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CLINICAL STUDY

Preoperative platelet-to-lymphocyte ratio is a predictor of prognosis in patients with ampullary carcinoma

Demirci NS[1], Ozdemir NY[2], Erdem GU[1], Bozkaya Y[1], Yazici O[1], Zengin N[2]

Ankara Numune Training and Research Hospital, Dept of Medical Oncology, Ankara, Turkey.
drserkannebi@yahoo.com

ABSTRACT

AIM: To emphasize the significance of the platelet-to-lymphocyte ratio (PLR) in estimating the postoperative prognosis or survival measures in patients with carcinoma of the ampulla of Vater.

METHODS: We retrospectively reviewed 82 patients, who underwent pancreaticoduodenectomy for ampullary carcinoma between July 2001 and April 2014. We investigated the predictive significance of the preoperative PLR for disease-free survival (DFS) or overall survival (OS). The possible correlations between the PLR and clinical or pathological features were also evaluated.

RESULTS: The 5-year DFS and OS rates of the patients with carcinoma of the ampulla of Vater after pancreaticoduodenectomy were 51 % and 64 %, respectively. Multivariate analysis revealed a significantly worse OS in patients with a PLR ≥ 212 [hazard ratio (HR): 3.446; 95% confidence interval (CI): 1.4–8.43; p = 0.007], lymphovascular invasion (HR: 2.973; 95% CI: 1.25–7.03; p = 0.013), or pathological stage pT3/4 (HR: 2.761; 95% CI: 1–7.1; p = 0.035). Similarly, DFS was significantly worse in patients with lymphovascular invasion (HR: 2.24; 95% CI: 1.1–4.56; p = 0.025) or stage pT3/4 (HR: 2.243; 95% CI, 1.03–4.84; p = 0.04).

CONCLUSION: The preoperative PLR shows a predictive significance for the prognosis of postoperative patients with carcinoma of the ampulla of Vater. We suggest that because of its predictive value, the PLR can be used in the development of further approaches to monitor and manage patients with poor prognosis *Tab. 4, Fig. 1, Ref. 45)*. Text in PDF *www.elis.sk.*

KEY WORDS: reoperative platelet-to-lymphocyte ratio, predictor of prognosis, ampullary carcinoma.

Abbreviations: DFS – Disease-free survival, LVI – Lymphovascular invasion, OS – Overall survival, N – Regional nodal metastasis, PLR – Platelet-to lymphocyte ratio, PNI – Perineural invasion, SM – Surgical margin, T stage – Tumour stage

Introduction

Ampullary adenocarcinomas are exceedingly rare, accounting for only 0.2–0.5 % of all gastrointestinal malignancies and approximately 6 % of periampullary tumours (1). The development of ampullary adenocarcinomas has shown an increasing trend (2). In addition to ampullary adenocarcinomas, other members of the periampullary tumour family include distal cholangiocarcinoma and pancreatic or duodenal adenocarcinoma. Ampullary adenocarcinomas have the most favourable prognosis compared to other periampullary tumours. It is difficult to distinguish ampullary adenocarcinomas from other members of the periampullary tumour family preoperatively. The 5-year survival rate after resection of ampullary carcinomas ranges from 30 % to 70 % (3–6). At the time of diagnosis, 80 % of patients are eligible for resection, but approximately half of the cases recur (7, 8). This high rate of recurrence emphasizes the importance of seeking prognostic markers for surgical resection.

Various clinical or pathological features have been used previously to predict the postoperative prognosis of the patients with carcinoma of the ampulla of Vater, such as T stage, positive surgical margins, lymph node involvement, perineural invasion, lymphovascular invasion, histological subtype, tumour grade, and evidence of jaundice (9–13).

It was previously reported that numerous inflammatory markers, such as: the serum albumin level, C-reactive protein level, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio (PLR), and modified Glasgow prognostic score, have a prognostic significance in various malignancies (14–19).

The aim of this study was to determine whether the preoperative PLR has a prognostic significance in patients undergoing ampullary adenocarcinoma resection. Additionally, we evaluated the possible association between the PLR and the clinical or pathological features of the patients.

Patients and methods

From the retrospectively reviewed database of Ankara Numune Training and Research Hospital, Department of Medical Oncology, we recruited 82 patients with histologically proven

[1]Ankara Numune Training and Research Hospital, Department of Medical Oncology, Ankara, Turkey, and [2]Yildirim Beyazit University Faculty of Medicine, Department of Medical Oncology, Ankara, Turkey

Address for correspondence: N.S. Demirci, Ankara Numune Training and Research Hospital, Dept of Medical Oncology, 06100 Altindag, Ankara, Turkey.
Phone: +903125084600, Fax: +903125084914

non-metastatic ampullary carcinoma, who underwent curative pancreaticoduodenectomy, including R0 or R1 resection, between July 2001 and May 2014.

All the patients were over 18 years of age, and some had undergone adjuvant therapies. Patients with metastatic disease at the time of diagnosis (thus not eligible for surgical intervention), those, who were medically inoperable by other means, those previously treated for another primary malignancy, and those who, were pregnant were excluded from the study.

Preoperative blood counts were measured routinely in venous blood samples from all the patients. The PLR was then calculated as the platelet count divided by the lymphocyte count.

Initially, the association between clinicopathological parameters and disease-free (DFS) or overall survival (OS) rate following pancreaticoduodenectomy was investigated using univariate and multivariate analyses. Age, sex, pathological stage of the tumour (pT stage), evidence of regional lymph node metastasis, lymphovascular invasion, perineural invasion, surgical margin positivity, whether adjuvant therapy was used, postoperative Eastern Cooperative Oncology Group (ECOG) performance score, and the PLR were the parameters evaluated in the analyses. The cut-off PLR value was determined as the median PLR: 212. Recurrence of ampullary carcinoma is defined as a newly formed local or distant metastatic tumour evident in imaging studies such as: ultrasonography, magnetic resonance imaging, or computed tomography, during follow-up. This retrospective review was initially approved by the Ethical Committee of Ankara Numune Training and Research Hospital.

Statistical analysis

χ^2 tests were used for comparative analysis of the categorical data. The Statistical Package for the Social Sciences, version 18.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. P-values less than 0.05 were deemed to indicate a statistical significance. Descriptive statistics were reported as percentages and medians. Survival analysis was performed using the Kaplan–Meier method. Variables with a $p < 0.1$ on univariate analysis were further evaluated by Cox regression analysis using backward selection to determine independent predictors of survival. DFS was defined as the interval from the first day of the surgery to the date of initial recurrence or death due to any cause, whichever occurred first. OS was defined as the interval from the first day of the surgery to the date of death due to any cause or the last follow-up.

Results

Eighty-two patients were enrolled in this study, and the patient´s characteristics are shown in Table 1. The median age of the population was 63 years (range, 37–83 years), and 48 of the patients were males (58.5 %). Of the 82 patients, 43.9 % were stage pT1/2 and 56.1 % pT3/4. Metastasis to the regional lymph nodes was evident in 41.5 % of the patients. Seven patients (8.5 %) had microscopically positive surgical margins. Adjuvant treatment was administered in 54 patients (65.9 %). Lymphovascular invasion (LVI) was evident in 34.1 % of the patients and perineural invasion (PNI) in 28 % of the patients. The ECOG performance status of patients was 0/1 in 73.2 % of the population, and the most common symptom observed was jaundice (58.5 %).

Tab. 1. Patient's characteristics.

Characteristics	No of patients, n=82 (%)
Age, years	
Median	63
Range	37–83
<65	47 (57.3)
≥65	35 (42.7)
Sex	
Mele	48 (58.5)
Female	34 (41.5)
PLR	
Median	212
Range	79.5–614.2
Low	41 (50)
High	41 (50)
Jaundice	
Yes	48 (58.5)
No	34 (41.5)
ECOG performance status	
0–1	60 (73.2)
2–3	22 (26.8)
pT stage	
1–2	36 (43.9)
3–4	46 (56.1)
Regional Lymph Node Metastasis	
Positive	34 (41.5)
Negative	48 (58.5)
Lymphovascular invasion	
Yes	28 (34.1)
No	46 (56.1)
Perineural invasion	
Yes	23 (28)
No	51 (62.2)
Surgical margin	
Positive	7 (8.5)
Negative	75 (91.5)
Adjuvant treatment	
Yes	54 (65.9)
No	28 (34.1)

ECOG: Eastern cooperative oncology group, PLR: platelet-lymphocyte ratio, High PLR: PLR ≥ 212, pT: pathological tumor stage

Tab. 2. Clinicopathological features in relation to the platelet to lymphocyte ratio.

Features	PLR		p
	<212 (n=41)	≥212 (n=41)	
Age, years (<65/≥65)	27/14	20/21	0.118
Sex (m/f)	22/19	26/15	0.370
pT stage (T1–T2/T3–T4)	18/23	18/23	1
Regional Lymph Node Metastasis (yes/no)	25/16	23/18	0.654
Surgical Margin Status (positive/negative)	5/36	2/39	0.236
Lymphovascular invasion (yes/no)	13/23	15/23	0.766
Perineural invasion (yes/no)	12/24	11/27	0.684
Jaundice (yes/no)	26/15	22/19	0.370
ECOG performance status (0–1/3)	32/9	28/13	0.319
Adjuvant Treatment (yes/no)	26/15	28/13	0.641

ECOG: Eastern cooperative oncology group, PLR: platelet-lymphocyte ratio, pT: pathological tumor stage

Tab. 3. Univariate and multivariate analyses of clinicopathological features in relation to disease free survival after pancreaticoduodenectomy for carcinoma of the ampulla of Vater.

Patients	n (%)	3-year Disease free survival (%)	5-year Disease free survival (%)	10-year Disease free survival (%)	Univariate analysis	Multivariate analysis	
					DFS P-value	Hazard ratio (95% CI)	DFS P-value
All patient groups	82	58	51	43			
Age, years							
<65	47 (57.3)	59	52	48	0.756		
≥65	35 (42.7)	56	51	34			
ECOG Performance status							
0–1	60 (73.2)	59	53	46	0.531		
2–3	22 (26.8)	53	42	28			
Sex							
Male	48 (58.5)	58	52	38	0.614		
Female	34 (41.5)	57	50	50			
Jaundice							
Yes	48 (58.5)	51	45	34	0.301		
No	34 (41.5)	67	58	52			
Regional Lymph Node Metastasis							
Positive	34 (41.5)	54	46	40	0.340		
Negative	48 (58.5)	61	55	47			
PLR							
Low	41(50)	68	65	46	0.027	1.997 (0.98–4.07)	0.057
High	41 (50)	48	40	40			
Lymphovascular invasion							
Yes	28 (34.1)	46	32	26	0.006	2.249 (1.1 –4.56)	0.025
No	46 (56.1)	70	67	55			
Perineural invasion							
Yes	23 (28)	63	46	–	0.334		
No	51 (62.2)	60	57	49			
pT stage							
1–2	36 (43.9)	64	64	54	0.027	2.243 (1.03–4.84)	0.04
3–4	46 (56.1)	54	40	34			
Surgical margin							
Positive	7 (8.5)	40	40	–	0.082		
Negative	75 (91.5)	60	52	46			
Adjuvant Treatment							
Yes	54 (65.9)	50	42	39	0.063		
No	28 (34.1)	71	66	53			

ECOG: Eastern cooperative oncology group, PLR: platelet-lymphocyte ratio, High PLR: PLR ≥ 212, pT: pathological tumor stage

The median PLR was 212 (range, 79.5–614.2). Patients with a preoperative PLR ≥ 212 represented 50 % of the whole population. No significant associations were evident between the PLR and any of the clinicopathological parameters (Tab. 2).

The median follow- up from the date of the first diagnosis was 42.4 months (range, 1.68–164 months). The 5-year DFS and OS rates of the patients with an indication of ampullary carcinoma following pancreaticoduodenectomy were 51% and 64%, respectively (Tabs 3 and 4).

On univariate analysis, the factors with a potential prognostic value for DFS and OS were investigated. These parameters were age, sex, ECOG performance status, evidence of jaundice, pT stage, regional lymph node involvement, LVI, PNI, surgical margin positivity, history of adjuvant treatment, and the PLR. DFS was found to be significantly worse in the patients with a high PLR (p = 0.027), LVI (p = 0.006), or stage pT3/4 (p = 0.027) (Tab. 3).

On multivariate analysis, LVI (hazard ratio (HR): 2.249; 95% confidence interval [CI]: 1.1–4.56; p = 0.025) and pT3/4 (HR: 2.243; 95% CI: 1.03–4.84; p = 0.04) remained independent and significant predictors of a poor DFS. In addition, a PLR ≥ 212 (HR: 1.99; 95% CI: 0.98–4.07; p = 0.057, figure-1a) also tended to be associated with a poor DFS. On the other hand, DFS was not associated with age, sex, preoperative ECOG score, preoperative evidence of jaundice, T stage, PNI, LVI, regional lymph node metastasis, surgical margin positivity, or adjuvant therapy (Tab. 3).

Table 4 summarizes the relationships between the clinicopathological features and OS rate according to the univariate and multivariate analyses. In the univariate analysis, the OS rates of the patients with a high PLR (p = 0.006), pT3/4 (p = 0.018), positive surgical margin (p = 0.015), LVI (p = 0.002), or PNI (p = 0.025) were significantly worse. In the multivariate analysis, pT3/4 (HR: 2.761; 95% CI: 1.07–7.1; p = 0.035), LVI (HR: 2.973;

Tab. 4. Univariate and multivariate analyses of clinicopathological features in relation to overall survival after pancreaticoduodenectomy for carcinoma of the ampulla of Vater.

Patients	n (%)	3-year Overall survival (%)	5-year Overall survival (%)	10-year Overall survival (%)	Univariate analysis	Multivariate analysis	
					OS P-value	Hazard ratio (95% CI)	OS P-value
All patient groups	82	75	64	53			
Age, years							
<65	47 (57.3)	80	71	62	0.156		
≥65	35 (42.7)	68	53	35			
ECOG Performance status							
0–1	60 (73.2)	75	68	57	0.317		
2–3	22 (26.8)	75	46	34			
Sex							
Male	48 (58.5)	73	70	57	0.696		
Female	34 (41.5)	78	58	52			
Jaundice							
Yes	48 (58.5)	73	60	51	0.723		
No	34 (41.5)	78	70	56			
Regional Lymph Node Metastasis							
Positive	34 (41.5)	67	54	43	0.064		
Negative	48 (58.5)	80	71	64			
PLR							
Low	41(50)	92	79	61	0.006	3.446 (1.4–8.43)	0.007
High	41 (50)	57	47	47			
Lymphovascular invasion							
Yes	28 (34.1)	66	47	34	0.002	2.973 (1.25–7.03)	0.013
No	46 (56.1)	84	81	71			
Perineural invasion							
Yes	23 (28)	67	49	41	0.025		
No	51 (62.2)	81	75	63			
T stage							
1–2	36 (43.9)	85	78	64	0.018	2.761;95%CI, 1.07–7.1	0.035
3–4	46 (56.1)	67	52	45			
Surgical margin							
Positive	7 (8.5)	54	36	–	0.015		
Negative	75 (91.5)	77	64	58			
Adjuvant Treatment							
Yes	54 (65.9)	66	54	64	0.057		
No	28 (34.1)	89	79	51			

ECOG: Eastern cooperative oncology group, PLR: platelet-lymphocyte ratio, High PLR: PLR ≥ 212, pT: pathological tumor stage

95% CI: 1.25–7.03; p = 0.013), and a high PLR (HR: 3.446; 95% CI: 1.4–8.43; p = 0.007) (Fig. 1) remained independent and significant prognostic predictors of poor OS. On the other hand, OS was not associated with age, sex, preoperative ECOG score, evidence of jaundice, PNI, regional lymph node metastasis, or adjuvant therapy.

Discussion

We found the PLR to be predictive of the prognosis of the patients after resection of ampullary carcinoma. To our knowledge, this is the most comprehensive study, involving a large number of patients, to evaluate the predictive utility of PLR for the postoperative prognosis of the patients with ampullary carcinoma.

Today, although still unclear, systemic inflammatory response seems to play an important role in tumour initiation, invasion, or progression (20). In numerous studies, it was previously reported that the microenvironment of the tumour is important for tumour progression as well as survival (21).

Evaluation of numerous immune mediators, such as interleukin-1 (IL-1), IL-3, and IL-6, showed that systemic inflammation increased the number of circulating thrombocytes and the megakaryocyte burden (22, 23). Transforming growth factor beta, IL-10, and other inhibitory cytokines secreted by inflammatory cells located in the tumour microenvironment, decrease the numbers of tumour-infiltrating and -circulating lymphocytes. Thus, the inflammatory response is disturbed in malignancy (24).

Recently, various inflammatory markers that are readily accessible and cost effective were identified and utilized to evaluate the prognosis of several malignancies (25–27). As mentioned previously, it was reported that inflammatory factors such as: albumin, C-reactive protein, and the PLR have a prognostic significance in

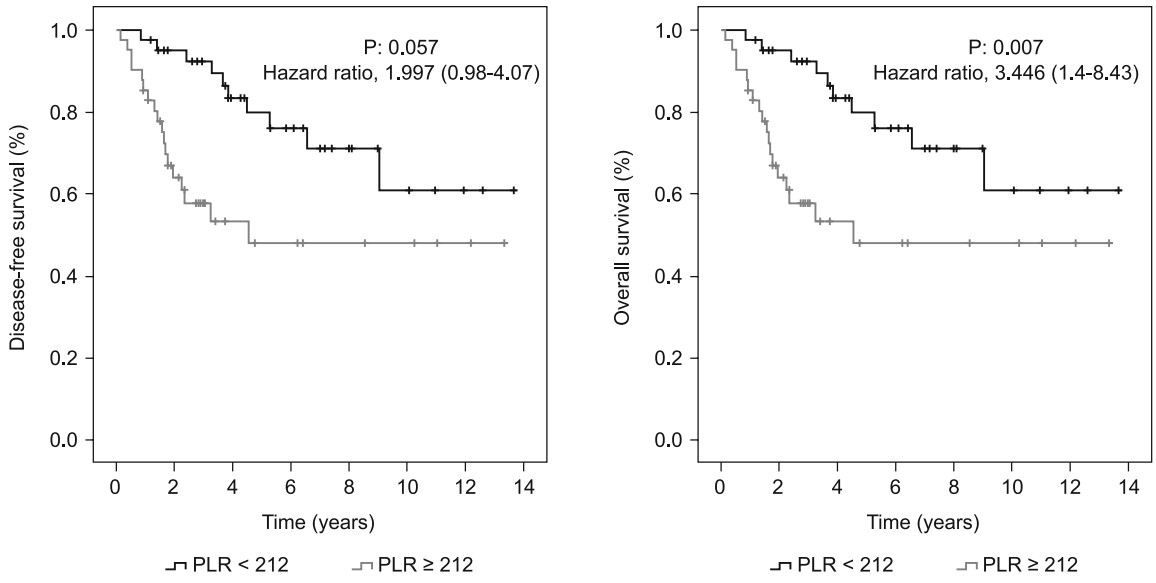

Fig. 1. Kaplan–Meier curves for disease-free (a) and overall (b) survival after pancreaticoduodenectomy.

numerous types of malignancies (28, 29). A high PLR has been associated with poor prognosis in numerous types of malignancies, namely breast, gastric, colorectal, ovary, pancreas, hepatocellular, and lung cancers (30–36). Unfortunately, the underlying mechanism is not yet clear. Platelets may cause expansion, as well as progression, of the tumour, because they stimulate angiogenesis via vascular endothelial growth factor production (37). Besides vascular endothelial growth factor, platelets produce several other growth factors, including transforming growth factor beta and platelet-derived endothelial cell growth factor (38, 39), that contribute to tumour growth (40). Platelet-derived pro-angiogenic mediators secreted during adhesion and aggregation of platelets also play significant roles in tumour expansion or potentially metastasis (41). According to this previous knowledge, the levels of thrombocytosis and lymphopenia act in conjunction with the level of systemic inflammation and, therefore, may reflect the PLR. Thrombocytosis and lymphocytopenia in peripheral blood increase the PLR. In more conceptual terms, thrombocytosis and lymphopenia are already considered when monitoring cancer patients, because they have been correlated with poor prognosis in many malignancies (42–45).

To our knowledge, only one previous study, by Smith et al. including 75 patients, has investigated the association between the PLR and the survival of resected ampullary carcinoma patients (19). In that study, the median follow-up of 22.5 months was conducted, a cut-off PLR of 160 was used. The PLR was determined in 65 patients, of whom 26 had a PLR > 160. The OS rates were significantly poor in patients with a high PLR (78.7 vs. 16.6 months, respectively; $p < 0.001$), positive lymph nodes (47.8 vs 14.4 months; $p = 0.001$), tumour diameter > 2 cm (44.3 vs 16.6 months; $p = 0.036$), and positive surgical margins (78.7 vs 11.5 months; $p < 0.001$).

Similarly, we found that positive surgical margins, lymph node involvement, and evidence of PNI were positively correlated with a worse OS in this study. Additionally, we previously reported that advanced T stage (HR: 2.761; 95% CI: 1–7.1; $p = 0.035$), LVI (HR: 2.973; 95% CI: 1.25–7.03; $p = 0.013$), and a high PLR (HR: 3.446; 95% CI: 1.4–8.43; $p = 0.007$) were independently and significantly correlated with a worse OS. LVI and T stage are predictors of a poor DFS in the patients with ampullary carcinomas (13). As expected, patients with a positive LVI and advanced T stage had worse DFS rates in our study.

Although not significant, patients in our cohort, who previously received adjuvant therapy, had lower OS rates. The fact that these patients had an initial clinical or pathological diagnosis suggestive of a poor prognosis might be the reason for this.

As previously emphasized, various clinicopathological features, including T stage, positive surgical margins, lymph node involvement, PNI, LVI, histological subtype, tumour grade, and evidence of jaundice, have predictive value for the prognosis of patients with carcinoma of the ampulla of Vater (9–13). Although correlations between the PLR and clinical or pathological features in various types of malignancies were reported previously, we did not detect such correlations (Tab. 2).

In our study, a high PLR was significantly correlated with OS in the univariate and multivariate analyses. Regarding DFS, there was a significant correlation between DFS and the PLR in the univariate analysis, but not statistically significant in the multivariate analysis.

The most important limitation of this study was its retrospective design. Additionally, certain factors that potentially affect prognosis (e.g., tumour grade, histological subtype, and the adjuvant therapy protocol) were not evaluated. However, this is the

most comprehensive study to evaluate the potential predictive value of the PLR for the postoperative prognosis and survival of patients with ampullary carcinoma.

Conclusion

Here, we suggest that the preoperative PLR may be predictive of survival in patients with ampullary carcinoma. Because it is a cost-effective and readily accessible measure, the PLR is a useful marker in almost all cases. By predicting the patients with a poor prognosis beforehand, the PLR may help with future efforts to monitor and manage patients with ampullary carcinoma.

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