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Prognostic role of platelet lymphocyte ratio (PLR) among patients with hepatocellular carcinoma undergoing liver transplantation

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Abstract

Aim: Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide, but it is so aggressive that is the third most common cause of cancer related death. We aim to study the role of PLR in prognosis of HCC and to see if it can be a predictor of overall survival and disease-free survival among HCC patients that received liver transplantation in our center.

Materials and Methods: This is a single center retrospective analysis of prospectively collected data. The study was carried out in liver transplant institute of Inonu University, Malatya, Turkey. Consecutive patients that received liver transplantation for HCC and survive for at least 90 days post transplantation were included in the study. Data was collected regarding age, gender, presence or absence of cirrhosis, cause of cirrhosis, number of nodules, maximum size of the tumor, preoperative PLR, pre-transplant GGT, type of transplant, presence or absence of microvascular invasion, overall survival and disease-free survival. The study was censored on June 2022. Data was analyzed using SPSS version 25.

Results: Platelet lymphocyte ratio was found to be significantly associated with some poor prognostic factors of HCC in our patients. We found that PLR is significantly associated with maximum tumor diameter (MTD) and total tumor diameter (TTD) with p= <0.0001 and 0.0016 respectively. Univariate analysis revealed that PLR is a predictor of worse DFS or OS but when subjected to multivariate analysis, we found that PLR is not an independent predictor of OS and DFS.

Conclusion: Platelet lymphocyte ratio is associated with poor prognostics feature of hepatocellular carcinoma.

Introduction

Liver cancer is a global health challenge and its incidence is having been increasing worldwide. It is estimated that by 2025, the annual incidence of liver cancer will be >1 million patients [1, 2]. Hepatocellular carcinoma (HCC) is the most common form of liver cancer and accounts for about 90% of cases. Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide, but it is so aggressive that is the third most common cause of cancer related death [1-3]. Most HCC arise in the presence of background liver cirrhosis and the extent of liver dysfunction has a major impact on survival, sometimes even more than the tumor itself [4,5].

There has been tremendous progress in the treatment of HCC but surgical resection and liver transplantation are still the most effective treatments [6]. Recurrence is one of the important factors affecting the long-term survival of patients after surgical treatment [7]. The 5-year recurrence rates after surgical resection and liver transplantation are as high as 70% and 35%, respectively [8]. Some of the important predictors of recurrence after resection or transplant include microscopic or macroscopic vascular invasion and level of tumor differentiation [8–10].

The association between cancer and thrombosis was established by Armand Trousseau in the mid-1880s, it was later revealed that this association was due to increase in platelet activation by the cancer cell [11]. Cancers cells secretes thrombin which result in direct activation of platelets while some cell are said to express tissue factor and ADP both of which play a role in thrombocytosis and

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platelet activation [12,13]. The association between lymphocyte and cancer has also been documented in many studies. The level of lymphocytes in the peripheral blood and the level of Tumour infiltrative lymphocyte (TIL) have been revealed to be a prognostic marker in colorectal and ovarian cancer [14,15]. There is evidence that combining these parameters in the form of platelet-lymphocyte ratio (PLR) or neutrophil lymphocyte ratio (NLR) can serve as prognostic markers in cancers like colorectal cancer and gastric cancer.

The role of PLR in prognosis of patients with HCC after TACE and curative resections have been studied much more extensively compared to the role in prognosis after liver transplantation [16–18]. The aim of the study is to study the role of PLR in prognosis of HCC and to see if it can be a predictor of overall survival and disease-free survival among HCC patients that received liver transplantation in our center.

Materials and Methods

Study design and study location

This is a single center retrospective analysis of prospectively collected data. The study was carried out in liver transplant institute of Inonu University, Malatya, Turkey. Inonu University ethical approval was obtained from the Health Sciences Non-Interventional Clinical Research Ethics Committee (Date: 04-10-2022, Decision no: 2022/3916). Consecutive patients that received liver transplantation for HCC from January 2006 to June 2022 and survived for at least 90 days post transplantation were included in the study. Follow up protocol for patients that underwent transplantation for HCC in the center was described in a previous publication [19].

Data collection

Data was collected regarding age, gender, presence or absence of cirrhosis, cause of cirrhosis, number of nodules, maximum size of the tumor, preoperative PLR, pretransplant GGT, type of transplant, presence or absence of microvascular invasion, overall survival and disease free survival. The study was censored on June 2022.

Definitions

1. Overall survival was defined as the period from transplant to the time of patients' death or when the study was censored.
2. Disease free survival is defined as the period from transplant to appearance of evidence of recurrence disease or death.

Outcomes

The primary outcome of this study is the overall survival of the patients after liver transplantation for HCC. The secondary outcome is Disease free survival.

Statistical analysis

Data was analyzed using SPSS version 25 (IBM SPSS Statistics software version 25.0 (Statistical Package for the Social Sciences, Inc, Chicago, IL, USA). Distribution of the parameters was evaluated with Shapiro-Wilk and Kolmogorov-Smirnov tests.

Quantitative variables are expressed as median (range), mean ± SD or mean ± standard error of mean. Qualitative variables are expressed as ratio and percentage.

Comparisons were achieved with Mann- Whitney U test for quantitative variables and with Chi-square test, for qualitative variables. (Assumptions: Variables are categorical, all observations are independent, cells in the contingency table are mutually exclusive and Expected value of cells should be 5 or greater in at least 80% of cells).

Cutoffs for quantitative variables were identified by constructing Receiver Operating Characteristics (ROC) curve. The variable generated by grouping the quantitative variable was then compared using univariate analysis methods with p value < 0.05 considered significant. Those with p <0.05 were then subject to multivariate analysis using the cox regression analysis to identify independent risk factors predicting OS and DFS.

Results

Baseline characteristics

Receiver operating characteristics (ROC) curve was used in identifying the cutoff of PLR. A cutoff of 110 was identified; area under the curve (AUC) was 0.601(95% CI) and a p vale of <0.0001 (Figure 1). High PLR was defined as PLR $>$ 110 while a low PLR was defined as PLR $\leq$ 110. Four hundred and six patients that received liver transplantation for HCC in our institute were included for analysis. The median age of the patients was 56.00 years with a range of 2 to 70 years. The males constituted 86% with a male to female ratio of 6:1. About 33.5% of the patients are Child-Pugh's class A, 43.3% were in class B

Table 1. Association between PLR and bad prognostic tumor characteristics.

		Low PLR	High PLR	P value
MTD in cm	≤5	232	73	<0.0001
	>5	52	49	
TTD in cm	≤8	219	80	0.016
	>8	65	42	
Pre-transplant GGT	≤104	188	74	0.309
	>104	95	47	
Pre-transplant AFP	≤200	240	90	0.006
	>200	40	31	
Number of nodules	Single	139	63	0.618
	Multiple	145	59	
Tumour differentiation	Well	123	47	0.158
	Moderately	122	49	
	Poorly	39	26	
Vascular invasion	Absent	171	48	0.002
	Microvascular	86	50	
	Macrovascular	26	22	

MTD; maximum tumor diameter, TTD; total tumour diameter, AFP; alpha-feto protein.

Table 2. Univariate and Multivariate Cox regression analysis of factors associated with DFS.

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
AFP(≤200 vs >200)	2.312 (1.612-3.315)	<0.0001	0.530 (0.443-0.880)	0.001
GGT(≤104 vs >104)	2.010 (1.447-2.792)	<0.0001	0.576 (0.438-0.952)	0.001
PLR (≤110 vs >110)	1.814 (1.300-2.530)	<0.0001		
MTD (≤5cm vs >5cm)	3.986 (2.862-5.550)	<0.0001	0.325 (0.261-0.733)	<0.001
TUMOUR DIFFERENTIATION (well vs moderate vs poor)	1.926 (1.536-2.417)	<0.0001	0.408 (0.269-0.846)	<0.001

MTD; maximum tumor diameter, TTD; total tumor diameter, AFP; alpha-feto protein, PLR; platelet lymphocyte ratio, GGT; gamma-gluteryl transferase.

Table 3. Univariate and Multivariate Cox regression analysis of factors associated with OS.

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
AFP(≤200 vs >200)	2.030 (1.392-2.960)	<0.0001	0.657 (0.456-0.991)	0.037
GGT(≤104 vs >104)	2.031 (1.443-2.859)	<0.0001	0.599 (0.554-1.368)	0.005
PLR (≤110 vs >110)	1.963 (1.310-2.769)	<0.0001		
MTD (≤5cm vs >5cm)	3.658 (2.595-5.156)	<0.0001	0.362 (0.349-0.728)	<0.001
TUMOUR DIFFERENTIATION (well vs moderate vs poor)	1.851(1.465-2.340)	<0.0001	0.597 (0.277-0.933)	0.002

MTD; maximum tumor diameter, TTD; total tumor diameter, AFP; alpha-feto protein, PLR; platelet lymphocyte ratio, GGT; gamma-gluteryl transferase.

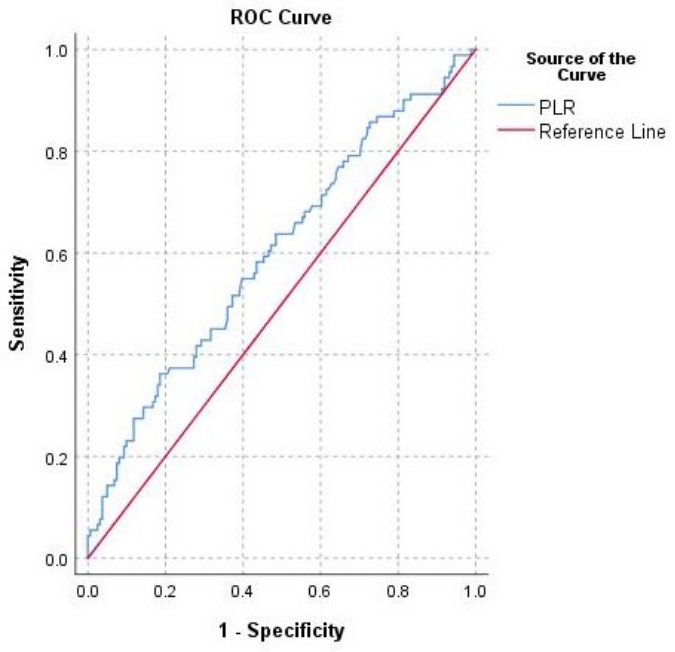

Figure 1. Receiver Operator Characteristics (ROC) Curve used in identifying the cut-off of Platelet-Lymphocyte ratio.

while 23.4% were in class C. There is background liver cirrhosis in 98% of the patients. The commonest cause of cirrhosis in the patients was viral hepatitis in 80% followed by cryptogenic in 13%. Alcohol, Budd Chiari disease and metabolic cirrhosis contributed to only 5.2%. The median size of the tumor was 3.00cm with a range of 0.1 to 24.0cm and around half of the patients (49.8%) had a single tumor. About 41.9% of the tumors were well differentiated, 42.1% moderately differentiated and only 16.0% were poorly differentiated. When we assessed the pattern of vascular invasion in the study, we found that microvascular invasion affected 34.2% of the while macrovascular invasion was seen in 11.8% of the patients. No macrovascular or microvascular invasion was seen in 54% of the patients.

Association between PLR and pathologic characteristics of tumor

Platelet lymphocyte ratio was found to be significantly associated with some poor prognostic factors of HCC in our patients. We found that PLR is significantly associated with maximum tumor diameter (MTD) and total tumor diameter (TTD) with p= <0.0001 and 0.0016 respectively. Patients with PLR more than 110 tend to have a larger tumor of more than 5 cm which is a bad prognostic feature. The pre transplant level of alpha fetoprotein (AFP) is also significantly associated with PLR with a p value of 0.006. Patients with PLR > 110 tend to have AFP of more than 200. Platelet lymphocyte ratio also significant predict vascular invasion before liver transplantation with a p value of 0.002. However, PLR doesn't significantly affect the tumor differentiation or the number of nodules. Table 1 shows the relationship between PLR and some prognostic features of HCC.

Prognostic factors affecting survival

Disease free survival (DFS)

Univariate analysis revealed that factors like age, gender, CTP class, number of nodules, and non tumor liver tissue have no effect on DFS. However, factors like MTD, AFP, GGT, MVI, PLR, number of nodules and level of tumor differentiation were found to be associated with

poor DFS. These parameters were then subjected to multivariate analysis and only MTD, pre transplant GGT, pre-transplant AFP and level of tumor differentiation were found to be independent predictors of worse DFS (p= <0.001, 0.001, 0.001 and <0.001 respectively and HR=0.325, 0.576, 0.530 and 0.408 respectively) Table 2.

Overall survival (OS)

Overall survival was not affected by age, gender, CTP class, and non tumour liver tissue. However, univariate analysis revealed that MTD, TTD, NLR, AFP, GGT, MVI, PLR, number of nodules and level of tumor differentiation. These parameters were then subjected to multivariate analysis and only MTD, pre transplant GGT, pre-transplant AFP and level of tumour differentiation were found to be independent predictors of worse OS (p= <0.001, 0.005,0.037 and 0.002 respectively and HR=0.362, 0.599, 0.657 and 0.597, respectively).

Discussion

Outcome of liver transplantation or resection for HCC has been studied extensively and multiple parameters have been identified as poor prognostic indicators in HCC. These parameters include MTD, total tumor diameter (TTD), pre transplant GGT, pre transplant AFP, number of nodules, level of tumor differentiation and vascular invasion [20–25]. In our study, we found a significant association between the level of PLR and MTD, TTD, pre transplant AFP and presence of vascular invasion. Patients with PLR > 110 tend to have higher MTD, TTD, pre-transplant AFP and they tend to have microvascular or macrovascular invasion (p= <0.0001, 0.016, 0.006 and 0.002 respectively). The association between PLR and MTD diameter has been reported in multiple studies with Yang et al. [26] reporting a significant association between the two parameters. This was also confirmed by findings of Xia et al. [27] and Karaogullarindan et al. [28]. Suner and Carr [29] also found a significant association between level of PLR and the MTD when they evaluated 1024 patients. Our finding of significant association between PLR and level of tumor differentiation, vascular invasion and level of pre-transplant AFP was supported by most of the reports in literature. Yang et al found the association between elevated PLR and vascular invasion, serum AFP and level of tumor differentiation. This is similar to findings of Suner et al. [30] and Ker et al. [31].

The role of PLR in predicting survival after different treatment for HCC has been studied with conflicting results reported. Our study assessed the role of PLR in predicting disease free survival after liver transplantation for HCC and we found that there is no significant association between the two parameters. This is similar to the findings of clinical trial by Parisi et al. [32] which found that elevated PLR is not associated with poor DFS after liver transplantation. Harimoto et al. [32] also studied the role of PLR in patents with HCC after LDLT and they found that the elevation of PLR doesn't affect the DFS. The association between PLR and DFS after transplantation was also explored by Xia et al. [27] and Lai et al. [33] but their findings suggested that elevated PLR is associated with poor DFS after liver transplantation. Disease free survival after curative resection for HCC has been found to be affected by pre transplant PLR with Yang et al. [26] reporting shorting sorter DFS in patients with elevated PLR of > 150 before resection. However, there have been conflicting findings in other studies [17].

Overall survival (OS) of patients with HCC after any type of treatment depends on multiple factors. Platelet lymphocyte ratio has been explored as a predictor of OS after TACE for HBV related HCC and the results showed that higher PLR are associated with poor overall survival in these group of patients [34]. Overall survival after other treatment modalities were also investigated and multiple studies reported improved OS in patients with low PLR compared to those with high PLR [13,14,17,25,34,35]. The role of PLR in predicting OS after liver transplantation for HCC revealed conflicting findings. Our study revealed that the level of pre transplant PLR is of no value in predicting overall survival after liver transplant for HCC. This is similar to the findings of a clinical trial by Parisi et al. [32] in which they found that elevation of PLR is not associated with poor overall survival. However, Xia et al. [27] in a study of 343 adult patients who received liver transplant for HCC found that high PLR of >125 is associated with poor OS.

The difference between our findings and those that found that PLR predicts both DFS and OS may be due a few reasons. One of the reasons is the cutoff values of PLR in different studies. We use the cutoff of 110; some studies reported the use of PLR of 70.44 while other studies used a value of 150. Another reason may be the heterogeneity of our patients; we included both pediatric and adult patients that underwent liver transplantation for HCC while some studies only studied adults that were transplanted for HCC.

Conclusion

Platelet lymphocyte ratio is associated with poor prognostic features of HCC. Despite the associated of PLR with poor prognostic factors of HCC, it has no effect on both DFS and OS.

Ethics approval

Inonu University for this study ethical approval was obtained from the Health Sciences Non-Interventional Clinical Research Ethics Committee (Date: 04-10-2022, Decision no: 2022/3916).

List of abbreviations

MTD; maximum tumor diameter, TTD; total tumor diameter, AFP; alpha-feto protein, PLR; platelet lymphocyte ratio, GGT; gamma-gluteryl transferase, PVTT; portal vein tumor thrombosis, NLR; neutrophil lymphocyte ratio.

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