Original Article

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Abnormal platelet count correlates with poor survival in hepatocellular carcinoma

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Abstract

Background: Normal platelet (PLT) plays a vital role in thrombosis, the inflammatory response, and liver regeneration. The effect of abnormal PLT counts has been seldom explored in hepatocellular carcinoma (HCC); hence, this investigation was conducted to evaluate the prognostic importance of preoperative abnormal PLT count in HCC patients after liver resection retrospectively.

Methodology: The PLT counts were determined using Sysmex XT-1800i automated hematology analyzer and its matching reagents. Patients were divided into two groups: a normal PLT group and an abnormal PLT group. Chi-square test, Kaplan–Meier method, and Cox univariable and multivariable regressions were utilized to analyze the data.

Results: A total of 391 HCC patients who underwent liver resection were included in this study. The overall survival (OS) rates were 59% and 31%, and the median survival time was 69 months and 31 months in the normal and abnormal PLT groups, respectively. The PLT level was associated with OS in univariate and multivariate analyses (hazard ratio [HR], 1.991 [95% confidence interval {CI}, 1.412–2.808] and HR, 2.217 [95% CI, 1.556–3.159], respectively).

Conclusions: Patients with normal PLT had a better outcome in terms of OS. The results suggested that abnormal PLT count is an independent prognostic factor for HCC patients after liver resection.

Keywords: hepatocellular carcinoma, platelet, prognosis

1 Introduction

Liver cancer is the sixth most prevalent cancer and third most common global cause of cancer-related deaths [1]. Hepatocellular carcinoma (HCC) constitutes >80% of primary liver cancers and is a major public health problem [2]. In Asia, approximately 80% of HCC cases, which are most commonly derived from chronic hepatitis B virus (HBV) infection, develop in the presence of liver cirrhosis [3]. In recent years, the incidence of HCC in Asia–Pacific regions has had a significant increase [4]. Despite improvements in the screening and treatment options for HCC, most of the patients are not treated early but at advanced stages of disease [5]. Currently, liver resection still remains the first-line treatment for HCC. Unfortunately, the prognosis of HCC

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patients remains unsatisfactory and the 5-year survival rate is just about 5%-6% after tumor resection [6,7]. However, with the advancement of perioperative management and surgical techniques in HCC patients over the past few years, the operative mortality after liver resection has improved substantially and is already <5% in high-volume centers [8]. Although the prognosis of cancers has been proven to be associated with the sizes of tumors and their tumor/node/metastasis (TNM) stages, platelet (PLT) level also seems to be a vital prognostic factor in HCC [9-11].

We all know that PLT, by releasing several inflammatory mediators such as serotonin, transforming growth factor (TGF)- β , and PLT-derived growth factor (PDGF), plays a crucial role in thrombosis, the inflammatory response, liver regeneration [12,13], and the regulation of angiogenesis [14,15]. Consequently, the functions of PLT will be affected if its quantities or functions are abnormal and some pathological changes will also take place thereafter. To date, abnormal PLT count has attracted increasing attention as an independent prognostic factor for some cancers. It has been reported that patients with high PLT counts have a worse prognosis in lung cancer [9], renal cell carcinoma [10], gastric cancer [11], and so on. Previous studies have also revealed that HCC patients with low PLT count undergo a high risk of hepatic insufficiency and liver failure [16,17]. The effects of abnormal PLT values have been seldom explored for HCC; hence, this investigation was conducted to evaluate whether preoperative abnormal PLT values are associated with poor prognosis of HCC patients after liver resection retrospectively.

2 Materials and methods

2.1 Patients

Accordingly, 391 patients were enrolled in this retrospective study between 2004 and 2012, and all of them were pathologically diagnosed as PHCC (primary HCC) and underwent surgery for resection of primary tumor in a single center (Department of Hepatobiliary Surgery, Fuzong Clinical College, Fujian Medical University, Fujian, China). The patients included did not suffer from any hematological or autoimmune diseases. The medical records containing patient age, gender, histologic grade, tumor size, tumor location, TNM stage, PLT levels, survival rate, and preoperative serum alpha fetoprotein (AFP) levels were obtained from the database of the Department of Hepatobiliary Surgery, Fuzhou General Hospital.

2.2 Follow-up

All patients were followed regularly after the day of surgical resection. Follow-up data were collected until May 2015 or until patient death from medical records, telephone interviews, and the Index system of Social Security Death. Overall survival (OS) was defined as the interval between liver resection and date of death or the last time of follow-up.

2.3 Methods

Approximately 2 mL plasma was obtained from each patient included in our study, and all the plasma samples comprised venous blood obtained on empty stomach early in the morning. The samples were collected in anticoagulant tubes of EDTA-K2, and the PLT counts were obtained in 2 hours. The results were all obtained using a Sysmex XT-1800i automated hematology analyzer and its matching reagents (Kobe, Japan). The normal reference value of PLT is $(100-300) \times 10^9/L$, and the abnormal value of PLT is $>300 \times 10^9/L$ (high PLT group) or $<100 \times 10^9/L$ (low PLT group). Patients were divided into two groups: a normal PLT group and an abnormal PLT group (including low PLT group and high PLT group).

2.4 Statistical analysis

All statistical analyses were performed with using SPSS 17.0 statistical software (SPSS, Chicago, IL, USA), and P -values < 0.05 were defined as statistically significant. The association between PLT values and the baseline characteristics of included patients on the one hand and survival on the other was assessed by using the chi-square test (χ^2 -test). The relationships of each baseline characteristics and PLT counts and with the 5-year overall median survival time (MST, in months) were evaluated using Kaplan–Meier survival analysis and the log-rank test. Associations between PLT counts and each baseline characteristics with the risk of death were assessed using univariate and multivariate Cox proportional-hazards regression model analyses.

2.5 Assessment

In this study, TNM staging and the histological grade staging were conducted based on the standards of TNM Classification of Malignant Tumors and the World Health Organization Classification of Tumors, respectively. Each pathologic characteristic was assessed by two doctors of pathology. They resolved their differences through discussion or by consultation with a third doctor to determine whether the outcomes were right.

3 Results

3.1 Patient characteristics

The baseline characteristics of the 391 patients who underwent liver resection for HCC in a single institution are summarized in Table 1. No significant differences were observed in age, gender, histological grade, tumor size, tumor location, TNM stage, PLT level, survival, and serum AFP level of HCC patients.

3.2 Association between PLT count and characteristics of patients

In our cohort, 391 patients were included. The assessment process of PLT was successful, and 329 (84.1%) patients had normal PLT counts, whereas 62 (15.9%) patients showed an abnormal PLT count (28 included in high PLT group and 34 in low PLT group). Baseline characteristics (including age, gender, histological grade, serum AFP level, tumor location, TNM stage, survival, and tumor size) of the patients are presented in Table 2.

All 391 patients with HCC were divided into two groups: a normal PLT group ($n = 329$) and an abnormal PLT group ($n = 62$). We used the chi-square test to compare the differences between the two groups. The results demonstrated that PLT level had no relationship to age, gender, histological grade, serum AFP level, tumor location, or tumor size but was associated with TNM stage and survival (Table 2).

3.3 Association between PLT levels and HCC in patients after liver resection

In our study, 391 patients underwent liver resection. Kaplan–Meier curves were used to analyze the association between OS and PLT. The OS rates were 59% (195/329), 18% (5/28), and 41% (14/34) in the groups with normal PLT, high PLT, and low PLT levels, respectively. The MST for patients in the normal PLT group was 69 months. Nevertheless, the MST was 20 months and 47 months for the groups with high PLT and low PLT levels, respectively. The survival of the 329 patients with normal PLT level was significantly better than that of the 28 patients with high PLT and 34 patients with low PLT levels (69 vs. 20 months and 69 vs. 47 months; $P < 0.001$), as depicted in Figure 1. Considering that the number of cases is limited for both the high PLT group and the low

Tab. 1: Baseline characteristics of patients

Characteristics	Cases (n=391)	
	n	%
Age, years		
≤55	108	27.6
>55	283	72.4
Gender		
Male	345	88.2
Female	46	11.8
Histological grade		
Well/moderately differentiated	373	95.4
Poorly differentiated	18	4.6
Tumor size, cm		
≤5 cm	235	60.1
>5 cm	156	39.9
Tumor location		
Left	103	26.3
Right	288	73.7
TNM stage		
I/II	319	81.6
III	72	18.4
PLT level		
Normal	329	84.1
Abnormal	62	15.9
Survival		
Alive	214	54.7
Dead	177	45.3
Serum AFP level, mg/L		
≤400	242	61.9
>400	149	38.1

PLT group, compared with the normal PLT group, we combined these two groups into an abnormal PLT group. Thus, the OS rates were 59% (195/329) and 31% (19/62) in the normal and abnormal PLT groups, respectively. The MST for patients in the normal PLT group was 69 months. In contrast, for the abnormal PLT group, the MST was 31 months. The survival of the 329 patients with normal PLT level was significantly better than that of the 62 patients with abnormal PLT levels (69 vs. 31 months; $P<0.001$), as shown in Figure 2.

We used the Cox univariate model to evaluate the association between OS and all baseline characteristics. It was found that histological grade, serum AFP level, TNM stage, tumor size, and PLT level could be significant indicators for the OS rate. The value of HR for histological grade was 0.491 (95% CI, 0.266–0.907; $P<0.05$), the HR for serum AFP level was 1.887 (95% CI, 1.402–2.540; $P<0.001$), the HR for TNM stage was 3.147 (95% CI, 2.286–4.332; $P<0.001$), the HR for tumor size was 3.120 (95% CI, 2.308–2.417; $P<0.001$), and the HR for PLT was 1.991 (95% CI, 1.412–2.808; $P<0.001$). On Cox multivariate analysis of the OS, serum AFP level, TNM stage, tumor size, and PLT level were independent prognostic factors. The HR for serum AFP level was 1.675 (95% CI, 1.221–2.299; $P<0.001$), the HR for TNM stage was 1.617 (95% CI, 1.105–2.367; $P<0.05$), the HR for tumor size was 2.460 (95% CI, 1.731–3.496; $P<0.001$), and the HR for PLT level was 2.217 (95% CI, 1.556–3.159; $P<0.001$; Table 3).

4 Discussion

In our study, the PLT counts of 391 HCC patients were examined using Sysmex XT-1800i automated hematology analyzer. All the patients were divided into two groups: normal PLT group and abnormal PLT group (including high PLT group and low PLT group). Statistical analysis showed that PLT level was associated with

Tab. 2: Association between PLT level and characteristics of patients (n=391)

Characteristics	PLT level		P-value
	Normal (%)	Abnormal (%)	
Age, years			
≤55	90 (27.4)	18 (29.0)	0.787
>55	239 (72.6)	44 (71.0)	
Gender			
Male	287 (87.2)	58 (93.5)	0.157
Female	42 (12.8)	4 (6.5)	
Histological grade			
Well/moderately differentiated	316 (96.0)	57 (91.9)	0.156
Poorly differentiated	13 (4.0)	5 (8.1)	
Serum AFP level, µg/L			
≤400	200 (60.8)	42 (67.7)	0.301
>400	129 (39.2)	20 (32.3)	
Tumor location			
Left	86 (26.1)	17 (27.4)	0.834
Right	243 (73.9)	45 (72.6)	
TNM stage			
I/II	274 (83.3)	45 (72.6)	0.046
III	55 (16.7)	17 (27.4)	
Survival			
Dead	134 (40.7)	43 (69.4)	0.000
Alive	195 (59.3)	19 (30.6)	
Tumor size, cm			
≤5 cm	199 (60.5)	36 (58.1)	0.721
>5 cm	130 (39.5)	26 (41.9)	

Note: Bold values are significant at $P < 0.05$.

TNM stage and survival, and patients with TNM stage III or short survival often had tumors with abnormal PLT level. Moreover, patients with abnormal PLT levels had a significantly poorer prognosis than those with normal PLT levels ($P < 0.001$). Therefore, PLT has been proven to be an independent prognostic factor for HCC patients who underwent liver resection (HR, 2.217; 95%CI, 1.556–3.159). Our study also confirmed that serum AFP level, TNM stage, and tumor size were associated with the OS of patients with liver resection in univariate and multivariate analyses, which was consistent with the results in previous literatures [18,19].

Kim *et al.* [20] found that patients with non-small cell lung cancer with preoperative thrombocytosis suffered an increased risk of death and disease recurrence and had a worse prognosis. Hu *et al.* [21] also reported that thrombocytosis was a negative prognostic factor for gastric cancer patients and it was meaningful for PLT to be a cancer recurrence monitor. Similar results of thrombocytosis were presented in ovarian cancer [22], glioblastoma [23], and so forth. As for patients with thrombocytopenia, the prognostic value of low PLT levels has still not been reported in solid tumors. In our study, however, low PLT level was considered an unfavorable prognostic indicator.

Our study revealed that the MST of the normal PLT group is 69 months and the MST of abnormal PLT group is 31 months. Therefore, PLT was associated with OS and can be considered an independent prognostic factor for HCC patients after liver resection. Moreover, PLT counts can be examined easily, the results can be obtained quickly, and the examination is extremely inexpensive. Therefore, as an independent prognostic factor, the advantages of PLT are very obvious when compared to serum AFP level, TNM stage, and tumor size.

The OS of HCC patients has been linked to PLT counts [24–26], which is an independent predictor of hepatocarcinogenesis as well [27–29], although the mechanism underlying the poor prognosis of abnormal PLT is not yet completely understood. In 1872, Reiss *et al.* [30] initially reported the relationship between high PLT counts and malignant tumors. To date, thrombocytosis has been believed to be present in approximately 10%–57% of patients with different solid tumors [31].

Fig. 1: Kaplan–Meier curves for the overall survival of 391 patients after liver resection (groups with normal PLT vs. low PLT vs. high PLT levels). MST = median survival time; PLT = platelet.

Fig. 2: Kaplan–Meier curves for the overall survival of 391 patients after liver resection (normal PLT group vs. abnormal PLT group). MST = median survival time; PLT = platelet.

Tab. 3: Univariate and multivariate Cox regression analysis of overall survival

Characteristics	Univariate analysis	P-value	Multivariate analysis	P-value
	HR (95% CI)		HR (95% CI)	
Age, years				
≤55	1.00	0.667	1.00	0.879
>55	0.931 (0.671–1.291)		0.974 (0.697–1.362)	
Gender				
Male	1.00	0.121	1.00	0.285
Female	0.658 (0.388–1.117)		0.747 (0.438–1.275)	
Histological grade				
Well/moderately differentiated	1.00	0.023	1.00	0.128
Poorly differentiated	0.491 (0.266–0.907)		0.616 (0.331–1.149)	
Tumor location				
Left	1.00	0.618	1.00	0.486
Right	0.917 (0.653–1.289)		0.885 (0.629–1.247)	
Serum AFP level, mg/L				
≤400	1.00	0.000	1.00	0.001
>400	1.887 (1.402–2.540)		1.675 (1.221–2.299)	
TNM				
I/II	1.00	0.000	1.00	0.013
III	3.147 (2.286–4.332)		1.617 (1.105–2.367)	
Tumor size, cm				
≤5 cm	1.00	0.000	1.00	0.000
>5 cm	3.120 (2.308–2.417)		2.460 (1.731–3.496)	
PLT level				
Normal	1.00	0.000	1.00	0.000
Abnormal	1.991 (1.412–2.808)		2.217 (1.556–3.159)	

Note: Bold values are significant at $P < 0.05$.

However, the associations between thrombocytosis and poor prognosis of some cancers are still unclear. Nevertheless, several mechanisms for the associations between them have been reported, as follows: (1) some humoral factors related to tumors, such as interleukin-1, interleukin-6, and granulocyte colony-stimulating factor, may play a vital role in speeding the growth of megakaryocytes and the production of PLT [32–34]. The activation of these humoral factors, especially interleukin-6, can promote the proliferation of tumor cells [35,36]. (2) Some experimental studies have demonstrated that cancer cell-activated PLT can induce adhesion, growth, and distant metastasis. The tumor cells can be protected from immune responses, which results in growth and dissemination of cancer because PLT can adhere to the tumor cells with the help of its procoagulant surface [37]. (3) Several reports [38,39] have revealed that high PLT is associated with the size of HCC, and with larger size of tumor comes higher PLT level, which implied that the higher PLT might be associated with the growth of tumor. In addition, the research by Jain *et al.* [40] further revealed that high PLT can promote the growth of tumor because PLT can produce thymidine phosphorylase, which activates the process of angiogenesis. (4) Czokalo *et al.* [36] also reported that high PLT can promote the adhesion of tumor cells to the vascular endothelial layer. Although Sitia *et al.* [41] suggested that anti-PLT drugs, such as aspirin and clopidogrel, could prevent hepatocarcinogenesis in the management of immune-mediated chronic HBV infection in an animal model, to date, it is still unclear whether PLT accelerates or impedes HCC occurrence.

As for HCC patients with thrombocytopenia, until now, there is no direct evidence to prove the relationship between low PLT level and the prognosis of tumors. However, we all know that as a surrogate marker for liver cirrhosis, thrombocytopenia is closely related to the development of HCC [42–44]. Furthermore, thrombocytopenia is also linked to smaller HCC size, mainly because they can grow, causing more liver damage that is associated with liver parenchyma [39,45]. In addition, Soubrane *et al.* concluded that a low PLT count seemed to be a reliable predictor of sinusoidal obstruction syndrome (SOS) [46], which can

increase not only portal hypertension but also spleen size. Moreover, liver stiffness because of SOS can contribute to the subsequent development of thrombocytopenia [47]. A meta-analysis by Choi *et al.* [48] showed that portal hypertension increases mortality, morbidity, complications, and liver failure in HCC patients, and some research reports also confirmed that thrombocytopenia reflecting the degree of hypertension leads to similar outcomes [16,49,50]. Moreover, a decreased PLT level was significantly related with elevated AFP levels [28,51,52], and both of them are related with HCC recurrence [53,54]. Thus, although thrombocytopenia can only reflect hepatic fibrosis and portal hypertension, it can indirectly imply poor prognosis for HCC patients.

From the foregoing discussion, we argue that the level of PLT should be regarded as an important participant in the progression and prognosis of HCC. Although tumor progression and metastasis may result from PLT, as shown in previous studies, the molecular mechanisms why abnormal PLT can lead to poor prognosis of cancer patients still need further research.

There is no doubt that our study has some limitations. First, this work was retrospective, and the sample size of abnormal PLT patients was relatively small. Second, we only considered the abnormality of PLT in terms of numbers without considering the abnormality in quality, when all included patients were divided into two groups. Third, perioperative management and anti-HBV therapy may have an influence on the prognosis of patients. Last, the abnormality of PLT counts might result from other diseases apart from HCC, as well as hematological and autoimmune diseases.

Our study suggests that PLT level is an independent prognostic factor for HCC patients who underwent liver resection. PLT will become one of the important indicators, along with serum AFP level, TNM stage, and tumor size, for judging the prognosis of HCC. The results of the current study will play a crucial role in the management of PLT and the development of individualized medicine for HCC patients.

Conflict of interest: The authors state no conflicts of interest.

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