



## Role of systemic inflammation in predicting the prognosis of ampulla of Vater carcinoma

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### ABSTRACT

**Background:** Ampulla of Vater carcinoma (AVC) is known to have better prognosis than other periampullary cancers that need pancreaticoduodenectomy for cure. However, up to 60% of patients who underwent curative resection develop recurrence, and the disease progresses rapidly in many patients. Inflammatory factors are known to be prognostic indicators related to poor overall survival (OS) in patients with other gastrointestinal cancers. This retrospective review aimed to assess the prognostic significance of the preoperative neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and Glasgow Prognostic Score (GPS) in patients who underwent curative resection for AVC.

**Method:** We retrospectively reviewed and abstracted data from the medical records of 169 patients who underwent surgical resection for AVC from January 2009 through December 2013. We investigated the association between the preoperative NLR, PLR, and GPS and disease-free survival (DFS) and OS.

**Results:** In multivariable analysis, both high NLR and PLR were not associated with poor DFS but were significantly related to poor OS (NLR: hazard ratio [HR] 1.916, 95% confidence interval [CI] 1.181–3.108,  $p = 0.008$ ; PLR: HR 1.758, 95% CI 1.071–2.886,  $p = 0.026$ ). GPS was not a significant prognostic factor for either DFS or OS in both univariable and multivariable analyses. Young age was not related to OS but was significantly associated with poor DFS in both univariable and multivariable analyses (HR 0.356, 95% CI 0.163–0.778,  $p = 0.010$ ).

**Conclusion:** As systemic inflammatory markers, high preoperative NLR and PLR were related to poor OS in patients with AVC with curative resection.

### 1. Introduction

Ampulla of Vater carcinoma (AVC) is a rare malignancy, comprising < 1% of all gastrointestinal malignancies [1–6]. However, it is the second most common periampullary cancer, accounting for 12.7–32.2% of surgically resectable periampullary cancers [2,4–6]. In Korea, the incidence of AVC is higher than that in other countries [7]. AVC shows a better prognosis than other periampullary cancers that need pancreaticoduodenectomy for cure, such as pancreatic and distal bile duct malignancies [3,4,6,8,9]. One of the plausible explanations is that AVC causes ampullary obstruction earlier in its natural course and the subsequent typical obstructive symptoms, such as painless jaundice,

may manifest and be detectable in the early stage of the disease [3,8]. Consequently, the curative resection rate of AVC (50–60%) is higher than that of other periampullary cancers, and the 5-year overall survival (OS) has also been reported to be higher (40.6–68%) [1–3,9,10]. However, up to 60% of patients who undergo curative resection experience recurrence and the disease progresses rapidly in many patients [3,4,9,10].

Chemotherapy and chemoradiation have been reported effective adjuvant treatment modalities in general biliary tract cancer including AVC; however, no standard adjuvant treatment has been established. The rarity of the disease and its relatively favourable prognosis may be the main reasons for the ambiguities in the application of adjuvant

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treatment [3,8,10]. Although the TNM (tumor, node, metastasis) stage is considered to be the most important prognostic factor, there remains a clinical need for additional prognostic factors that can help in making more accurate prognostic predictions [1–3,9,10].

Since the relationship between cancer and inflammation was proposed by Virchow in 1863 [11,12], several systemic inflammatory factors have been reported in patients with gastrointestinal cancers, including pancreatic cancer [12–20]. The Glasgow Prognostic Score (GPS; calculated as the combination of preoperative serum C-reactive protein [CRP] and albumin concentrations), preoperative neutrophil-to-lymphocyte ratio (NLR), and preoperative platelet-to-lymphocyte ratio (PLR) have been suggested as factors predicting the prognosis of several different types of cancer [1,2,12–19,21,22].

Some investigators have reported the correlation between the above-mentioned inflammatory factors and the prognosis of AVC; however, the evidence remains insufficient [1,2,22]. Therefore, we aimed to assess the prognostic significance of the preoperative NLR, PLR, and GPS in patients who have had curative resection for AVC.

## 2. Methods

We retrospectively reviewed and abstracted data from the medical records of 169 patients who underwent surgical resection for AVC from January 2009 through December 2013 at the Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine. Of these patients, 3 were excluded because of having non-curative resection. One of the excluded patients had a mesenteric mass that was revealed to be a metastatic adenocarcinoma by frozen biopsy during the operation. Another patient had hepatic metastasis that was not found in the preoperative evaluation. The other patient had residual multiple metastatic lymph nodes after surgical resection. In addition, another 3 patients were excluded because of a histological diagnosis of neuroendocrine carcinoma. Finally, the remaining 163 patients were included for the analysis (Fig. 1).

Preoperative serological values were routinely measured for each patient, and the latest results of preoperative laboratory tests were used in this study. Absolute white blood cell and subset counts and other serological markers were routinely determined in peripheral venous samples. Pathological TNM stage was determined according to the 8th edition of the Cancer Staging Manual of the American Joint Commission on Cancer [23].

The NLR was calculated by dividing the neutrophil count by the lymphocyte count [1,12–14,16–18,21,22]. Similarly, the PLR was determined as the ratio of the platelet count and the lymphocyte count [13,14]. The GPS was calculated as previously described [2,15,16,21], and all patients were classified into 3 groups according to GPS, as follows: GPS 0, normal albumin ( $\geq 3.5$  g/dL) and normal CRP ( $\leq 1.0$  mg/dL);

GPS 1, low albumin ( $< 3.5$  g/dL) or elevated CRP ( $> 1.0$  mg/dL); and GPS 2, both low albumin ( $< 3.5$  g/dL) and elevated CRP ( $> 1.0$  mg/dL). Complications after surgical resection were categorized according to the Clavien-Dindo classification of surgical complications [24].

Recurrence of AVC was defined as newly detected local or distant metastatic tumors by imaging modalities including ultrasonography, computed tomography, magnetic resonance imaging, or positron emission tomography-computed tomography, with or without increases in serum tumor markers.

In this study, we retrospectively investigated the association between preoperative NLR and postoperative disease-free survival (DFS) and OS in patients with AVC undergoing surgical resection. The same investigation was done to evaluate the association between PLR and DFS and OS. In addition, as a subgroup analysis, the association between GPS and DFS and OS was investigated in the same manner.

### 2.1. Statistical analysis

Statistical analyses were conducted using PASW statistics version 18.0 (IBM Corp., Armonk, NY, USA). Categorical variables were presented as numbers and percentages, and continuous variables were expressed as mean  $\pm$  standard deviation. We analysed the correlations between clinicopathological variables and DFS or OS after surgical resection by using univariable analysis. The following variables were evaluated: age, sex, co-morbidity, American Society of Anesthesiologists (ASA) score, the type of operation, presence of preoperative biliary drainage, duration of operation, transfusion, tumor markers (carbohydrate antigen 19–9, carcinoembryonic antigen), complications after surgical resection, tumor stage based on pathology (pT stage), status of lymph node metastasis based on pathology (pN stage), resection margin involvement, adjuvant therapy, NLR, PLR, and GPS.

The clinicopathological continuous variables were classified into 2 groups for the survival analysis, as follows: age  $< 65$  or  $\geq 65$  years as in a previous study [1], and duration of operation  $< 400$  or  $\geq 400$  min as the approximate value of the mean. The cut-off values of NLR and PLR were determined as the approximate values of their medians (NLR median: 1.75, PLR median: 128.96).

Next, we investigated the relationship between clinicopathological variables and each inflammatory factor by using the  $\chi^2$  test and linear relationship to evaluate the differences of baseline characteristics in each group.

The Cox proportional regression model was used for both univariable and multivariable analyses. Univariable analysis was performed to evaluate the prognostic significance of each variable, and results were presented as crude hazard ratios (HRs) with 95% confidence intervals (CIs). Adjusted HR was calculated using the Cox proportional regression model with the variables that had a significant crude HR or difference in the  $\chi^2$  test. All values were considered statistically significant at  $p < 0.05$ .

## 3. Results

The mean age of the 163 patients was  $61.77 \pm 9.82$  years; 78 (47.9%) of them were men and 85 (52.1%) were women. Of the 163 patients, 12 (7.3%) underwent laparoscopic surgical resection. Preoperative biliary drainage was performed in 110 (67.5%) patients. A total of 69 (42.3%) patients had an operation time of  $> 400$  min, and 48 (29.4%) patients needed red blood cell transfusion during the operation. The percentage of patients with preoperative NLR  $\geq 2$  was 39.3%, and that with PLR  $\geq 130$  was 48.5%. In 132 of 163 patients, the GPS could be determined, as follows: 0 in 66 (40.5%), 1 in 49 (30.1%), and 2 in 17 (10.4%) patients. The baseline characteristics and the results of univariable analysis between each of the variables and DFS or OS are shown in Tables 1a and 1b.

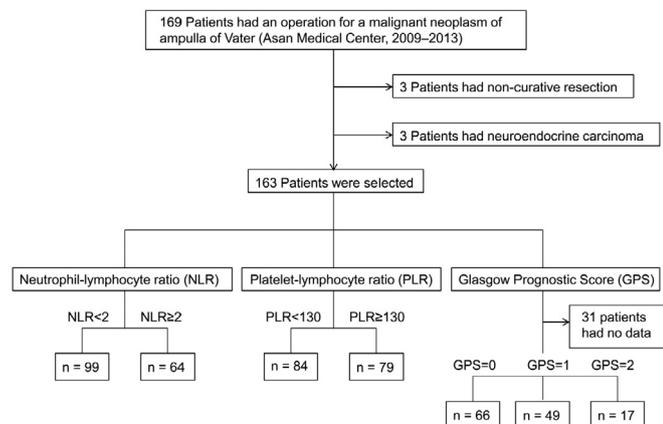


Fig. 1. Overview of patient selection.

**Table 1a**  
Patients' characteristics of clinicopathological variables. (Total N = 163).

Factor	No. patients (%)	Mean ± SD	Range
Age (years)		61.77 ± 9.82	39–94
< 65	100 (61.3)		
≥ 65	63 (38.7)		
Sex			
Male	78 (47.9)		
Female	85 (52.1)		
Co-morbidity			
No	75 (46.0)		
Yes	88 (54.0)		
ASA score			
1	14 (8.6)		
2	144 (88.3)		
3	5 (3.1)		
Operation			
PPPD & PD & TDA & TP	151 (92.7)		
Lap-PPPD & Lap-PD	12 (7.3)		
Preoperative biliary drainage			
Absent	53 (32.5)		
Present	110 (67.5)		
Duration of operation (min)		402.2 ± 88.84	161–725
< 400	94 (57.7)		
≥ 400	69 (42.3)		
Transfusion			
No	115 (70.6)		
Yes	48 (29.4)		
CA 19-9		108.22 ± 524.13	0.60–5470.00
Normal	114 (69.9)		
Elevated (> 37 U/mL)	45 (27.6)		
No data	4 (2.5)		
CEA		2.77 ± 4.71	0.36–40.90
Normal	127 (77.9)		
Elevated (> 5 ng/mL)	11 (6.7)		
No data	25 (15.3)		
Complications (Clavien-Dindo classification)			
None	2 (1.2)		
Grade I	31 (19.0)		
≥ Grade II	130 (79.8)		
≥ Grade IIIa	19 (11.7)		
pT stage			
T1 & T2	74 (45.4)		
T3 & T4	89 (54.6)		
LN metastasis			
Absent	105 (64.4)		
Present	58 (35.6)		
Resection margin involvement			
No	161 (98.8)		
Yes	2 (1.2)		
Adjuvant therapy			
No	114 (69.9)		
Yes	49 (30.1)		
Neutrophil-lymphocyte ratio (NLR)		2.17 ± 1.48	0.55–10.29
< 2	99 (60.7)		
≥ 2	64 (39.3)		
Platelet-lymphocyte ratio (PLR)		154.96 ± 81.67	22.6–505.05
< 130	84 (51.5)		
≥ 130	79 (48.5)		
Glasgow Prognostic Score (GPS)			
0	66 (40.5)		
1	49 (30.1)		
2	17 (10.4)		
No data	31 (19.0)		

SD = standard deviation.

ASA = American Society of Anesthesiologists.

PPPD = pylorus-preserving pancreatoduodenectomy.

PD = pancreatoduodenectomy.

TDA = Transduodenal ampullectomy.

TP = Total pancreatectomy.

Lap-PPPD = laparoscopic pylorus-preserving pancreatoduodenectomy.

Lap-PD = laparoscopic pancreatoduodenectomy.

CA 19–9 = cancer antigen 19-9.

CEA = carcinoembryonic antigen.

LN = lymph node.

In univariable analysis, patients with elevated tumor markers (HR 2.148, 95% CI 1.233–3.742), advanced pT stage (HR 3.900, 95% CI 2.044–7.439), lymph node metastasis (HR 3.577, 95% CI 2.071–6.178), resection margin involvement (HR 4.433, 95% CI 1.074–18.295), PLR ≥ 130 (HR 2.042, 95% CI 1.171–3.561), and adjuvant therapy (HR 3.369, 95% CI 1.959–5.793) had significantly worse DFS. Meanwhile, OS was significantly worse in patients with advanced pT stage (HR 3.411, 95% CI 1.960–5.933) and pN stage (HR 3.605, 95% CI 2.207–5.888), resection margin involvement (HR 4.311, 95% CI 1.051–17.673), high PLR (HR 1.896, 95% CI 1.159–3.102), and adjuvant therapy (HR 2.092, 95% CI 1.288–3.401). Moreover, higher NLR was significantly associated with worse OS (HR 1.901, 95% CI 1.176–3.072) (Tables 1–2).

The clinicopathological features between the high and low NLR, PLR, and GPS groups are summarized in Table 2. High NLR was significantly associated with younger age ( $p = 0.039$ ) and the presence of preoperative biliary drainage ( $p = 0.047$ ). There was a significant association between high PLR and female sex ( $p = 0.014$ ). There was no significant association between GPS and other clinicopathological variables.

Tables 3–5 show the relationship between each inflammatory marker and DFS or OS. In multivariable analyses of each inflammatory marker and the variables which had a significant crude HR or difference in the  $\chi^2$  test, pathological variables such as advanced pT stage (DFS: HR 2.790, 95% CI 1.340–5.808,  $p = 0.006$ ; OS: HR 2.927, 95% CI 1.649–5.197,  $p < 0.001$ ), lymph node metastasis (DFS: HR 3.116, 95% CI 1.657–5.859,  $p < 0.001$ ; OS: HR 3.027, 95% CI 1.818–5.041,  $p = < 0.001$ ), and resection margin involvement (DFS: HR 11.364, 95% CI 2.288–56.439,  $p = 0.003$ ; OS: HR 10.619, 95% CI 2.418–46.632,  $p = 0.002$ ) had significant associations with both DFS and OS. High NLR (HR 1.916, 95% CI 1.181–3.108,  $p = 0.008$ ) and high PLR (HR 1.758, 95% CI 1.071–2.886,  $p = 0.026$ ) were significantly related to OS but were not related to DFS. On the other hand, GPS was not associated with either DFS or OS.

#### 4. Discussion

In this study, both high NLR and PLR were not associated with poor DFS, but they were significantly related to poor OS (NLR: HR 1.916, 95% CI 1.181–3.108,  $p = 0.008$ ; PLR: HR 1.758, 95% CI 1.071–2.886,  $p = 0.026$ ). On the other hand, GPS was not significant as a prognostic factor for either DFS or OS in both univariable and multivariable analyses. Young age was not related to OS but was significantly associated with poor DFS in both univariable and multivariable analyses (HR 0.356, 95% CI 0.163–0.778,  $p = 0.010$ ).

In previous studies, tumor-related parameters, including TNM stage, lymphovascular invasion, perineural invasion, tumor differentiation type, and surgical margin involvement, have been reported as prognostic factors after surgical resection in patients with AVC [4–6,8,9,25–27]. Moreover, several recent studies have revealed similar results showing that patient-related factors or serological markers, especially indicators of systemic inflammatory responses such as NLR, PLR, and GPS, are prognostic factors for AVC as well as tumor-related parameters [1,2,22]. In this study, advanced pathologic T stage, regional lymph node metastasis, and resection margin involvement were independent and significant prognostic factors of poor DFS and OS in AVC. Furthermore, high NLR and PLR were also significant independent risk factors of OS in AVC. However, GPS was not significantly associated with DFS or OS in this study.

A few studies have provided clues to explain the relationship between high NLR or high PLR and poor prognosis in patients with malignancies. Neutrophilia may contribute to the development and progression of cancer by releasing cytokines such as vascular endothelial

**Table 1b**  
Univariable analyses of clinicopathological variables in relation to DFS and OS after surgical resection for AVC.

Factor	DFS HR (95% CI, P value)	OS HR (95% CI, P value)
Age (years)		
< 65		
≥ 65	0.412 (0.212–0.801, p = 0.009)	1.039 (0.636–1.699, p = 0.878)
Sex		
Male		
Female	0.704 (0.410–1.210, p = 0.204)	0.747 (0.462–1.207, p = 0.234)
Co-morbidity		
No		
Yes	0.788 (0.459–1.351, p = 0.386)	1.048 (0.647–1.698, p = 0.849)
ASA score		
1		
2	1.369 (0.493–3.796, p = 0.546)	2.022 (0.632–6.463, p = 0.235)
3	1.980 (0.221–17.750, p = 0.542)	7.212 (1.612–32.278, p = 0.010)
Operation		
PPPD & PD & TDA & TP		
Lap-PPPD & Lap-PD	1.023 (0.369–2.834, p = 0.966)	0.864 (0.314–2.380, p = 0.778)
Preoperative biliary drainage		
Absent		
Present	1.661 (0.888–3.107, p = 0.112)	1.594 (0.919–2.765, p = 0.097)
Duration of operation (min)		
< 400		
≥ 400	1.322 (0.771–2.268, p = 0.310)	1.110 (0.684–1.802, p = 0.671)
Transfusion		
No		
Yes	1.613 (0.925–2.813, p = 0.092)	1.438 (0.876–2.361, p = 0.151)
CA 19-9		
Normal		
Elevated (> 37 U/mL)	2.148 (1.233–3.742, p = 0.007)	1.514 (0.903–2.538, p = 0.116)
CEA		
Normal		
Elevated (> 5 ng/mL)	2.481 (1.104–5.573, p = 0.028)	1.712 (0.733–3.997, p = 0.214)
Complications (Clavien-Dindo classification)		
≥ Grade II	1.985 (0.848–4.643) p = 0.114	1.269 (0.665–2.422, p = 0.471)
≥ Grade IIIa	0.600(0.217–1.664, p = 0.327)	0.843(0.385–1.845, p = 0.668)
pT stage		
T1 & T2		
T3 & T4	3.900 (2.044–7.439, p < 0.001)	3.411 (1.960–5.933, p < 0.001)
LN metastasis		
Absent		
Present	3.577 (2.071–6.178, p < 0.001)	3.605 (2.207–5.888, p < 0.001)
Resection margin involvement		
No		
Yes	4.433 (1.074–18.295, p = 0.039)	4.311 (1.051–17.673, p = 0.042)
Adjuvant therapy		
No		
Yes	3.369 (1.959–5.793, p < 0.001)	2.092 (1.288–3.401, p = 0.003)
Neutrophil-lymphocyte ratio (NLR)		
< 2		
≥ 2	1.640 (0.954–2.819, p = 0.074)	1.901 (1.176–3.072, p = 0.009)
Platelet-lymphocyte ratio (PLR)		
< 130		
≥ 130	2.042 (1.171–3.561, p = 0.012)	1.896 (1.159–3.102, p = 0.011)
Glasgow Prognostic Score (GPS)		
0		
1	1.006 (0.528–1.915, p = 0.987)	1.116 (0.620–2.010, p = 0.714)
2	1.821 (0.810–4.092, p = 0.147)	1.352 (0.610–2.997, p = 0.458)

DFS = disease-free survival.

OS = overall survival.

HR = hazard ratio.

CI = confidence interval.

ASA = American Society of Anesthesiologists.

PPPD = pylorus-preserving pancreatoduodenectomy.

PD = pancreatoduodenectomy.

TDA = Transduodenal ampullectomy.

TP = Total pancreatectomy.

Lap-PPPD = laparoscopic pylorus-preserving pancreatoduodenectomy.

Lap-PD = laparoscopic pancreatoduodenectomy.

CA 19-9 = cancer antigen 19-9.

CEA = carcinoembryonic antigen.

LN = lymph node.

**Table 2**  
Clinicopathological features of patients according to the inflammation-based prognostic scores.

Factor	NLR		P value	PLR		P value	GPS			P value
	< 2 (n = 99)	≥2 (n = 64)		< 130 (n = 84)	≥ 130 (n = 79)		0 (n = 66)	1 (n = 49)	2 (n = 17)	
Age (years)			0.039			0.881				0.078
< 65	67 (67.7%)	33 (51.6%)		52 (61.9%)	48 (60.8%)		46 (69.7%)	26 (53.1%)	9 (52.9%)	
≥ 65	32 (32.3%)	31 (48.4%)		32 (38.1%)	31 (39.2%)		20 (30.3%)	23 (46.9%)	8 (47.1%)	
Sex			0.399			0.014				0.736
Male	50 (50.5%)	28 (43.8%)		48 (57.1%)	30 (38.0%)		32 (48.5%)	21 (42.9%)	8 (47.1%)	
Female	49 (49.5%)	36 (56.3%)		36 (42.9%)	49 (62.0%)		34 (51.5%)	28 (57.1%)	9 (52.9%)	
Co-morbidity			0.267			0.604				0.371
No	49 (49.5%)	26 (40.6%)		37 (44.0%)	38 (48.1%)		33 (50.0%)	24 (49.0%)	6 (35.3%)	
Yes	50 (50.5%)	38 (59.4%)		47 (56.0%)	41 (51.9%)		33 (50.0%)	25 (51.0%)	11 (64.7%)	
ASA score			0.094			0.221				0.394
1	12 (12.1%)	2 (3.1%)		6 (7.1%)	8 (10.1%)		6 (9.1%)	2 (4.1%)	1 (5.9%)	
2	84 (84.8%)	60 (93.8%)		74 (88.1%)	70 (88.6%)		58 (87.9%)	46 (93.9%)	15 (88.2%)	
3	3 (3.0%)	2 (3.1%)		4 (4.8%)	1 (1.3%)		2 (3.0%)	1 (2.0%)	1 (5.9%)	
Operation			1.000			0.624				0.814
PPPD & PD & TDA & TP	92 (92.9%)	59 (92.2%)		77 (91.7%)	74 (93.7%)		59 (89.4%)	46 (93.9%)	15 (88.2%)	
Lap-PPPD & Lap-PD	7 (7.1%)	5 (7.8%)		7 (8.3%)	5 (6.3%)		7 (10.6%)	3 (6.1%)	2 (11.8%)	
Preoperative biliary drainage			0.047			0.369				0.077
Absent	38 (38.4%)	15 (23.4%)		30 (35.7%)	23 (29.1%)		24 (36.4%)	12 (24.5%)	3 (17.6%)	
Present	61 (61.6%)	49 (76.6%)		54 (64.3%)	56 (70.9%)		42 (63.6%)	37 (75.5%)	14 (82.4%)	
Duration of operation (min)			0.345			0.859				0.197
< 400	60 (60.6%)	34 (53.1%)		49 (58.3%)	45 (57.0%)		39 (59.1%)	30 (61.2%)	6 (35.3%)	
≥ 400	39 (39.4%)	30 (46.9%)		35 (41.7%)	34 (43.0%)		27 (40.9%)	19 (38.8%)	11 (64.7%)	
Transfusion			0.144			0.103				0.137
No	74 (74.7%)	41 (64.1%)		64 (76.2%)	51 (64.6%)		51 (77.3%)	31 (63.3%)	11 (64.7%)	
Yes	25 (25.3%)	23 (35.9%)		20 (23.8%)	28 (35.4%)		15 (22.7%)	18 (36.7%)	6 (35.3%)	
CA 19-9	n = 98	n = 61	0.924	n = 84	n = 75	0.936	n = 65	n = 47	n = 17	0.135
Normal	70 (71.4%)	44 (72.1%)		60 (71.4%)	54 (72.0%)		53 (81.5%)	27 (57.4%)	13 (76.5%)	
Elevated	28 (28.6%)	17 (27.9%)		24 (28.6%)	21 (28.0%)		12 (18.5%)	20 (42.6%)	4(23.5%)	
No data	4									
CEA	n = 85	n = 53	0.749	n = 75	n = 63	0.212	n = 55	n = 41	n = 15	0.331
Normal	79 (92.9%)	48 (90.6%)		71 (94.7%)	56 (88.9%)		53 (96.4%)	36 (87.8%)	14 (93.3%)	
Elevated	6 (7.1%)	5 (9.4%)		4 (5.3%)	7 (11.1%)		2 (3.6%)	5 (12.2%)	1 (6.7%)	
No data	25									
Complication			0.238			0.698				0.887
< Grade II	23 (23.2%)	10 (15.6%)		18 (21.4%)	15 (19.0%)		15 (22.7%)	10 (20.4%)	3 (17.6%)	
≥ Grade II	76 (76.8%)	54 (84.4%)		66 (78.6%)	64 (81.0%)		51 (77.3%)	39 (79.6%)	14 (82.4%)	
< Grade IIIa	90 (90.9%)	54 (84.4%)	0.204	73 (86.9%)	71 (89.9%)	0.555	60 (90.9%)	42 (85.7%)	16 (94.1%)	0.533
≥ Grade IIIa	9 (9.1%)	10 (15.6%)		11 (13.1%)	8 (10.1%)		6 (9.1%)	7 (14.3%)	1 (5.9%)	
pT stage			0.986			0.126				0.736
T1 & T2	45 (45.5%)	29 (45.3%)		43 (51.2%)	31 (39.2%)		30 (45.5%)	25 (51.0%)	6 (35.3%)	
T3 & T4	54 (54.5%)	35 (54.7%)		41 (48.8%)	48 (60.8%)		36 (54.5%)	24 (49.0%)	11 (64.7%)	
LN metastasis			0.08			0.203				0.643
Absent	69 (69.7%)	36 (56.3%)		58 (69.0%)	47 (59.5%)		39 (59.1%)	34 (69.4%)	10 (58.8%)	
Present	30 (30.3%)	28 (43.8%)		26 (31.0%)	32 (40.5%)		27 (40.9%)	15 (30.6%)	7 (41.2%)	
Resection margin involvement			1.000			1.000				0.452
No	98 (99.0%)	63 (98.4%)		83 (98.8%)	78 (98.7%)		66 (100%)	47 (95.9%)	17 (100%)	
Yes	1 (1.0%)	1 (1.6%)		1 (1.2%)	1 (1.3%)		0 (0%)	2 (4.1%)	0 (0%)	
Adjuvant therapy			0.538			0.798				0.22
No	71 (71.7%)	43 (67.2%)		58 (69.0%)	56 (70.9%)		42 (63.6%)	39 (79.6%)	12 (70.6%)	
Yes	28 (28.3%)	21 (32.8%)		26 (31.0%)	23 (29.1%)		24 (36.4%)	10 (20.4%)	5 (29.4%)	

ASA = American Society of Anesthesiologists.  
 PPPD = pylorus-preserving pancreatoduodenectomy.  
 PD = pancreatoduodenectomy.  
 TDA = Transduodenal ampullectomy.  
 TP = Total pancreatectomy.  
 Lap-PPPD = laparoscopic pylorus-preserving pancreatoduodenectomy.  
 Lap-PD = laparoscopic pancreatoduodenectomy.  
 CA 19-9 = cancer antigen 19-9.  
 CEA = carcinoembryonic antigen.  
 LN = lymph node.  
 NLR = neutrophil-to-lymphocyte ratio.  
 PLR = platelet-to-lymphocyte ratio.  
 GPS = Glasgow Prognostic Score.

growth factor (VEGF), reactive oxygen species, basic fibroblast growth factor, and prostaglandin E2. These cytokines promote angiogenesis and inhibit the function of cytotoxic T cells, and consequentially promote the growth of cancer cells, micrometastases, or recurrence [28–32]. In addition, it has also been reported that the activity of

tumor-associated macrophages is associated with a high NLR. Tumor-associated macrophages release some cytokines, in particular interleukin (IL)-6 and IL-8, which promote systemic neutrophilia [33,34]. Furthermore, VEGF and other cytokines, mainly IL-1 and IL-6, secreted by tumor cells induce thrombocytosis through the exaggerated

**Table 3**

Adjusted multivariable analyses of clinicopathological variables and NLR in relation to DFS and OS after surgical resection for adenocarcinoma of the ampulla of Vater.

Factor	DFS			OS		
	HR	95% CI	P value	HR	95% CI	P value
Age (years)						
< 65						
≥ 65	0.356	0.163–0.778	0.010	–	–	–
pT stage						
T1 & T2						
T3 & T4	2.790	1.340–5.808	0.006	2.927	1.649–5.197	< 0.001
LN metastasis						
Absent						
Present	3.116	1.657–5.859	< 0.001	3.027	1.818–5.041	< 0.001
Resection margin involvement						
No						
Yes	11.364	2.288–56.439	0.003	10.619	2.418–46.632	0.002
NLR						
< 2						
≥ 2	1.828	0.985–3.394	0.056	1.916	1.181–3.108	0.008

DFS = disease-free survival.

OS = overall survival.

HR = hazard ratio.

CI = confidence interval.

LN = lymph node.

NLR = neutrophil-to-lymphocyte ratio.

stimulation of megakaryocyte differentiation [35,36]. Platelets may promote tumor proliferation and angiogenesis by releasing proangiogenic factors such as VEGF, enhance extravasation of tumor cells, and facilitate metastasis formation [37–40]. Moreover, thrombocytosis might be related to cancer-associated thrombosis [37].

Inflammatory factors are known to be prognostic factors in patients with other gastrointestinal cancers, including oesophageal, gastric, colorectal, pancreatic, and gallbladder cancers; cholangiocarcinoma; and hepatocellular carcinoma [12–21,41]. However, only a few studies have investigated inflammation-based prognostic factors in a limited cohort of patients with AVC [1,2,22]. Moreover, there is a lack of evidence to evaluate the impact of NLR, PLR, and GPS together on survival in a large cohort of patients with AVC. Therefore, the present study can

help in understanding the correlation between inflammatory factors and survival in patients with AVC.

This study has several limitations. Like any other retrospective study, it may have a selection bias. Although more patients were enrolled in this study than in previous studies, it was still a single-institution study; thus, the results may not be representative of the total population of patients with AVC. Therefore, the impact of inflammatory factors such as NLR, PLR, and GPS on the survival of patients with AVC should be investigated in a population-based cohort in the near future. In addition, we chose approximate values of the medians as the cut-off values for NLR and PLR, because there were no widely accepted criteria, and this might have affected the results. Furthermore, GPS could not be analysed for all study patients because

**Table 4**

Adjusted multivariable analyses of clinicopathological variables and PLR in relation to DFS and OS after surgical resection for adenocarcinoma of the ampulla of Vater.

Factor	DFS			OS		
	HR	95% CI	P value	HR	95% CI	P value
Age (years)						
< 65						
≥ 65	0.397	0.183–0.860	0.019	–	–	–
pT stage						
T1 & T2						
T3 & T4	2.802	1.351–5.814	0.006	2.911	1.646–5.147	< 0.001
LN metastasis						
Absent						
Present	3.347	1.802–6.217	< 0.001	3.066	1.857–5.063	< 0.001
Resection margin involvement						
No						
Yes	12.040	2.455–59.038	0.002	11.278	2.562–49.650	0.001
PLR						
< 130						
≥ 130	–	–	–	1.758	1.071–2.886	0.026

DFS = disease-free survival.

OS = overall survival.

HR = hazard ratio.

CI = confidence interval.

LN = lymph node.

PLR = platelet-to-lymphocyte ratio.

**Table 5**

Adjusted multivariable analyses of clinicopathological variables and GPS in relation to DFS and OS after surgical resection for adenocarcinoma of the ampulla of Vater.

Factor	DFS			OS		
	HR	95% CI	P value	HR	95% CI	P value
Age (years)						
< 65						
≥65	0.437	0.193–0.989	0.047	–	–	–
CEA						
Normal						
Elevated (> 5 ng/mL)	3.092	0.977–9.788	0.055	–	–	–
pT stage						
T1 & T2						
T3 & T4	2.179	0.977–4.860	0.057	3.351	1.735–6.470	< 0.001
LN metastasis						
Absent						
Present	3.171	1.523–6.605	0.002	3.552	1.999–6.310	< 0.001
Resection margin involvement						
No						
Yes	24.620	4.091–148.173	< 0.001	12.428	2.764–55.871	0.001
Adjuvant therapy						
No						
Yes	2.429	1.077–5.479	0.032	–	–	–
GPS						
0						
1	0.779	0.321–1.890	0.580	–	–	–
2	2.488	1.051–5.890	0.038	–	–	–

DFS = disease-free survival.

OS = overall survival.

HR = hazard ratio.

CI = confidence interval.

CEA = carcinoembryonic antigen.

LN = lymph node.

PLR = platelet-to-lymphocyte ratio.

GPS = Glasgow Prognostic Score.

there were many missing values of preoperative serum albumin or CRP level. Despite these limitations, this study was based on one of the largest patient populations who underwent curative resection for AVC.

In conclusion, high preoperative NLR and PLR, which represent systemic inflammation, could predict poor OS in patients with AVC after curative surgical resection.

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