Preoperative platelet-lymphocyte ratio is an independent prognostic factor in ampullary carcinoma following pancreaticoduodenectomy

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Abstract. The objective of the present study was to evaluate whether preoperative platelet-lymphocyte ratio (PLR) and neutrophil-lymphocyte ratio (NLR) could predict the prognosis for curative resected ampullary carcinoma. A total of 94 patients were retrospectively included over a 6-year period in which consecutive cases underwent pancreaticoduodenectomy for ampullary malignancy. Preoperative blood results were available in the 94 cases of resected ampullary carcinoma. Preoperative PLR and NLR cut-off values of 226.8 and 2.58 were determined to represent the optimal cut-off values in the cases for survival analysis. PLR remained a significant independent predictor of survival in multivariate analysis (Cox, P<0.001) in addition to tumor differentiation (P<0.001), nodal status (P<0.001) and stage (P<0.001). While NLR failed to serve as a prognostic factor in univariate (P=0.0637) and multivariate (P=0.164) survival analysis. Furthermore, the nodal involvement rate was higher in high PLR group (74.2 vs. 19.05%, P<0.001). Preoperative PLR and NLR merit further evaluation as a prognostic index in curative resected ampullary carcinoma. Additionally, it is a candidate predictor for the lymph node metastasis.

Introduction

Ampullary carcinoma is a rare histological type of gastrointestinal (GI) malignancies accounting for approximately 0.2-0.5% worldwide (1,2). The radical and beneficial surgery is pancreatoduodenectomy for resectable ampullary malignancies (3,4).

Carbohydrate antigen 19-9 (CA19-9) and bilirubin are well-established preoperative markers for indicting the prognosis of ampullary carcinoma (5-7). However, they exhibit unreliable and inconsonant characteristics in different studies with different patient cohorts (8,9). The critical disadvantages of CA19-9 and bilirubin are the deterioration in low sensitivity and specificity in jaundiced patients (9-11) and the ball-valve effects, as elevated CA19-9 and bilirubin associated with ampullary lesions can be intermittent) (1).

Therefore, simple, easily available and credible biomarkers for prognosis for patients with ampullary carcinoma are needed (12). Systematic inflammatory response (SIR) has been proven to be closely associated with cancer initiation, promotion, malignant conversion, invasion and metastasis (13-16). Several inflammatory biomarkers are routinely available from the pre-treatment routine blood test, including platelet count, platelet to lymphocyte ratio (PLR) and neutrophil to lymphocyte ratio (NLR). PLR and NLR have been the most frequently inflammatory biomarkers used to assess the prognosis in a number of different types of cancer (7,17,18), including ovarian cancer. Nevertheless, only one previous article has explored PLR as prognostic factor in ampullary carcinoma (7), and, to the best of our knowledge, there are no studies regarding NLR. Therefore, it is necessary to provide more evidence regarding the prognostic role of PLR and NLR in ampullary carcinoma.

Therefore, an aim of the present study was to determine whether preoperative PLR and NLR are preoperative predictive indicators for patients with ampullary carcinoma following curative surgery, then providing additional evidence to for physicians to make an improved clinical decision prior to surgery and theoretically helping to identify tumor progression.

Materials and methods

A total of 94 complete ampullary carcinoma (AC) cases who received surgery were included in the present study and diagnosed with AC by pathology. Retrospective data were extracted from the consecutive 94 patients (50 males and 44 females; median age 62 years; age range, 39-82 years) undergoing pylorus-preserving pancreaticoduodenectomy

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(PPPD) or classical Kausch-Whipple (Whipple) resection between January 2010 and September 2016 at the Peking Union Medical University Hospital (Beijing, China). The cases were excluded if: i) The patient succumbed within 30 days after surgery; ii) there was incomplete information; iii) the cancer was mixed type; iv) the patient received non-radical surgery; v) the patient succumbed during follow-up. Patient demographics, operative details, and the histological characteristics of the resected specimen were all extracted and numbered as Patient ID, due to no personal information being collected. A positive resection margin (R1) was defined as tumor involvement of margin under microscopic examination without any involvement in physical examination. While, R2 was defined as tumor involvement of the margin under microscopic examination, as well as involvement in physical examination No R2 resections were identified. Details of preoperative biliary drainage and adjuvant therapy were also collected, and survival data were obtained. The preoperative full blood count, CA19-9, and concurrent bilirubin levels were recorded where available. The normal diagnostic reference interval for serum CA19-9 was based on the previous study and our laboratory specification. For pre-operative CA19-9 a cut-off value of >150 kU/l was used to define the high-risk group for CA19-9 when recorded in the absence of concurrent cholestasis, such as bilirubin ≤35 μmol/l, and a cut-off value of >300 kU/l was used in the presence of cholestasis, such as bilirubin >35 μmol/l. For pre-operative CA19-9 a cut-off value of >255.5 kU/l was used (19,20).

Additionally, the PLR optimum cut-off point 226.8 was determined represent the optimum stratification point at which the survival differences between two groups was maximized. The pathological stage of the ampullary carcinoma was based on the update 8th edition of American Joint Committee On Cancer (AJCC) (21) by two pathologists independently who were blind to the study. The pathological report was offered and authorized by the Affiliated Pathology Department of Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (Beijing, China).

Statistical analysis. Continuous data were described and present as the median ± interquartile range (IQR) or 95% confidence intervals (CI). Relationships between the two continuous variables were analyzed using Spearman's rank correlation. Comparative analysis of categorical data was based on χ^2 or Fisher's exact tests. Survival data were analyzed using log rank testing for univariate analysis and Cox proportional hazards with forward-stepwise regression for multivariate analysis. Survival analysis by the continuous variable was categorized by the optimum cut-off of baseline platelet/netrophil to lymphocyte ratio value, which were defined by maximally selected Log-rank statistics (22,23). Patients who died within 30 days after surgery were excluded from survival analysis. P<0.05 was considered to indicate a statistically significant difference. Statistical analysis was performed using R software version 3.4.0 for Windows (GUI front-end), Graph Pad Prism 7.00 (GraphPad Software, Inc., La Jolla, CA, USA) and IBM SPSS Statistics 20 for Windows (IBM Corp., Armonk, NY, USA).

Table I. Demographics along with the preoperative CA19-9 and full blood count results of Ampullary carcinoma cases who received pancreaticoduodenectomy.

Demographics	Number
No. of patients identified	94
Male/female	50:44
Median age (IQR)	62 (54-68) years
Overall median survival time (95% CI)	48 (39.7-56.3) months
Surgery	
Whipple	89
PPPD	5
Preoperative intervention for biliary stenting	
No	47
Yes	47
Adjuvant therapy received	
No	82
Yes	12
Preoperative CA19-9 results available	76
Median preoperative CA19-9 (IQR)[a]	76.2 (15 to 256) U/ml
Number of jaundiced cases at time of CA19-9 estimation (bilirubin >35 μmol/l)	
Jaundice	51
No jaundice	45
Preoperative FBC available	94
Within 7 days	68
Following 7 days	26
Median platelet-lymphocyte ratio (IQR)	152.6 (114.7 to 229.6)
Neutrophilia present (>7.5x10^6/ml)	8
Lymphocytopaenia present (<1.0x10^6/ml)	13
Thrombocytosis present (>400x10^6/ml)	0

[a]Regarding the IQR, when the value was <0.6, it was taken as 0.6 for stastastic analysis; the median value may be <76.2. IQR, interquartile range; CI, confidence interval; CA19-9, Carbohydrate antigen 19-9. PPPD, pancreaticoduodenectomy; FBC, full blood count.

Results

Patient clinicopathological features according to preoperative PLR. A total of 345 consecutive patients underwent pancreatoduodenectomy (PPPD and Whipple) for pancreatic or perampullary tumors during the study period. Among them, 97 cases had histologically confirmed carcinoma arising from the ampulla of Vater. A single patient (1.03% of the patient cohort) who died within 30 days following surgery was excluded from the subsequent survival analyses. Two patients were also excluded for incomplete information. Finally, 94 complete AC cases were included in this study. There were a total of 71 censored cases with a median follow-up time of 21 months

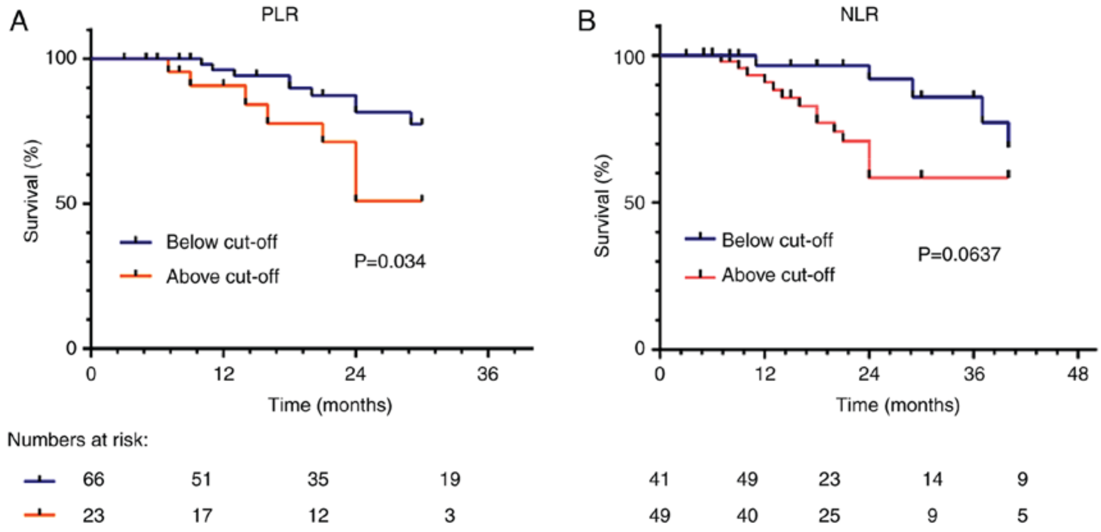

Figure 1. (A) Kaplan-Meier cumulative survival curves for ampullary carcinoma patients stratified by PLR ≤226.83; (B) Kaplan-Meier cumulative survival curves for ampullary carcinoma patients stratified by NLR ≤2.58. PLR, preoperative platelet-lymphocyte ratio; NLR, preoperative neutrophil-lymphocyte ratio.

(IQR=12-30 months). Median overall survival time of the study group was 48 months (95% CI=39.7 to 56.3 months). The demographics of patients in the study along with the preoperative full blood count results were listed in Table I.

Outcomes. The median survival time stratified by preoperative CA19-9 levels (at a cut-off value of ≤150 or ≤300 kU/l in jaundiced cases, the cut-off value of 255.5 for all cases), PLR (at cut-off value ≤226.83), NLR (at cut-off value ≤2.58) and total bilirubin (Tbil) level (at the cut-off 12.6 µmol/l /211.7 µmol/l) as well as the other various histological subgroups were shown in Table II.

The corresponding survival curves when stratifying by PLR and NLR are shown in Fig. 1A. No significant associations between CA19-9 and PLR (Spearman, rho=1, P=0.097) or between Tbil and platelet-lymphocyte ratio (Spearman, rho=1, P=0.13) were identified. Significant correlation was observed between Tbil and CA19-9 (Spearman, rho=0.487, P=0.000), PLR and NLR (spearman, rho=0.727, P=0.000); NLR and tbil (Spearman, rho=0.184, P=0.077) NLR and CA19-9 (Spearman, rho=0.107, P=0.354).

Associations between PLR and pathological characteristics. The correlation between preoperative indices and postoperative histological characteristics using χ^2 was listed in Table III. The higher PLR is, the higher proportion of positive lymph node is (P<0.01). No significances were identified between CA19-9 and nodal status, tumor differentiation or stage. Neither between Tbil or NLR and those characteristics.

Analysis of multiple prognostic factors. The results of a multivariate survival analysis using Cox Log rank proportional hazards with forward stepwise regression are shown in Table IV. In which preoperative indexes including CA19-9, Tbil, PLR and NLR alongside with histological indexes including stage, tumor differentiation and nodal status were presented. Nodal status failed to emerge as a significant variable in forward stepwise regression for it to demonstrate linear dependence with stage, and was therefore omitted from the final multivariate model. The supplementary Cox analysis including nodal status without stage showed that it was also an independent index with Hazard risk (HR) 5.026 (95% CI 3.937-6.416, P<0.001). The Cox analysis suggested that all the indexes included were independent prognostic variables in this patient group. The results of a multivariate survival analysis referring to NLR demonstrated NLR was not an independent prognostic index (P>0.05) (data not shown).

Risk stratification by Tbil and PLR. CA19-9 and PLR risk stratification is less satisfactory for the high-risk group only identified 1cases. Consequently risk stratification by Tbil and PLR was conducted. The high-risk group was defined as when Tbil and PLR values were above the cut-off. Low-risk groups were determined when both of two parameters were below the cut-off. and intermediate-risk group is conformed that either PLR or Tbil was above the cut-off.

Table V demonstrates that the only significant difference among the three risk groups was adjuvant therapy with a trend toward an increased likelihood of adjuvant therapy in the high-risk groups compared with the low-risk group (Fisher's exact, P<0.001). No significant difference was found in the proportion of patients undergoing preoperative biliary drainage when comparing the three risk groups (P=0.650). There was no difference in survival when comparing cases who did (n=12) or did not (n=80) receive adjuvant therapy in the whole patient group (median survival were >60 (95% CI=NR) months and 46, Log rank, P=0.0956). Similarly, there was no significant difference in the proportion of patients who undergoing preoperative biliary drainage (median survival >60 (95% CI=NR) months and 40 (95% CI=23.891 to 56.109) months respectively-Log rank, P=0.138).

Analysis of risk model using cox regression. Table VI demonstrates that the risk model being an independent predictive value with a hazard ratio 1.78 and 19.973 in intermediate-risk and high-risk group respectively compared with low-risk group (P<0.0001). Tumor-node-metastasis (TNM) was also

Table II. Median overall survival times (log rank) according to preoperative CA19-9, Tbil, platelet-lymphocyte ratio and histological hub-groups in the overall study group.

Characteristics	Number of patients	Median survival (months)	P-value
Preoperative CA19-9			0.499
Below cut-off	50	48 (36.5-59.4)	
Above cut-off	26	37 (33-63)	
Preoperative CA19-9			0.01[a]
≤255.5	54	NR (>60 months)	
>255.5	22	37 (16.1-57.9)	
Preoperative PLR			0.255
≤160	49	48 (40-56)	
>160	45	40 (NR)	
Preoperative PLR			0.0177[a]
≤226.83	63	48 (NR)	
>226.83	31	24 (NR)	
Preoperative NLR			0.0637
≤2.58	34	46 (NR)	
>2.58	60	48 (6.938-89.062)	
Nodal involvement			0.0018[a]
Negative	59	NR (66-NR)	
Positive	35	33 (20.3-45.7)	
Tumor differentiation			0.0187[a]
Well/moderate	69	48 (38.9-57.1)	
Poor	25	24 (12.6-35.4)	
Stage			0.003[a]
0 and I	32	NR (30-NR)	
II	27	40 (NR-NR)	(0.0083)
III and IV	35	46 (36.8-55.2)	
Nerve invasion			0.4176
Positive	12	NR (24-NR)	
Negative	82	48 (38.4-57.6)	
ICE			0.459
Positive	20	NR (33-NR)	
Negative	74	37 (31.4-42.6)	

[a]P<0.05. PLR, preoperative platelet-lymphocyte ratio; NLR, preoperative neutrophil-lymphocyte ratio; CA19-9, Carbohydrate antigen 19-9; ICE, intravascular tumor cell thrombus; NR, no statistical results available.

an independent factor in the final cox regression as well (P<0.0001). While nodal (df=0) status and CA19-9 (P=0.078) failed to emerge as significant covariates on forward stepwise regression and was excluded from the final model.

Analysis of predictive prognostic value of PLR and NLR by subgroup analysis. subgroup survival analysis according to PLR and NLR showed PLR was predictive marker in subgroup (male, CA19-9 below-cutoff, jaundice, Mediated/high Differentiation subgroup, rather than other subgroups. While NLR show prognostic value in subgroup (age ≤60 years, CA19-9 above cut-off, jaundice and mediated/high differentiation subgroup) rather than the other subgroups (data not shown). After adjusting for interfering factors related to PLR/NLR and/or probability of tumor recurrence, low NLR patients continued to display a better outcome with bordline difference (P=0.0637) (Fig. 1B). Particularly, significant differences were shown in postmenopausal patients (HR=2.81, 95% CI 1.14 to 6.88, P=0.0243), node negative cancers (HR=5.31, 95% CI 1.19 to 23.70, P=0.0292) (data not shown).

Discussion

The present study identified preoperative PLR as an independent prognostic factor for curative resectable ampullary carcinoma. The results were in agreement with a previous report by Smith *et al* (7); however, as it was based on a larger

Table III. The association between preoperative indices and postoperative histological characteristics using χ^2.

Characteristics	CA19-9 (kU/l)			Tbil (μmol/l)			PLR			NLR		
	≤255.5	>255.5	P-value	≤190	>190	P-value	≤226.83	>226.83	P-value	≤2.58	>2.58	P-value
LN			0.361			0.733			<0.001[a]			0.148
LN (+)	22	7		30	5		12	23		13	22	
LN (-)	31	16		49	10		51	8		31	28	
Tumor			0.128			0.215			>0.100			0.889
Well/moderate	39	16		60	9		54	15		32	37	
Poor	11	10		19	6		20	5		12	13	
Stage			0.096			0.211			0.058			0.068
0 and I	20	5		29	3		28	4		20	12	
II	11	11		20	7		23	4		11	16	
III and IV	19	10		30	5		23	12		13	22	

[a]P<0.001. CA19-9, Carbohydrate antigen 19-9; Tbil, total bilirubin; PLR, preoperative platelet-lymphocyte ratio; NLR, preoperative neutrophil-lymphocyte ratio; LN, lymph node.

number of cases, the present study contained more detailed analyses, and was performed in accordance with, at the time of analysis, the most up to date AJCC (21). The definition of tumor stage, which was adjusted by evidence-based studies, demonstrated a better guidance for the prognosis in ampullary cancer (1,21). Furthermore, the present study extracted the first examination results of all the preoperative indices to exclude potentially influencing variables, including the preoperative bile drainage. In terms of the optimum cut-off values of CA19-9, bilirubin and PLR, various cut-off values were borrowed from previous ampullary carcinomas and other solid carcinomas studies (24,25). Firstly, the maximally selected log-rank statistics, the statistical analysis designed for the optimum cut-off value of continuous variable based on the Log-rank survival analysis were applied, which was run in R software (26) (data not shown). To some extent, it contributed to the conclusion that the preoperative PLR was related to the lymph node involvement and prognosis in ampullary cancer following surgical resection.

Furthermore, in the present study, a risk prediction model was established using PLR and Tbil, which demonstrated a good performance in univariate (P=0.0004) and multivariate (P<0.0001) survival analysis. While the risk model using PLR and CA19-9 demonstrated a less satisfactory performance with (P=0.002) and showed dependent predictive value at the expense of all the other predictors (P<0.05). This maybe partly due to the correlation between the CA19-9 and TNM notwithstanding the border significant difference (P=0.053) and between PLR and nodal involvement (P=0.025).

The present study demonstrates for the first time, to the best of our knowledge, the prognostic role of NLR in resectable ampullary cancer and the prognostic value of PLR/NLR in specific patient subgroups, as the PLR exhibited a prognostic value in a number of specific subgroups, including males, CA19-9 below cutoff, jaundice and mediated/high differentiation subgroups. While NLR exhibited prognostic value in subgroup (age ≤60 years, CA19-9 above cut-off, jaundice, Mediated/high Differentiation subgroup) in spite of border significance in univariate analysis (P=0.0637; Table II). Previous studies (27,28) have indicated that NLR was a potential independent and significant indicator of a positive outcome in patients with carcinoma of the ampulla of Vater following a pancreaticoduodenectomy. The present study was similar with the conclusions of Haruki *et al* (27) with a larger study case 94 vs. 37 patients. An additional similar study, with a patient cohort of 87 patients concluded that high NLR had a significantly worse Eastern Cooperative Oncology Group performance score as well as an independent and significant predictive factor of prognosis in patients with ampullary carcinoma (26). However, the present study demonstrated that the predictive roles of NLR for LN metastasis. Two previous meta-analysis regarding the prognostic role of NLR in cancer concluded that a high-pretreatment blood NLR may serve as an adverse prognostic indicator for patients with advanced tumors (29) and predictor of survival in patients with pancreatic cancer (30). However, a previous study reported that a cut-off value of 5 indicated a worst progression free survival (HR 2.23, 95% CI 1.54-3.23, P=0.019) (29). A latter study included a total of 2,035 patients in 9 cohorts and suggested that an elevated NLR was a predictor of survival in patients with pancreatic

Table IV. Multivariate (Cox proportional hazards) survival analysis.

Characteristics	Coefficient	SE	Wald	HR	95% CI	P-value
PLR	1.099	0.144	58.412	3.001	2.264-3.978	<0.001
Tbil (μmol/l)						<0.001
Tb<17.1	-	-	35.548	-	-	
Tb<190	1.634	0.279	34.310	5.125	2.966-8.854	
Tb≤190	1.446	0.351	16.985	4.245	2.134-8.442	
CA19-9	0.416	0.137	9.185	1.516	1.158-1.984	0.002
Differentiation	1.450	0.176	67.999	4.264	3.021-6.019	<0.001
Stage (21)						<0.001
0 and I	-	-	-	-	-	
II	1.307	0.234	31.126	3.697	2.335-5.852	
III and IV	2.416	0.217	123.429	11.200	7.313-17.152	

CI, confidence interval; SE, standard error of regression coefficient; HR, hazard ratio; Tbil, total bilirubin; CA19-9, Carbohydrate antigen 19-9.

Table V. Tumor characteristics according to total bilirubin/platelet-lymphocyte ratio risk stratification.

Characteristics	High	Intermediate	Low	P-value
Lymph node status				0.206
LN(+)	3	16	16	
LN(-)	3	18	38	
Differentiation				0.682
Well/moderate	6	21	42	
Poor	2	10	13	
Resection margin status				0.058
Positive	1	0	0	
Negative	5	30	59	
Preoperative biliary stenting				0.702
No	2	13	29	
Yes	3	17	27	
Adjuvant therapy received				<0.01[a]
No	2	26	54	
Yes	4	4	4	
Stage (21)				0.086
0 and I	0	10	22	
II	3	7	17	
III and IV	3	14	18	

[a]P<0.01. P-value was calculated using Fisher's exact text. LN, lymph node.

cancer without analyzing the cut-off values heterogeneity (28). More large-scale perspective studies, which include a training cohort (the cohort used to calculate the optimum cut-off values as an independent cohort) and validated cohort (a cohort used to validate the efficiency and validity of the optimum cut-off values based on the training cohort) are needed in the future to determine the optimal cut-off values. Additionally, concerning the clinical role of NLR, more detailed studies included the subgroups analysis or propensity score analysis are required to exclude confounding factors.

In 8th AJCC, the assessment of lymph node metastasis was used to predict the prognosis (21). When the OS time was compared according to the lymph node metastasis, the prognostic correlation for patients with N1 (number of metastatic lymph nodes ≥1) or N2 (number of metastatic lymph nodes ≥4) was not clear (21). In addition, in the present study OS time was compared according to the stage, and tumor differentiation, there were no significant differences between stage 0 and I or between well and moderate differentiation. Furthermore, there were no significant effects of nerve or

Table VI. Cox regression Tbil/PLR risk stratification and tumor histlogical characteristics.

Variable	Coefficient (B)	SE	Wald	HR	95% CI	P-value
Tbil/PLR risk groups						
Low risk	-	-	-	-	-	-
Intermediate risk	0.58	0.111	27.325	1.786	1.437-2.220	<0.001
High risk	2.993	0.352	72.395	19.973	10.006-39.723	<0.001
Stage (21)						
0 and I	-	-	-	-	-	-
II	1.671	0.227	54.239	5.317	3.408-8.295	<0.001
II and IV	2.789	0.215	168.955	16.266	10.682-24.771	<0.001

SE, standard error of regression coefficient; HR hazard ratio; Tbil, total bilirubin; PLR, preoperative platelet-lymphocyte ratio.

vessel invasion. Following combined and the aforementioned variables were adjusted and, the lymph status, TNM stage and tumor differentiation were demonstrated as independent prognostic indices for the ampullary cancers which were consistent with the AJCC stage based evidences.

In addition, the present study demonstrated that PLR could serve as a predictor for the lymph node (LN) metastasis in the patient cohort of the present study by χ^2 test (shown in Table III). LN metastasis is the strongest prognostic predictor for ampullary cancer, while preoperative serum CA19-9 was not associated with the TNM stage, pathologic differentiation or the tumor size (31-33) (shown in Table III), which may serve as an explanation for the prognostic role of PLR.

However, the cut-off values of PLR were not consistent in different study backgrounds. Some studies have reported that a PLR >300 could predict a worse survival in ovarian cancers (34,35), whereas other studies have reported different PLR values from 203 to 299 as prognostic factors in ovarian cancer (36,37). In resectable gastric cancer, higher pre-operative PLR at cut-off 208 showed decreased overall survival time and disease-free survival (24). Another study about advanced pancreatic cancer proved that patients divided by PLR <200 vs. ≥200 with 9.1 vs. 4 months overall survival time, respectively (25). In present study, the optimum PLR cut-off value was calculated at 226.83 to predict overall survival following curative surgery.

The critical prognostic role of preoperative PLR in ampullary cancers is well known; however, its mechanism of action has not been completely elucidated in previous studies (7,38). Previous research has demonstrated that tumor cells could increase the peripheral blood platelet count via proinflammatory mediators and other mechanisms such as CA19-9 induced inflammatory molecules (39-43). Meanwhile, these inflammatory factors could also decrease the lymphocyte counts such as IL-6 (43,44). Furthermore, the role of platelets as a negative regulator in immune system has been recently demonstrated, reporting that platelet was the main regulator to decrease the adoptive T cell count and obliterate its immunologic function *in vitro* by producing transforming growth factor (TGF)-β (45). Therefore, the platelet to lymphocyte ratio could be considered as a relative active inflammation or/and inhibitive immune reaction (46). Platelet count increase has been observed in numerous types of tumors at earlier century and then proved to be a negative predictor in some cancers latterly (47-49). As critical roles in host immune response, lower levels of lymphocytes were associated with a poor prognosis of a variety of tumor types, including breast and colon cancer (50). Therefore, high level of PLR was associated with poor prognosis of many various solid tumors (51). These results have the potential to provide evidence for the antitumor role of the anti-platelet drugs.

Referring to the lymph node metastasis, studies have previously reported that PLR may have the prospective potential to predict nodal involvement in patients with gastric cancer (29), vulvular squamous cell sarcoma (30), and endometrial adenocarcinoma (31). The majority of these demonstrated a higher PLR in nodal involvement group, which was also observed in the present study (30,31); however, a single hemolytic inflammatory index is not a practical guide in clinical use for the accurate predication of lymph node metastasis. Therefore, other studies concerning PLR should include other preoperative indicators such as NLR (29) and contrast-enhanced computerized tomography (52) to establish a model with satisfactory specificity and sensitivity to predict nodal involvement.

Previous studies demonstrated that CA19-9 and bilirubin are independent prognostic factors in present study despite different cut-off values (5,8). Additionally, to the best of our knowledge, there is no existing evidence suggesting that preoperative biliary stenting has an influence on operative mortality or subsequent survival following a pancreaticoduodenectomy (53-55), an adjusted cut-off value of bilirubin to 190 µmol/l (elevated the best cut-off via maximally selected log-rank statistics) was used for the survival benefit of preoperative biliary drainge. Sex showed no significance in univariate survival analysis of median survival time 42 months for males and >60 months for females (P=0.7746). Age with median survival time of 42 months vs. >60 months at a cut off 58 years old (P=0.1749 demonstrated no significant impact in the overall survival between the patients with and without preoperative biliary drainage at cut-off 190 µmol/l (data not shown). Similarly, there was no significant difference in survival with and without postoperative adjuvant chemotherapy with a median survival >60 vs. 46 months in line with previous studies (56-58). Hence, age, sex, preoperative biliary drainage and adjuvant therapy were unlikely to act as a significant confounding factors when interpreting the survival data.

In addition, it is well established that CA19-9 is positively correlated with bilirubin (9-11). Therefore, these two prognostic markers and the PLR alongside with other univariates with statistics significance in Kaplan-Meier analyses were analyzed using Cox Log-rank proportional hazards with forward step-wise regression. Elevated preoperative CA19-9 level, bilirubin level, PLR, poor differentiation, nodal metastases, and advanced stage all exhibited the trend toward poorer survival in univariate and multivariate analysis, which was consistent with the results obtained by previous studies (6,11). Additionally, a previous study demonstrated that preoperative elevated serum CA19-9 (cut-off 36 kU/l) and total bilirubin (cut-off 1 mg/ml) levels were prognostic factors in ampullary adenocarcinoma and demonstrated an association with the pathological pancreatobiliary type that which proved aggressively invasive, which was closely associated with poor survival (2).

Jaundice was the most common symptom (50%, 47/94) in the present study, which is similar to previous studies, which accounted for 70-80% of the chief patient complaint (59,60). The decline in component ratio of jaundice in the present study may be attributed to the advanced economic and medical factors in China. The remaining chief complaints consist of physical discomfort (15.95%, 15/94) and other atypical digestive system complaints including abdominal pain (34.04%, 32/94). Jaundice is a prognostic factor in univariate Log-Rank analysis compared with a physical discomfort group (P=0.00095, >60 vs. 40 months). This supports the survival analysis of total bilirubin. So even compared with the atypical digestive symptom (P=0.0034, >60 vs. 30 months). However there was no significance between the jaundice and other atypical digestive symptoms (P=0.3291, 40 vs. 30 months).

The present study also had some limitations that should not be ignored. Firstly, as a respective study in a single center, all the indexes and pathological were collected from a computerized database, consequently the study cohort may have some unintentional selection bias. Secondly, the optimum cut-off was specifically suitable for the current patients cohort of 94 cases regarding the survival analysis. Finally, the relationship between certain peripheral hematological inflammatory components and the tumor histological items were not assessed in the present study, such as the novel pathological type neuroendocrine tumor. Thus, further large-scale prospective studies are required to verify the results obtained. Furthermore, other specific markers associated with ampullary carcinoma require investigation in future study.

Preoperative PLR and NLR possesses further evaluation as prognostic indices in curative resected ampullary carcinoma. Preoperative PLR is a candidate predictor for lymph node metastasis.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author's contributions

XH contributed to the conception and design of the study. WL and NZ contributed to the analysis data for the study. WW drafted the study and analyzed the data.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Peking Union Medical College Hospital, and all the participants have included the consent forms.

Patient consent for publication

All the patients provided consent for publication.

Competing interests

All the authors declare that they have no conflict of interests.

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