to tumor factors. *Clin Pract*. 2018;15(Spec Issue):625–634. doi:10.4172/clinical-practice.1000409

27. Lin KY, Chen QJ, Tang SC, et al. Prognostic implications of alpha-fetoprotein and C-reactive protein elevation in hepatocellular carcinoma following resection (PACE): a large cohort study of 2770 patients. *BMC Cancer*. 2023;23(1):1190. doi:10.1186/s12885-023-11693-6

28. Yang YT, Jiang JH, Yang HJ, Wu ZJ, Xiao ZM, Xiang BD. The lymphocyte-to-monocyte ratio is a superior predictor of overall survival compared to established biomarkers in HCC patients undergoing liver resection. *Sci Rep*. 2018;8(1):2535. doi:10.1038/s41598-018-20199-2

29. Shi W, Yan H, Liu X, et al. Development and validation of a novel prognostic nomogram based on platelet and CD8(+)T cell counts in hepatocellular carcinoma patients with portal vein tumor thrombosis. *J Hepatocell Carcinoma*. 2024;11:1049–1063. doi:10.2147/JHC.S452688

30. Malehmir M, Pfister D, Gallage S, et al. Platelet GPIbalpha is a mediator and potential interventional target for NASH and subsequent liver cancer. *Nat Med*. 2019;25(4):641–655. doi:10.1038/s41591-019-0379-5

31. He AD, Xie W, Song W, et al. Platelet releasates promote the proliferation of hepatocellular carcinoma cells by suppressing the expression of KLF6. *Sci Rep*. 2017;7(1):3989. doi:10.1038/s41598-017-02801-1

32. Carr BI, Cavallini A, D'Alessandro R, et al. Platelet extracts induce growth, migration and invasion in human hepatocellular carcinoma in vitro. *BMC Cancer*. 2014;14(1):43. doi:10.1186/1471-2407-14-43

33. Padickakudy R, Pereyra D, Offensperger F, et al. Bivalent role of intra-platelet serotonin in liver regeneration and tumor recurrence in humans. *J Hepatol*. 2017;67(6):1243–1252. doi:10.1016/j.jhep.2017.08.009