Neutrophil to Lymphocyte Ratio Predicts Therapeutic Outcome After Pancreaticoduodenectomy for Carcinoma of the Ampulla of Vater

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Abstract. *Background: Preoperative systemic inflammatory response is associated with a poor long-term prognosis after resection of malignant tumors. Several indicators of systemic inflammation have been reported to be predictive of outcomes, but have not been fully investigated. The aim of the present study was to evaluate the significance of the preoperative neutrophil to lymphocyte ratio (NLR) in therapeutic outcomes after pancreaticoduodenectomy for carcinoma of the ampulla of Vater. Patients and Methods: The study comprised of 37 patients who had undergone pancreaticoduodenectomy for carcinoma of the ampulla of Vater between January 2000 and December 2011. We retrospectively investigated the relation between preoperative NLR and disease-free as well as overall survival. Results: In multivariate analysis, preoperative biliary drainage (p=0.044) and pN2 or pN3 (p=0.027) status were independent and significant predictors of cancer recurrence, while significant predictors of overall survival consisted of pN2 or pN3 (p=0.025) and NLR ≥3 (p=0.026). Conclusion: Preoperative NLR is an independent and significant indicator of long-term outcome in patients with carcinoma of the ampulla of Vater after pancreaticoduodenectomy. Measurement of NLR may help decision making in the postoperative management of patients with carcinoma of the ampulla of Vater.*

Carcinoma of the ampulla of Vater is a rare malignancy accounting for fewer than 1% of gastrointestinal malignancies and up to 20% of all periampullary tumors (1, 2). Surgical resection is a potentially curative treatment for carcinoma of the ampulla of Vater, and the resection rate is 50-60% (3). The 5-year survival rate after surgical resection has been reported to range between 40.9% and 67.9% (3-6). However, up to 50% of patients develop relapse after curative resection of such a disease (7), and this clearly influences survival. Therefore, assessment of prognostic indicators is important for postoperative management after surgical resection.

Recently, several prognostic factors related to systemic inflammation have been reported in patients with various types of malignancies. The Glasgow Prognostic Score (GPS), calculated by the combination of serum C-reactive protein (CRP) and albumin concentrations, preoperative neutrophil-to-lymphocyte ratio (NLR), and preoperative platelet-to-lymphocyte ratio (PLR) have been advocated to predict cancer-specific survival (8-14). We also reported a prognostic value of GPS for carcinoma of the ampulla of Vater (15) and gallbladder cancer (16). However, the prognostic value of NLR in patients with carcinoma of the ampulla of Vater has not been reported. Therefore, in this study, we retrospectively investigated the relation between preoperative NLR and disease-free as well as overall survival in patients with carcinoma of the ampulla of Vater after pancreaticoduodenectomy.

Patients and Methods

Between January 2000 and December 2011, 40 patients with carcinoma of the ampulla of Vater underwent pancreaticoduodenectomy at the Department of Surgery, Jikei University Hospital, Tokyo, Japan. Out of these, three patients were excluded, one patient due to non-curative resection with microwave coagulation therapy for liver metastasis, and two patients who were lost to follow-up, leaving the remaining 37 patients for this study.

Preoperatively, hemograms were routinely measured for each patient. Absolute white blood cell and subset counts were routinely determined in peripheral venous samples. The NLR was calculated by dividing the neutrophil count by the lymphocyte count. Preoperative biliary drainage was performed when the patients developed obstructive jaundice or cholangitis. Pathological stage was determined according to the fifth Japanese edition of the Japanese General Rules for Biliary Tract Cancer (17).

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Key Words: Carcinoma of the ampulla of Vater; neutrophil to lymphocyte ratio, systemic inflammatory response.

Firstly, we investigated the relation between clinicopathological variables and disease-free or overall survival after pancreaticoduodenectomy by univariate and multivariate analysis. The following eight variables were evaluated: age, gender, presence of preoperative biliary drainage, tumor stage based on pathology (pT stage), status of lymph node metastasis based on pathology (pN stage), duration of operation, intraoperative blood loss, and NLR. Clinicopathological continuous variables were classified into two groups for the survival analysis by log-rank test and the Cox proportional hazard regression model as follows: age <65 or ≥65 years, duration of operation <480 or ≥480 minutes, intraoperative blood loss <1,000 or ≥1,000 g and NLR <3 or ≥3. The cut-off value of NLR was determined in accordance with previous studies (12, 13).

Next, we investigated the relationship between clinicopathological variables and NLR by univariate analysis. The evaluated factors consisted of the following seven variables: age, gender, presence of preoperative biliary drainage, pT stage, pN stage,duration of operation, and intraoperative blood loss.

Recurrence of carcinoma of the ampulla of Vater was defined as newly-detected local or distant metastatic tumors by ultrasonogaphy, computed tomography, or magnetic resonance image with or without increase in serum carcinoembryonic antigen or carbohydrate antigen 19-9.

This retrospective study was approved by the Ethics Committee of The Jikei University School of Medicine (#21-121).

Statistical analysis. Data are expressed as the mean±standard deviation (SD). Univariate analysis was performed using the Mann–Whitney *U*-test and the Chi-square test. Univariate analysis of disease-free and overall survival was performed using the log-rank test, and the Cox proportional regression model with backward elimination stepwise approach for multivariate analysis. All *p*-values were considered statistically significant when the associated probability was less than 0.05. These analyses were conducted using IBM® SPSS statistics version 20.0 (IBM Japan, Tokyo, Japan).

Results

Patients' characteristics. Patients' characteristics are outlined in Table I as the mean±SD, range, or ratio. Among the study population, the mean age was 64.8 years with a range 44 to 80 years, and 21 of the patients were male. Preoperative biliary drainage was performed in 15 out of 37 patients. Patients with preoperative NLR ≥3 comprised 27%. Postoperative complications developed in 21 out of 37 patients (57%), consisting of surgical site infection in 12 (32%), pulmonary complication in four (11%), and grade B or C postoperative pancreatic fistula in 10 (27%).

In the present study, the 5-year disease-free survival and overall survival rates after pancreaticoduodenectomy for carcinoma of the ampulla of Vater were 73.4% and 82.1%, respectively.

Univariate and multivariate analyses of clinicopathological variables in relation to disease-free survival after pancreaticoduodenectomy for carcinoma of the ampulla of Vater. Table II lists the relationship between the clinical variables and disease-free survival after pancreaticoduodenectomy for carcinoma of the ampulla of Vater. In univariate analysis, disease-free survival was significantly worse in patients with preoperative biliary drainage (p=0.003), pT3 or pT4 (p=0.024), pN2 or pN3 (p<0.001), and NLR ≥3 (p=0.020, Figure 1A). In multivariate analysis, preoperative biliary drainage (p=0.044), and pN2 or pN3 (p=0.027) remained independent and significant predictors of poorer disease-free survival.

Table I. *Patients' characteristics*.

Factor	Mean±SD or ratio	Range
Age (years)	64.8±8.8	44-80
Gender (male:female)	21:16	
Preoperative biliary drainage (present:absent)	15:22	
pT stage (T1:T2:T3:T4)	11:12:10:4	
pN stage (N0:N1:N2:N3)	26:8:2:1	
Duration of operation (min)	483.3±90.1	245-701
Intraoperative blood loss (g)	882.0±543.5	70-2,345
Neutrophil-lymphocyte ratio (<3:≥3)	27:10	

pT stage, Tumor stage based on pathology; pN stage, the status of lymph node metastasis based on pathology.

Univariate and multivariate analyses of clinicopathological variables in relation to overall survival after pancreaticoduodenectomy for carcinoma of the ampulla of Vater. Table III lists the relationship between the clinical variables and overall survival after pancreaticoduodenectomy for carcinoma of the ampulla of Vater. In univariate analysis, overall survival was significantly worse in patients with preoperative biliary drainage (p=0.010), pT3 or pT4 (p=0.040), pN2 or pN3 (p=0.002), and NLR ≥3 (p=0.006, Figure 1B). In multivariate analysis, pN2 or pN3 (p=0.025) and NLR ≥3 (p=0.026) remained independent and significant predictors of poorer overall survival.

Association between clinicopathological variables and NLR. Table IV lists the relationship between clinicopathological variables and preoperative NLR. In univariate analysis, preoperative biliary drainage (p=0.006) and pT3 or pT4 (p=0.007) were significantly more frequent in the group with high NLR. pN Stage was comparable between the two groups.

Discussion

Various perioperative parameters have been reported to correlate with outcome after surgery in patients with carcinoma of the ampulla of Vater, including TNM stage, depth of infiltration (pT stage), regional lymph node

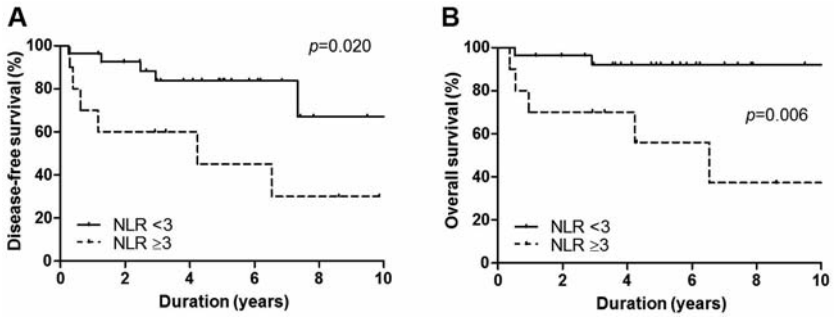

Figure 1. *Kaplan–Meier curves of disease-free (A) and overall (B) survival after pancreaticoduodenectomy for carcinoma of the ampulla of Vater. A neutrophil to lymphocyte ratio (NLR) ≥3 was significantly associated with worse disease-free survival (p=0.020) and overall (p=0.006) survival.*

Table II. *Univariate and multivariate analyses of clinicopathological variables in relation to disease-free survival after pancreaticoduodenectomy for carcinoma of the ampulla of Vater.*

Factor	N	Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	*p*-Value	Hazard ratio (95% CI)	*p*-Value
Age (years)					
≥65	19	0.6082 (0.1806-2.048)	0.422		NS
<65	18	1.00			
Gender					
Female	16	1.871 (0.5531-6.328)	0.314		NS
Male	21	1.00			
Preoperative biliary drainage					
Present	15	6.501 (1.893-22.32)	0.003	5.311 (1.046-26.965)	0.044
Absent	22	1.00		1.00	
pT stage					
pT3 or pT4	14	4.358 (1.212-15.66)	0.024		NS
pT1 or pT2	23	1.00			
pN stage					
pN2 or pN3	3	1.164 (46.27-29.200)	<0.001	5.523 (1.210-25.214)	0.027
pN0 or pN1	34	1.00		1.00	
Duration of operation (min)					
≥480	18	1.093 (0.3305-3.612)	0.885		NS
<480	19	1.00			
Intraoperative blood loss (g)					
≥1,000	13	0.6394 (0.1885-2.173)	0.474		NS
<1,000	24	1.00			
Neutrophil-lymphocyte ratio					
≥3	10	5.178 (1.301-20.61)	0.020		NS
<3	27	1.00			

pT stage, Tumor stage based on pathology; pN stage, the status of lymph node metastasis based on pathology; CI: confidence interval; NS: not significant.

involvement (pN stage), lymphovascular invasion, perineural invasion, tumor differentiation, and surgical margins (3, 4, 6, 18-20). In the present study, advanced lymph node metastasis was an independent and significant prognostic factor of poor disease-free and overall survival in univariate and multivariate analyses.

Recent studies have reported that the outcomes of patients with cancer were determined not only by tumor-related factors but also by host-related factors, in particular, a systemic inflammatory response (8-16). The host's inflammatory response to cancer and the systemic effects exerted by cancer cells lead to up-regulation of the inflammatory process. The

Table III. *Univariate and multivariate analyses of clinicopathological variables in relation to overall survival after pancreaticoduodenectomy for carcinoma of the ampulla of Vater.*

Factor	N	Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	*p*-Value	Hazard ratio (95% CI)	*p*-Value
Age (years)					
≥65	19	1.037 (0.2270-4.735)	0.963		NS
<65	18	1.00			
Gender					
Female	16	1.843 (0.4063-8.356)	0.428		NS
Male	21	1.00			
Preoperative biliary drainage					
Present	15	7.508 (1.613-34.967)	0.010		NS
Absent	22	1.00			
pT stage					
pT3 or pT4	14	5.135 (1.074-24.55)	0.040		NS
pT1 or pT2	23	1.00			
pN stage					
pN2 or pN3	3	319.9 (8.525-12,001)	0.002	8.595 (1.318-56.055)	0.025
pN0 or pN1	34	1.00		1.00	
Duration of operation (min)					
≥480	18	1.280 (0.2898-5.657)	0.744		NS
<480	19	1.00			
Intraoperative blood loss (g)					
≥1,000	13	0.3647 (0.07864-1.691)	0.198		NS
<1,000	24	1.00			
Neutrophil-lymphocyte ratio					
≥3	10	10.79 (1.982-58.71)	0.006	6.520 (1.245-34.134)	0.026
<3	27	1.00		1.00	

pT stage, Tumor stage based on pathology; pN stage, the status of lymph node metastasis based on pathology; CI: confidence interval; NS: not significant.

Table IV. *Univariate analysis of clinicopathological variables in relation to the neutrophil to lymphocyte ratio (NLR).*

Factor	NLR		*p*-Value
	<3 (n=27)	≥3 (n=10)	
Age (years)	64.5±8.8	65.5±9.2	0.625
Gender (male:female)	18:9	3:7	0.067
Preoperative biliary drainage (present:absent)	7:20	8:2	0.006
pT stage (T1:T2:T3:T4)	11:10:5:1	02:5:3	0.007
pN stage (N0:N1:N2:N3)	20:5:1:1	6:3:1:0	0.669
Duration of operation (min)	481.9±96.3	487.2±75.2	1.000
Intraoperative blood loss (g)	883.2±560.0	878.6±656.2	0.724

pT stage, Tumor stage based on pathology; pN stage, the status of lymph node metastasis based on pathology.

status of a systemic inflammatory response can be assessed by GPS and NLR. NLR was reported as a predictor of prognosis in patients with several types of digestive tract cancers, including esophageal, gastric, colorectal, pancreatic and gallbladder cancer, cholangiocarcinoma, liver metastasis from colorectal cancer, hepatocellular carcinoma (10-13). However, to the best of our knowledge, this is the first report of correlation between therapeutic outcome and carcinoma of the ampulla of Vater after pancreaticoduodenectomy.

The mechanism of the relation between the NLR and cancer-specific survival in patients with malignancy remains unclear. An elevated NLR represents neutrophilia, and

lymphocytopenia. Neutrophilia may aid in the development and progression of neoplasm through the release of vascular endothelial growth factor, a proangiogenic factor thought to be integral to tumor development (21, 22). Moreover, neutrophils have been reported to suppress the cytotoxic activity of lymphocyte and cytotoxic T-cells (23, 24). Lymphocytopenia may contribute to the development and promotion of malignancy through a poor lymphocyte-mediated immune response (25). These conditions may lead to the growth of cancer cells, micrometastases, or recurrence (26). Furthermore, tumor-associated macrophages (TAMs) have been reported to be associated with elevated NLR. TAMs express some cytokines, such as interleukins 6 and 8, which promote systemic neutrophilia (11).

In our study, preoperative biliary drainage was a significant risk factor for poor disease-free and overall survival by univariate analysis, and an independent predictor of poor disease-free survival by multivariate analysis. Preoperative elevated bilirubin has been reported to be risk factor of poor long-term survival (20). In the current study, patients with advanced pT stage and preoperative biliary drainage more frequently had an elevated NLR, which may indicate that preoperative biliary drainage is associated with local inflammation of the bile duct and that may influence systemic inflammation.

In summary, the preoperative NLR predicted the overall survival of patients with carcinoma of the ampulla of Vater after pancreaticoduodenectomy. Risk stratification using NLR is easy, inexpensive and less invasive because the NLR requires only a preoperative hemogram, that is standard procedure for perioperative management. Routine preoperative NLR measurement in patients undergoing curative treatment for carcinoma of the ampulla of Vater may provide a means of identifying patients with poorer prognosis and offer assistance in clinical decision making.

Conclusion

Preoperative NLR is an independent and significant indicator of the long-term outcome for patients after pancreatico-duodenectomy for carcinoma of the ampulla of Vater.

Conflicts of interest

The Authors declare that they have no conflicts of interest with regard to this study.

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