Original Article

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Platelet count as a double-edged sword: The impact of thrombocytosis and thrombocytopenia on long-term outcomes after hepatic resection for hepatocellular carcinoma

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SUMMARY: The prognostic significance of preoperative platelet counts among patients with hepatocellular carcinoma (HCC) undergoing curative resection remains controversial. The objective of the current study was to investigate the impact of preoperative platelet count on long-term outcomes after HCC resection. Patients who underwent curative-intent resection for HCC between 2000 and 2021 at 10 hepatobiliary centers in China were retrospectively analyzed. Patients were categorized based on platelet count within 2 weeks before surgery: thrombocytopenia (< 100×10^9/L), normal platelet count (100-299 × 10^9/L), and thrombocytosis (≥ 300×10^9/L). The primary outcomes were overall survival (OS) and recurrence-free survival (RFS). Among 3,116 patients, 655 (21.0%) had thrombocytopenia, 2,374 (76.2%) had normal platelet counts, and 87 (2.8%) had thrombocytosis. The 5-year OS was 52.7%, 56.0%, and 40.2% for thrombocytopenia, normal platelet count, and thrombocytosis groups, respectively ($p < 0.001$ among the three groups); the corresponding 5-year RFS was 39.3%, 39.3%, and 26.9%, respectively ($p = 0.001$ among the three groups). Multivariable analysis identified both thrombocytopenia (HR 1.215, 95% CI 1.045-1.413, $p = 0.011$) and thrombocytosis (HR 1.307, 95% CI 1.130-1.511, $p < 0.001$) as independent risk factors for worse OS, and thrombocytosis was independently associated with worse RFS (HR 1.523, 95% CI 1.196-1.939, $p = 0.001$). Both thrombocytopenia and thrombocytosis were associated with worse survival after HCC resection, with thrombocytosis also predicting higher risk of recurrence. Routine preoperative platelet count may serve as a valuable and practical prognostic marker for risk stratification among patients with HCC undergoing resection.

Keywords: hepatocellular carcinoma, hepatectomy, platelet, thrombocytosis, thrombocytopenia, recurrence

1. Introduction

Hepatocellular carcinoma (HCC) remains a significant global health burden, ranking as the sixth most common cancer and the third leading cause of cancer-related deaths worldwide (*1,2*). Despite recent advances in diagnostic and therapeutic strategies, the prognosis for HCC remains poor, with a 5-year survival rate of only 18% (*3,4*). Although curative resection is the primary treatment for patients with localized HCC, long-term outcomes remain unsatisfactory, with 5-year recurrence rates exceeding 50% (*5-11*). Identifying prognostic factors is crucial to improve patient selection, optimize perioperative management, and guide postoperative surveillance.

The complex interplay between HCC and the

hematologic system, particularly the role of platelets, has gained increasing attention in recent years (*12,13*). Platelets, traditionally recognized for their crucial role in hemostasis, are now understood to be active participants in tumor biology, influencing processes such as angiogenesis, immune modulation, and metastasis (*14-17*). Among patients with chronic liver disease, thrombocytopenia is common due to portal hypertension, hypersplenism, and decreased thrombopoietin production (*17-20*). In contrast, thrombocytosis can occur in various malignancies, including HCC, as a paraneoplastic phenomenon (*21,22*).

The prognostic significance of platelet count among patients with HCC undergoing curative resection remains controversial. Several studies have reported associations between thrombocytopenia and poor outcomes related to HCC, while the impact of thrombocytosis on HCC prognosis has been less extensively studied (*23-26*). These conflicting results may be attributed to differences in study populations, sample sizes, and definitions of thrombocytopenia and thrombocytosis. A meta-analysis of 15 studies noted that thrombocytopenia was associated with worse overall and disease-free survival among patients with HCC undergoing various treatments (*27*). The mechanisms underlying this association may include impaired liver regeneration, compromised immune function, and increased perioperative complications (*28*). Some reports have suggested that thrombocytosis may be an adverse prognostic factor relative to HCC (*29-32*), while other studies have failed to demonstrate a significant impact on long-term survival (*33,34*). These conflicting results may be attributed to differences in study populations, sample sizes, and definitions of thrombocytopenia and thrombocytosis.

To reconcile these conflicting findings and address existing knowledge gaps, this study aims to systematically investigate the impact of preoperative platelet levels on long-term outcomes following curative resection of HCC. It was hypothesized that both thrombocytopenia and thrombocytosis would be associated with worse survival and a higher incidence of recurrence. Considering the routine availability of platelet count as part of standard laboratory testing, our findings could have important clinical implications for preoperative risk stratification, perioperative management, and tailoring postoperative surveillance strategies in HCC patients undergoing curative resection.

2. Patients and Methods

2.1. Study design and patient population

This retrospective, multicentre cohort study included patients who underwent curative resection for initially diagnosed HCC between January 2000 and December 2021 at 10 hepatobiliary centres in China. The study protocol was approved by the institutional review board of each participating center, and the requirement for informed consent was waived due to the retrospective nature of the study. Inclusion criteria were: *i*) age ≥ 18 years; *ii*) histologically confirmed HCC; *iii*) curative resection with clear surgical margins (R0 resection); and *iv*) available preoperative platelet count data. Exclusion criteria were: *i*) extrahepatic metastasis; *ii*) prior local or systemic HCC treatment; *iii*) history of other malignancies; *iv*) incomplete clinical data or follow-up information; and *v*) perioperative mortality (death within 30 days after surgery).

2.2. Data collection and definitions

Demographic, clinical, laboratory, and pathological data were collected from electronic medical records. Preoperative platelet count was defined as the last value obtained within 2 weeks before surgery. As such, patients were categorized into three groups based on platelet count: thrombocytopenia, normal platelet count, and thrombocytosis. In China, almost all of hospitals routinely classify platelet counts < 100×10^9/L as thrombocytopenia and ≥ 300×10^9/L as thrombocytosis, reflecting local laboratory reference ranges and prior studies in Chinese HCC cohorts (*20,29,35,36*). Liver function was assessed using the Child-Pugh classification. Tumor characteristics, including size, number, differentiation, and macrovascular and microvascular invasion were determined by pathological examination. Cirrhosis was diagnosed based on histological findings or unequivocal clinical and radiological evidence.

2.3. Surgical procedures

All patients underwent curative resection with the goal of complete tumor removal and preservation of adequate future liver remnant. The choice of surgical approach (open or laparoscopic) and extent of resection (anatomical or non-anatomical) was at the discretion of the treating surgeon. Intraoperative ultrasound was routinely used to guide resection. Major hepatectomy was defined as resection of three or more Couinaud segments (*37*). Perioperative management, including the use of blood products, was performed according to each center's standard protocols.

2.4. Follow-up and outcome measures

Postoperative follow-up included physical examination, liver function tests, serum alpha-fetoprotein (AFP), and imaging studies (contrast-enhanced CT or MRI) every 3 months for the first 2 years, and then every 6 months thereafter. Recurrence was diagnosed based on typical imaging findings or histological confirmation when indicated. Treatment for recurrence was determined by a multidisciplinary team, considering tumor characteristics,

liver function, and patient preferences.

The primary outcome measures were overall survival (OS) and recurrence-free survival (RFS). OS was defined as the interval between the date of surgery and the date of death from any cause or last follow-up. RFS was calculated from the date of surgery to the date of first recurrence or last follow-up for recurrence-free patients. Patients who died without documented recurrence were censored at the date of death for RFS analysis.

2.5. Statistical analysis

Continuous variables were expressed as median (interquartile range) and compared using the Kruskal-Wallis test. Categorical variables were presented as numbers (percentages) and compared using the chi-square test or Fisher's exact test as appropriate. Survival curves were generated using the Kaplan-Meier method and compared using the log-rank test. Univariable and multivariable Cox proportional hazards models were used to identify factors associated with OS and RFS. Variables with $p < 0.1$ in univariable analysis were included in the multivariable model. Additionally, preoperative platelet count categories (thrombocytopenia and thrombocytosis) were included in all multivariable models regardless of univariable *P* values as they were the primary exposure variables of interest in our study hypothesis, following standard epidemiological practice for analysing pre-specified predictors. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated. All statistical analyses were performed using R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS version 25.0 (IBM Corp., Armonk, NY, USA). A two-sided $p < 0.05$ was considered statistically significant.

3. Results

3.1. Patient characteristics

A total of 3,116 patients were included in the final analysis (Figure 1). None of the included patients had undergone prior splenectomy, received aspirin or other antiplatelet therapy, or had platelet transfusion within two weeks before surgery. Median age was 52 years (IQR 44-60), and 2,728 (87.5%) were male. Hepatitis B virus (HBV) infection was the predominant etiology, which was present in 2,648 (85.0%) patients. Cirrhosis was diagnosed in 2,264 (72.7%) patients. Based on preoperative platelet count, there were 655 (21.0%) patients with thrombocytopenia, 2,374 (76.2%) with normal platelet count, and 87 (2.8%) with thrombocytosis.

The baseline characteristics of the three groups are summarized in Table 1. Patients with thrombocytopenia were more likely to have cirrhosis (92.4% *vs.* 68.1% *vs.* 49.4%, $p < 0.001$), worse liver function (Child-Pugh class B: 16.6% *vs.* 6.1% *vs.* 10.3%, $p < 0.001$), smaller tumors (≤ 5.0 cm: 66.1% *vs.* 47.0% *vs.* 21.4%, $p < 0.001$), and multiple tumors (54.0% *vs.* 44.0% *vs.* 36.8%, $p < 0.001$). In contrast, patients with thrombocytosis had larger tumors (> 5.0 cm: 78.6% *vs.* 53.0% *vs.* 33.9%, $p < 0.001$), incomplete tumor encapsulation (70.1% *vs.* 59.7% *vs.* 54.7%, $p = 0.007$), and were more likely to undergo intraoperative blood transfusion (32.2% *vs.* 15.2% *vs.* 19.4%, $p < 0.001$) and major hepatectomy (47.1% *vs.* 22.6% *vs.* 11.5%, $p < 0.001$).

3.2. Long-term outcomes

The median follow-up time was 50.3 months (IQR 22.0-

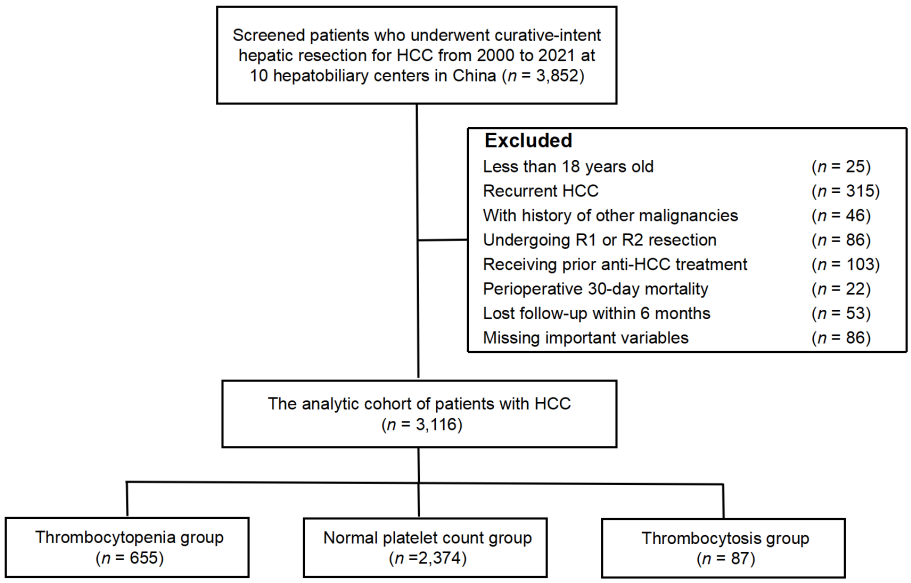

Figure 1. Flow diagram of patient selection. HCC, hepatocellular carcinoma.

65.0). During the study period, 1,565 (50.2%) patients died, and 1,895 (60.8%) experienced recurrence (Table 2). Analysis of mortality causes revealed differences between groups. In the thrombocytopenia group, a higher proportion of non-cancer deaths was observed (11.3%) compared to the normal platelet count (5.7%) and thrombocytosis groups (6.9%), with liver failure and upper gastrointestinal bleeding being the predominant non-cancer causes. The 1-, 3-, and 5-year OS for the entire cohort was 85.0%, 66.1%, and 54.9%, respectively. Kaplan-Meier analysis demonstrated differences in OS among the three platelet count groups (Figure 2). Meanwhile, 5-year OS was 52.7%, 56.0%, and 40.2% among patients with thrombocytopenia, normal platelet count, and thrombocytosis, respectively ($p < 0.001$).

The 1-, 3-, and 5-year RFS for the entire cohort was 66.1%, 47.9%, and 39.0%, respectively. Of note, RFS differed among the three groups, with 5-year recurrence-free being 39.3%, 39.3%, and 26.9% for the thrombocytopenia, normal platelet count, and

Table 1. Baseline characteristics of patients according to preoperative platelet count

n (%)	Normal platelet count group (*n* = 2,374)	Thrombocytopenia group (*n* = 655)	Thrombocytosis group (*n* = 87)	*p* among three groups
Male sex	2,086 (87.9)	567 (86.6)	75 (86.2)	0.622
Age > 65 years	352 (14.8)	76 (11.6)	13 (14.9)	0.109
Diabetes mellitus	175 (7.4)	68 (10.4)	6 (6.9)	0.039
HBV (+)	1,975 (83.2)	604 (92.2)	69 (79.3)	< 0.001
HCV (+)	59 (2.5)	23 (3.5)	0 (0)	0.104
ASA score > 2	336 (14.2)	83 (12.7)	18 (20.7)	0.121
Cirrhosis	1,616 (68.1)	605 (92.4)	43 (49.4)	< 0.001
Child–Pugh grade B	144 (6.1)	109 (16.6)	9 (10.3)	< 0.001
Preoperative AFP > 400 μg/L	536 (33.7)	162 (36.9)	19 (33.9)	0.459
Largest tumor size > 5.0 cm	842 (53.0)	149 (33.9)	44 (78.6)	< 0.001
Multiple tumors	1,044 (44.0)	354 (54.0)	32 (36.8)	< 0.001
Macrovascular invasion	245 (10.3)	63 (9.6)	10 (11.5)	0.803
Microvascular invasion	1,024 (43.1)	281 (42.9)	37 (42.5)	0.989
Incomplete tumor encapsulation	1,418 (59.7)	358 (54.7)	61 (70.1)	0.007
Satellite nodules	459 (19.3)	116 (17.7)	20 (23.0)	0.416
Poor differentiation	1,378 (86.7)	354 (80.6)	48 (85.7)	0.007
Laparoscopic approach	505 (21.3)	165 (25.2)	16 (18.4)	0.213
Intraoperative blood loss > 400 mL	634 (26.7)	259 (39.5)	33 (37.9)	< 0.001
Intraoperative blood transfusion	361 (15.2)	127 (19.4)	28 (32.2)	< 0.001
Major hepatectomy	536 (22.6)	75 (11.5)	41 (47.1)	< 0.001
Non-anatomical resection	1,830 (77.1)	549 (83.8)	54 (62.1)	< 0.001
Narrow resection margin (< 1 cm)	1,354 (57.0)	330 (50.4)	64 (73.6)	< 0.001

AFP, α-fetoprotein; ASA, American Society of Anesthesiologists; HBV, hepatitis B virus; HCV, hepatitis C virus.

Table 2. Long-term outcomes of patients according to preoperative platelet count

n (%)	Normal platelet count group (Group I, *n* = 2,374)	Thrombocytopenia group (Group II, *n* = 655)	Thrombocytosis group (Group III, *n* = 87)	*p* (II *vs.* I)	*p* (III *vs.* I)	*p* among three groups
Duration of follow-up*	50.0 ± 33.0	50.1 ± 32.1	40.8 ± 34.1	0.917	< 0.001	< 0.001
Death	1,153 (48.6)	350 (53.4)	62 (71.3)	0.027	< 0.001	< 0.001
Cancer-related	1,017 (42.8)	276 (42.1)	56 (64.4)	0.740	< 0.001	< 0.001
Non-cancer-related	136 (5.7)	74 (11.3)	6 (6.9)	< 0.001	0.624	< 0.001
Liver failure	65 (2.7)	38 (5.8)	3 (3.4)	< 0.001	0.705	< 0.001
Upper gastrointestinal bleeding	42 (1.8)	29 (4.4)	1 (1.1)	< 0.001	0.635	< 0.001
Other causes	29 (1.2)	7 (1.1)	2 (2.3)	0.792	0.335	0.568
Recurrence	1,444 (60.8)	387 (59.1)	64 (73.6)	0.734	0.010	0.034
Median OS, months**	77.9 (71.4, 84.5)	68.2 (58.6, 77.9)	34.6 (18.9, 50.4)	0.131	< 0.001	< 0.001
1 year, %	84.9	86.4	78.2			
3 years, %	66.6	76.5	48.2			
5 years, %	56.0	52.7	40.2			
8 years, %	43.6	39.7	24.8			
Median RFS, months**	32.5 (28.9, 36.2)	33.3 (25.8, 40.7)	15.0 (2.0, 28.0)	0.901	0.002	0.007
1 year, %	65.7	69.3	52.9			
3 years, %	48.2	48.5	35.5			
5 years, %	39.3	39.3	26.9			
8 years, %	27.4	21.8	15.6			

*Values are mean ± standard; **Values in parentheses are 95% confidence intervals. OS, overall survival; RFS, recurrence-free survival.

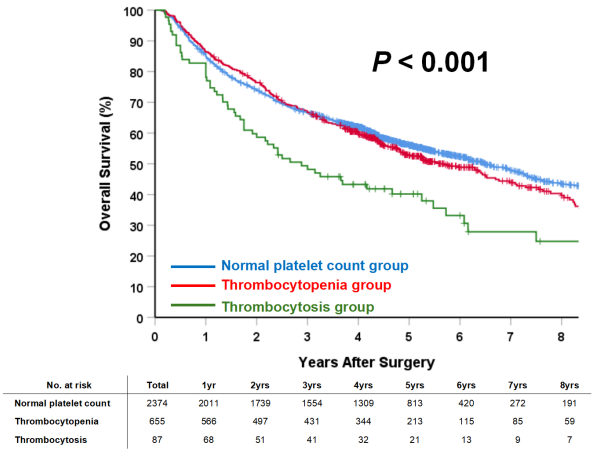

Figure 2. Kaplan-Meier curves of overall survival according to preoperative platelet count. $p = 0.131$ (thrombocytopenia *vs.* normal platelet count), $p < 0.001$ (thrombocytosis *vs.* normal platelet count), and $p < 0.001$ (thrombocytopenia *vs.* thrombocytosis).

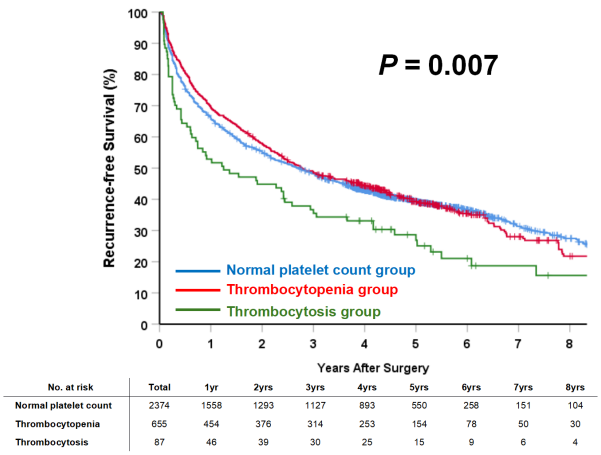

Figure 3. Kaplan-Meier curves of recurrence-free survival according to preoperative platelet count. $p = 0.901$ (thrombocytopenia *vs.* normal platelet count), $p = 0.002$ (thrombocytosis *vs.* normal platelet count), and $p = 0.003$ (thrombocytopenia *vs.* thrombocytosis).

Table 3. Univariable and multivariable Cox-regression analysis for overall survival

	Univariable analysis		Multivariable analysis	
	Hazard ratio (95% CI)	*p*	Hazard ratio (95% CI)	*p*
Sex (male *vs.* female)	1.068 (0.920-1.239)	0.387		
Age (> 65 *vs.* ≤ 65 years)	1.001 (0.869-1.152)	0.993		
Diabetes mellitus (yes *vs.* no)	0.965 (0.800-1.163)	0.709		
HBV (positive *vs.* negative)	1.083 (0.939-1.249)	0.275		
HCV (positive *vs.* negative)	1.240 (0.930-1.652)	0.143		
ASA score (> 2 *vs.* ≤ 2)	1.125 (0.979-1.292)	0.096	NA	0.976
Cirrhosis (yes *vs.* no)	1.346 (1.198-1.513)	< 0.001	1.238 (1.074-1.427)	0.003
Child-Pugh grade (B *vs.* A)	1.869 (1.605-2.177)	< 0.001	1.231 (1.013-1.496)	0.036
Preoperative platelet count				
Normal platelet count	Reference		Reference	
Thrombocytopenia	1.097 (0.973-1.236)	0.130	1.215 (1.045-1.413)	0.011
Thrombocytosis	1.762 (1.365-2.276)	< 0.001	1.307 (1.130-1.511)	< 0.001
Preoperative AFP (> 400 *vs.* ≤ 400μg/L)	1.832 (1.623-2.067)	< 0.001	1.251 (1.101-1.420)	0.001
Largest tumor size (> 5 *vs.* ≤ 5 cm)	2.658 (2.347-3.010)	< 0.001	1.753 (1.527-2.013)	< 0.001
Multiple tumors (yes *vs.* no)	1.242 (1.120-1.377)	< 0.001	NA	0.263
Macrovascular invasion (yes *vs.* no)	5.259 (4.609-6.000)	< 0.001	2.832 (2.373-3.379)	< 0.001
Microvascular invasion (yes *vs.* no)	2.483 (2.245-2.747)	< 0.001	1.313 (1.145-1.505)	< 0.001
Incomplete encapsulation (yes *vs.* no)	2.434 (2.178-2.720)	< 0.001	1.641 (1.414-1.905)	< 0.001
Satellite nodules (yes *vs.* no)	2.889 (2.591-3.222)	< 0.001	1.757 (1.531-2.017)	< 0.001
Tumor differentiation (poor *vs.* well)	1.910 (1.574-2.317)	< 0.001	NA	0.351
Surgical approach (open *vs.* laparoscopic)	1.004 (0.907-1.111)	0.943		
Blood loss (> 400 *vs.* ≤ 400 mL)	1.991 (1.762-2.250)	< 0.001	NA	0.983
Blood transfusion (yes *vs.* no)	2.370 (2.110-2.662)	< 0.001	1.429 (1.223-1.670)	< 0.001
Extent of hepatectomy (major *vs.* minor)	2.153 (1.929-2.402)	< 0.001	NA	0.602
Anatomical resection (no *vs.* yes)	0.942 (0.837-1.059)	0.318		
Resection margin (narrow *vs.* wide)	2.492 (2.235-2.778)	< 0.001	1.906 (1.682-2.159)	< 0.001

AFP, α-fetoprotein; ASA, American Society of Anesthesiologists; HBV, hepatitis B virus; HCV, hepatitis C virus; CI, confidence interval; NA, not available.

thrombocytosis groups, respectively ($p = 0.007$) (Figure 3).

3.3 Univariable and multivariable analyses for OS and RFS

In univariable and multivariable Cox regression analysis, both thrombocytopenia (HR 1.215, 95% CI 1.045-1.413, $p = 0.011$) and thrombocytosis (HR 1.307, 95% CI 1.130-1.511, $p < 0.001$) were independent risk factors for poor OS, along with other established prognostic factors (Table 3). In univariable and multivariable analysis regarding RFS, thrombocytosis remained an independent predictor (HR 1.523, 95% CI 1.196-1.939, $p = 0.001$),

Table 4. Univariable and multivariable Cox-regression analysis for recurrence-free survival

	Univariable analysis		Multivariable analysis	
	Hazard ratio (95% CI)	*p*	Hazard ratio (95% CI)	*p*
Sex (male *vs.* female)	0.984 (0.860-1.125)	0.808		
Age (> 65 *vs.* ≤ 65 years)	0.926 (0.816-1.050)	0.230		
Diabetes mellitus (yes *vs.* no)	1.051 (0.897-1.232)	0.538		
HBV (positive *vs.* negative)	1.790 (0.994-1.398)	0.058	NA	0.972
HCV (positive *vs.* negative)	1.216 (0.944-1.565)	0.130		
ASA score (> 2 *vs.* ≤ 2)	1.083 (0.957-1.225)	0.206		
Cirrhosis (yes *vs.* no)	1.350 (1.218-1.495)	< 0.001	1.323 (1.174-1.491)	< 0.001
Child-Pugh grade (B *vs.* A)	1.736 (1.509-1.999)	< 0.001	1.475 (1.238-1.758)	< 0.001
Preoperative platelet count				
Normal platelet count	*Reference*		*Reference*	
Thrombocytopenia	0.993 (0.892-1.105)	0.901	0.941 (0.843-1.050)	0.278
Thrombocytosis	1.463 (1.149-1.862)	0.002	1.523 (1.196-1.939)	0.001
Preoperative AFP (> 400 *vs.* ≤ 400μg/L)	1.568 (1.407-1.748)	< 0.001	1.127 (1.004-1.265)	0.042
Largest tumor size (> 5 *vs.* ≤ 5 cm)	2.190 (1.967-2.438)	< 0.001	1.511 (1.343-1.699)	< 0.001
Multiple tumors (yes *vs.* no)	1.193 (1.091-1.304)	< 0.001	NA	0.495
Macrovascular invasion (yes *vs.* no)	4.746 (4.184-5.385)	< 0.001	3.078 (2.597-3.649)	< 0.001
Microvascular invasion (yes *vs.* no)	2.123 (1.944-2.318)	< 0.001	1.134 (1.007-1.278)	0.039
Incomplete encapsulation (yes *vs.* no)	2.161 (1.966-2.374)	< 0.001	1.497 (1.320-1.699)	< 0.001
Satellite nodules (yes *vs.* no)	2.611 (2.361-2.888)	< 0.001	1.748 (1.539-1.986)	< 0.001
Tumor differentiation (poor *vs.* well)	1.834 (1.557-2.159)	< 0.001	1.198 (1.009-1.421)	0.039
Surgical approach (open *vs.* laparoscopic)	1.027 (0.887-1.190)	0.722		
Blood loss (> 400 *vs.* ≤ 400 mL)	1.695 (1.518-1.894)	< 0.001	NA	0.932
Blood transfusion (yes *vs.* no)	2.005 (1.800-2.233)	< 0.001	1.341 (1.162-1.549)	< 0.001
Extent of hepatectomy (major *vs.* minor)	1.918 (1.735-2.120)	< 0.001	NA	0.258
Anatomical resection (no *vs.* yes)	0.993 (0.893-1.104)	0.900		
Resection margin (narrow *vs.* wide)	2.122 (1.934-2.329)	< 0.001	1.834 (1.644-2.047)	< 0.001

AFP, α-fetoprotein; ASA, American Society of Anesthesiologists; HBV, hepatitis B virus; HCV, hepatitis C virus; CI, confidence interval; NA, not available.

while thrombocytopenia did not (HR 0.941, 95% CI 0.843-1.050, $p = 0.278$) (Table 4).

4. Discussion

This multicenter study demonstrated that preoperative platelet count was an independent predictor of long-term outcomes after curative resection for HCC. The findings of the present study demonstrated that both thrombocytopenia ($< 100 \times 10^9$/L) and thrombocytosis ($\geq 300 \times 10^9$/L) were independent predictors of worse OS, a "double-edged sword" phenomenon not previously established in HCC literature. Furthermore, thrombocytosis was an independent risk factor for postoperative recurrence, a finding not previously reported in the context of HCC resection. These results underscore the complex interplay among platelets, liver function, and tumor biology in HCC. By establishing preoperative platelet count levels as a robust and clinically accessible prognostic marker, this work provides a framework for refining risk stratification protocols, informing personalized treatment algorithms, and potentially improving outcomes in HCC patients selected for curative-intent resection. The "sweet spot" of normal platelet count identified in this study opens new avenues for preoperative optimization and targeted interventions in the management of HCC.

The adverse impact of thrombocytopenia on postoperative outcomes among patients with HCC has been reported in several previous studies (*23-26*). The results of the current study confirmed and extended these observations in a larger cohort. The mechanisms underlying this association were likely multifactorial. First, thrombocytopenia often reflects the presence of portal hypertension and advanced liver fibrosis or cirrhosis, which are known risk factors for poor outcomes after HCC resection (*38*). Indeed, in the present cohort, patients with thrombocytopenia had a higher prevalence of cirrhosis and worse liver function. Platelets also play important roles in liver regeneration and repair (*39*). Thrombocytopenia may impair liver regeneration capacity, leading to increased postoperative liver dysfunction and complications. In addition, platelets are involved in various aspects of the immune response against cancer (*40*). Thrombocytopenia may compromise antitumor immunity and promote tumor progression.

The prognostic significance of thrombocytosis in HCC has not been well-established, with conflicting results in the literature (*13,29,31*). The present study provided strong evidence that thrombocytosis was an independent predictor of both decreased OS and RFS. This finding is consistent with reports related to other malignancies, in which elevated platelet counts had been associated with advanced disease and poor prognosis (*41*). The mechanisms by which thrombocytosis may promote HCC progression include: *i*) production of

growth factors and cytokines that stimulate tumor growth and angiogenesis (*42*); *ii*) formation of platelet-tumor cell aggregates that facilitate metastasis (*43*); and *iii*) induction of epithelial-mesenchymal transition in tumor cells (*44*). In the present study, patients with thrombocytosis had larger tumors and were more likely to undergo major hepatectomy, suggesting a more advanced disease stage.

The discrepancy in our findings - where thrombocytopenia independently predicted worse OS but not RFS - provides important insights into the mechanisms through which low platelet counts affect outcomes. To further investigate this pattern, we performed additional analyses of mortality causes and conducted competing risk modeling. These analyses revealed that patients with thrombocytopenia had a higher proportion of non-cancer deaths (11.3%) compared to those with normal platelet counts (5.7%) or thrombocytosis (6.9%), with liver failure and upper gastrointestinal bleeding being the predominant non-cancer causes. When accounting for the competing risk of non-cancer mortality in our statistical models, thrombocytopenia was not significantly associated with cancer-specific mortality (subhazard ratio 1.108, 95% CI 0.952-1.289, $p = 0.186$), while thrombocytosis remained a significant predictor (subhazard ratio 1.401, 95% CI 1.172-1.674, $p < 0.001$). These findings suggest that thrombocytopenia primarily affects OS through liver-related complications rather than through direct effects on tumor biology. In contrast, thrombocytosis appears to have a more direct relationship with cancer progression, reflected in its significance across all outcome measures.

A notable methodological consideration in our study is the discrepancy between unadjusted Kaplan-Meier curves and multivariable analysis results for thrombocytopenia. While unadjusted survival curves showed similar patterns between thrombocytopenia and normal platelet count groups, multivariable analysis revealed thrombocytopenia as an independent risk factor after controlling for confounding variables (HR 1.215, $p = 0.011$). This highlights the importance of statistical adjustment when analyzing groups with substantial differences in baseline characteristics, as was the case in our cohort where patients with thrombocytopenia had significantly higher rates of cirrhosis (92.4% *vs.* 68.1%), worse liver function (Child-Pugh B: 16.6% *vs.* 6.1%), and smaller tumors (≤5 cm: 66.1% *vs.* 47.0%) compared to those with normal platelet counts. These confounding variables, if not properly adjusted for, can mask the true independent effect of thrombocytopenia on survival outcomes.

Interestingly, while both thrombocytopenia and thrombocytosis were associated with worse OS, only thrombocytosis independently predicted RFS. This discrepancy is further explained by our analysis of mortality causes, which revealed a higher proportion of non-cancer deaths in the thrombocytopenia group (11.3%) compared to other groups (5.7% and 6.9%). The mechanisms underlying this association likely reflect the role of thrombocytopenia as a marker of advanced liver dysfunction and portal hypertension, leading to increased risk of liver failure and variceal bleeding.

The findings of the current study have several important clinical implications. First, preoperative platelet count should be considered in the risk assessment of HCC patients being evaluated for curative resection. Patients with either thrombocytopenia or thrombocytosis may require more intensive preoperative optimization and closer postoperative surveillance. Second, the underlying causes of abnormal platelet counts should be thoroughly investigated and addressed when possible. For patients with thrombocytopenia due to hypersplenism, splenectomy or splenic artery embolization might be considered to improve platelet counts and potential outcomes (*45,46*). In cases of thrombocytosis, ruling out chronic inflammation or occult infection is crucial.

These results also raise the question of whether modulating platelet counts may improve outcomes in HCC patients. For patients with thrombocytopenia, platelet transfusion or thrombopoietin receptor agonists may be beneficial (*47*). However, the optimal timing and target platelet count for such interventions remain to be determined. Among patients with thrombocytosis, antiplatelet therapy could potentially mitigate the negative impact on prognosis. Preclinical studies have demonstrated promising results with aspirin and other antiplatelet agents in HCC models (*48*), but clinical evidence is still limited (*49,50*).

Several limitations of the present study should be considered. First, the retrospective nature of the study introduces the potential for selection bias and unmeasured confounding. Second, a single preoperative platelet count measurement was used, which may not fully capture the dynamic changes in platelet levels over time. Platelet counts can fluctuate daily in individual patients due to various physiological and pathological factors, adding uncertainty to the captured readings. This study did not account for post-operative platelet counts, which may differ significantly after hepatectomy due to increased liver stiffness, elevated portal pressure, and other surgical sequelae. Prospective studies incorporating serial platelet measurements throughout the perioperative period are warranted to elucidate the temporal dynamics of platelet fluctuations and their impact on longitudinal outcomes. Third, despite efforts to adjust for known prognostic factors, residual confounding cannot be completely ruled out. Fourth, the platelet count cutoffs in this study were tailored to regional clinical standards (100-300×10⁹/L), which differ from international reference ranges (150-450×10⁹/L). While this enhances the relevance of our findings to Chinese clinical practice, it may limit direct comparisons with studies from other regions. Fifth, we acknowledge that platelets interact with various components of the immune system, which may

influence HCC outcomes. However, our retrospective design spanning two decades and multiple centers precluded comprehensive immune cell profiling. Future studies should explore the relationship between platelet counts, immune cell populations (including neutrophils, lymphocytes, and regulatory T cells), and inflammatory markers to develop more integrated prognostic models. While we recognize the limitations of using a single biomarker for prognostic assessment, we believe identifying readily available, low-cost parameters with strong prognostic value has significant clinical utility, especially in resource-limited settings. Finally, the cohort consisted predominantly of HBV-related HCC patients from China, potentially limiting the generalizability of the findings to other populations.

In conclusion, this large multicentre study demonstrated that preoperative platelet count was an independent predictor of long-term outcomes after curative resection for HCC. Both thrombocytopenia and thrombocytosis were associated with worse OS, while thrombocytosis additionally predicts higher recurrence risk. These findings highlight the potential of platelet count as a simple yet valuable prognostic marker for risk stratification in HCC patients undergoing resection. Future studies should focus on validating these results in diverse populations and exploring potential therapeutic strategies targeting platelet-related pathways in HCC.

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