Glasgow Prognostic Score Predicts Therapeutic Outcome after Pancreaticoduodenectomy for Carcinoma of the Ampulla of Vater

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Abstract. *Background: Systemic inflammation, as evidenced by the Glasgow prognostic score (GPS), predicts cancer-specific survival in various types of cancer. The aim of this study was to evaluate the significance of GPS on the therapeutic outcome after pancreaticoduodenectomy for carcinoma of the ampulla of Vater. Patients and Methods: The subjects of this study were 30 patients who underwent elective pancreaticoduodenectomy for carcinoma of the ampulla of Vater. For the assessment of systemic inflammatory response using the GPS, patients were classified into three groups: patients with normal albumin (≥3.5 g/dl) and normal C-reactive protein (CRP) (≤1.0 mg/dl) as GPS 0 (n=23), those with low albumin (<3.5 g/dl) or elevated CRP (>1.0 mg/dl) as GPS 1 (n=5), and those with low albumin (<3.5 g/dl) and elevated CRP (>1.0 mg/dl) as GPS 2 (n=2). We retrospectively investigated the relationship between patients' characteristics, including GPS, and disease-free survival, as well as overall survival. Results: For disease-free survival, advanced tumor stage (p=0.0401), advanced lymph node metastasis (p<0.0001), and preoperative biliary drainage (p=0.0157) in univariate analysis, and advanced lymph node metastasis (p=0.0271) in multivariate analysis were significant and independent predictors of cancer recurrence. For overall survival, in both univariate and multivariate analyses, advanced lymph node metastasis (p=0.0006 and p=0.0411, respectively) and GPS 1 or 2 (p=0.0034 and p=0.0484, respectively) were significant and independent predictors of poor patient outcome. Conclusion: The GPS in patients with carcinoma of the ampulla of Vater is an independent prognostic predictor after elective pancreaticoduodenectomy.*

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Carcinoma of the ampulla of Vater is a relatively rare neoplasm, accounting for 0.06% to 0.2% of autopsy cases (1), and 12.7% to 32.2% of surgically-resectable periampullary malignancies (2, 3). Pancreaticoduodenectomy with regional lymph node resection is a potentially curative treatment for resectable carcinoma of the ampulla of Vater (4, 5). Despite improvements in preoperative evaluation, surgical techniques, and postoperative care, the 5-year survival rate has been reported to range between 40.6% and 68.0% (6-8). Therefore assessment of prognostic indicators is important for the postoperative management of patients with carcinoma of the ampulla of Vater after pancreaticoduodenectomy. The presence of a systemic inflammatory response, as evidenced by elevated C-reactive protein (CRP) concentration, may be related to poor outcome of cancer treatments (9, 10). Several recent studies have indicated that the measurement of the systemic inflammatory response by the combination of serum CRP and albumin concentrations, *i.e.* Glasgow prognostic score (GPS), predicts cancer-specific survival (11, 12), and postoperative infectious complications (13). In this study, we retrospectively investigated the relation between GPS and disease-free, as well as overall, survival after elective pancreaticoduodenectomy for carcinoma of the ampulla of Vater.

Patients and Methods

Between January 2001 and December 2010, 31 patients with carcinoma of the ampulla of Vater underwent elective pancreaticoduodenectomy at the Department of Surgery, Jikei University Hospital, Tokyo, Japan. Of these, one patient was excluded due to being lost to follow-up, leaving the remaining 30 patients for this study.

For the assessment of systemic inflammatory response using the GPS, the patients were classified into three groups: patients with normal albumin (≥3.5 g/dl) and normal CRP (≤1.0 mg/dl) as GPS 0 (n=23), those with low albumin (<3.5 g/dl) or elevated CRP (>1.0 mg/dl) as GPS 1 (n=5), and both low albumin (<3.5 g/dl) and elevated CRP (>1.0 mg/dl) as GPS 2 (n=2). We investigated the relationship between clinicopathological variables and disease-free, as well as, overall survival after elective pancreatic resection by

Table I. *Patients' characteristics*.

Factor	Mean±SD or Rate	Range
Age (years)	63.4±8.7*	44-80
Gender (male:female)	20:10	
Body mass índex (kg/m^2)	21.9±2.6	16.8-28.7
Duration of operation (min)	483.2±86.8	245-605
Blood loss (g)	853.4±512.1	100-2,345
Postoperative complications (present:absent)	19:11	
T Factor (pT1 or pT2:pT3 or pT4)	19:11	
Lymph node metastasis (pN0 or pN1:pN2 or pN3)	27:3	
Pre-operative biliary drainage (present:absent)	11:19	
Glasgow prognostic score (GPS 0:GPS 1:GPS2)	23:5:2	

T Factor: Tumor factor based on tumor pathology; *mean±SD.

univariate and multivariate analysis. The factors consisted of the following: age, gender, body mass index (BMI), duration of operation, intraoperative blood loss, postoperative complications, tumor factor (T factor) based on tumor pathology, status of lymph node metastasis on pathology, preoperative biliary drainage, and GPS. Next, we investigated the relationship between clinicopathological variables and GPS by univariate analysis. The factors consisted of the following: age, gender, BMI, duration of operation, intraoperative blood loss, T factor based on tumor pathology, status of lymph node metastasis on pathology, and preoperative biliary drainage. Clinicopathological continuous variables were classified into two groups for the log-rank test and the Cox proportional hazard regression model as follows: age <70 or ≥70 years, BMI <25 or ≥25, duration of operation <480 or ≥480 min, and intraoperative blood loss <1,000 or ≥1,000 g. Recurrence of pancreatic ductal adenocarcinoma 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 Jikei University School of Medicine (#21-121).

Statistical analysis. Data are expressed as the mean±standard deviation (SD). Univariate analysis was performed using the non-paired Student's *t*- and Chi-square tests. Analysis of disease-free and overall survival was performed using the log-rank test. Factors that significantly influenced overall survival were then used in the Cox proportional regression model for multivariate analysis. *p*-Values were considered statistically significant when the associated probability was less than 0.05.

Results

Patients' characteristics. Patients' characteristics are outlined in Table I. Among the study population, the mean age was 63.4 years, with a range from 44 to 80 years, 20 patients were male. GPS consisted of GPS 0 in 23, GPS 1 in 5, and GPS 2 in two patients, respectively. Postoperative complications developed in 19 out of 30 patients (63.3%), consisting of surgical site infection (SSI) in eight, pulmonary complications in four, and grade B or C postoperative pancreatic fistula in eight patients, respectively. In this study, the five-year disease-free and overall survival rates after pancreaticoduodenectomy for carcinoma of the ampulla of Vater were 72.3% (Figure 1A) and 82.4% (Figure 1B), 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 clinicopathological variables and disease-free survival after pancreaticoduodenectomy for carcinoma of the ampulla of Vater. In univariate analysis, advanced T factor (p=0.0401), advanced lymph node metastasis (p<0.0001), and pre-operative biliary drainage (p=0.0157) were significantly associated with worse disease-free survival. In multivariate analysis, advanced lymph node metastasis (p=0.0271) was the only independent risk factor associated with poor disease-free survival. Disease-free survival in GPS 0 cases tended to be better than that of GPS 1 or 2 cases, which failed to achieve statistical significance (Figure 2A; p=0.1166).

Univariate and multivariate analysis of clinicopathological variables in relation to overall survival after pancreatico-duodenectomy for carcinoma of the ampulla of Vater. Table III lists the relationship between the clinicopathological variables and overall survival after pancreaticoduodenectomy for carcinoma of the ampulla of Vater. In both univariate and multivariate analyses, advanced lymph node metastasis (p=0.0006 and p=0.0411, respectively) and GPS 1 or 2 (Figure 2B; p=0.0034 and p=0.0484, respectively) were significant and independent predictors of poor patients' overall survival. In univariate analysis, advanced T factor (p=0.0752), and preoperative biliary drainage (p=0.0672) tended to be associated with a worse overall survival rate, which did not achieve statistical significance.

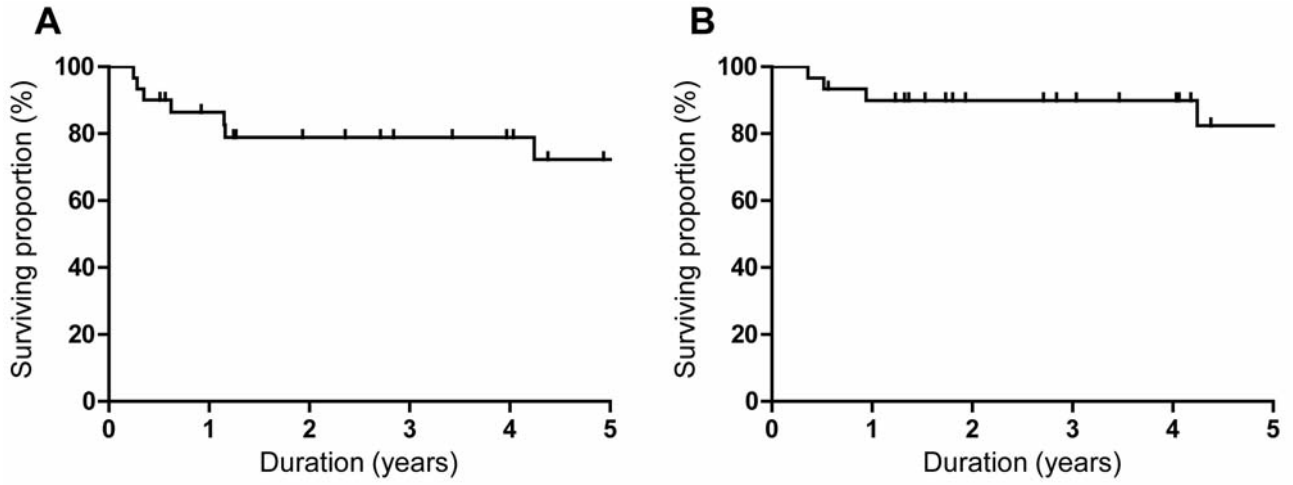

Figure 1. *The five-year disease-free and overall survival rates after elective pancreaticoduodenectomy for carcinoma of the ampulla of Vater were 72.3% (A) and 82.4% (B), respectively.*

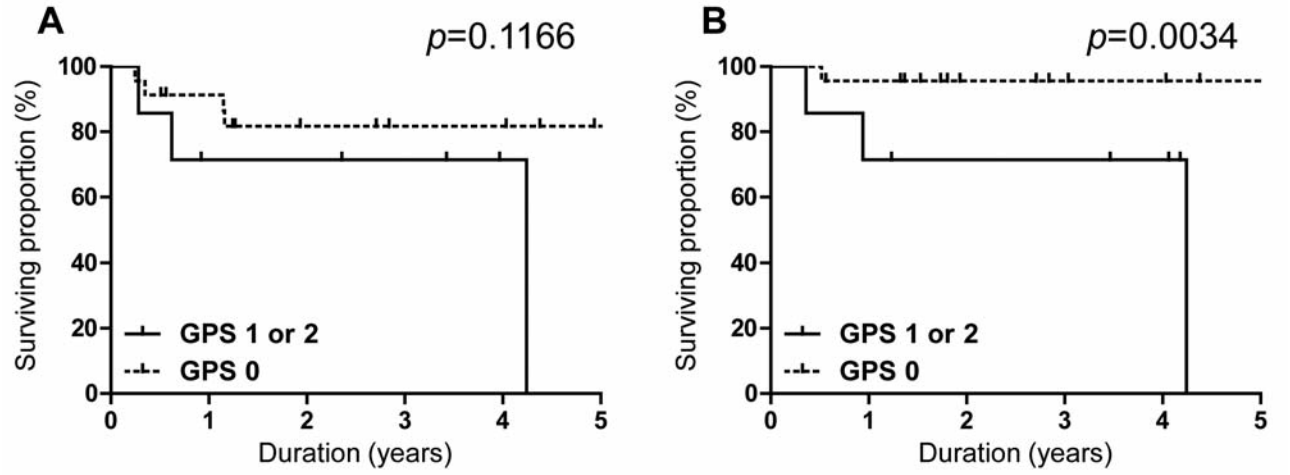

Figure 2. *Disease-free survival of patients with Glasgow prognostic score (GPS) 0 tended to be better than that of those with GPS 1 or 2, but this was confirmed not statistically (A). In statistical analysis, GPS 1 or 2 was a significant and independent predictor of poor patient prognosis in overall survival (B).*

Association between clinicopathological variables and GPS. Table IV lists the relationship between patient characteristics and GPS. Univariate analysis demonstrated that greater T factor was more frequent in patients with GPS 1 or 2 than in patients with GPS 0 (p=0.0021). All other factors in both GPS 0 and GPS 1 or 2 groups were comparable.

Discussion

In patients with carcinoma of the ampulla of Vater, pancreatic invasion, venous invasion, perineural invasion, poor differentiation, advanced tumor stage, and positive lymph node metastasis have been reported as risk factors of worse prognosis after pancreaticoduodenectomy (6-8). In this study, advanced lymph node metastasis was found to be a significant and independent risk factor of poor disease-free and overall survival in univariate and multivariate analyses. In univariate analysis, advanced T factor was a significant risk factor of poor disease-free survival, which tended to be associated with poor overall survival, however not significantly. GPS was first reported as a predictor of prognosis in unresectable non-small cell lung cancer in 2003 (14). Thereafter, GPS was shown to predict prognosis in patients with various types of unresectable cancer of the lung (15), breast (16), esophagus or stomach (17), pancreas (18), kidney (19) and colorectum (20). Therefore, GPS may be a useful predictor of outcome in

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

Factor		Univariate analysis		Multivariate analysis	
	N	Hazard ratio (95% CI)	*p*-Value	Hazard ratio (95% CI)	*p*-Value
Age (years)					
≥70	9	0.4093	0.2679		
<70	21	(0.0843-1.988)			
Gender					
Female	10	1.412	0.6642		
Male	20	(0.2977-6.693)			
Body mass index (kg/m^2)					
≥25	4	1.902	0.6287		
<25	26	(0.1405-25.76)			
Duration of operation (min)					
≥480	17	2.185	0.3401		
<480	13	(0.4922-9.695)			
Blood loss (g)					
≥1,000	10	0.8376	0.8265		
<1,000	20	(0.1718-4.085)			
Postoperative complications					
Present	19	0.4211	0.2697		
Absent	11	(0.0907-1.956)			
T Factor					
pT3 or pT4	11	5.139	0.0401	2.070	0.4528
pT1 or pT2	19	(1.077-24.52)		(0.3100-13.82)	
Lymph node metastasis					
pN2 or pN3	3	35425	<0.0001	17.321	0.0271
pN0 or pN1	27	(773.7-1,720,000)		(1.382-217.1)	
Preoperative biliary drainage					
Present	11	7.437	0.0157	2.493	0.3713
Absent	19	(1.460-37.87)		(0.3360-18.48)	
Glasgow prognostic score					
1 or 2	7	4.521	0.1166		
0	23	(0.6867-29.77)			

T Factor, Tumor factor based on tumor pathology; CI, confidence interval.

patients with unresctable and advanced malignancies. The evidence for a significant association between GPS and therapeutic outcome in patients with primary resectable cancer has been reported in colorectal (21), gastro-esophageal (22), urinary bladder (23), pancreatic (24), renal (25), and non-small cell lung cancer (26). We previously reported the utility of GPS as a predictor of prognosis in patients with unresectable liver metastases from colorectal cancer (27), and of postoperative complication in patients with hepatocellular carcinoma after hepatic resection (28). However, the reasons for the association between GPS, pre-treatment elevated serum CRP or low serum albumin concentrations, and prognosis, as well as postoperative complications in patients with various malignancies, remain unclear (29). As possible reasons for a relation between GPS and poor therapeutic outcome, elevated serum CRP is associated with a reduced lymphocyte count and with suppressed lymphocyte-mediated immunity (30), and a systemic inflammatory response and hypoalbuminemia reflect the loss of lean tissue and protein, which suppresses the immune function (31, 32). Canna *et al*. reported that low tumor T-lymphocyte infiltration induces tumor progression in patients undergoing curative resection of colorectal cancer (33). In this study, GPS was found to be positively-associated with advanced T factor in univariate analysis. These results suggest that GPS may reflect the malignant potential of the primary tumor rather than lymph node or distant organ metastasis. Since the survival benefit of adjuvant chemotherapy has not yet been established for carcinoma of the ampulla of Vater after surgery (34), further assessments of the mechanism(s) relating the systemic inflammatory response to poor outcome are necessary to improve the therapeutic outcome of carcinoma of the ampulla of Vater after pancreaticoduodenectomy. Patient risk stratification using GPS is easy and less invasive, because GPS comprises only

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

Factor		Univariate analysis		Multivariate analysis	
	N	Hazard ratio (95% CI)	*p*-Value	Hazard ratio (95% CI)	*p*-Value
Age (years)					
≥70	9	0.6308	0.6651		
<70	21	(0.0783-5.081)			
Gender					
Female	10	1.870	0.5496		
Male	20	(0.2406-14.54)			
Body mass index (kg/m^2)					
≥25	4	8.362	0.2393		
<25	26	(0.2433-287.3)			
Duration of operation (min)					
≥480	17	2.446	0.3763		
<480	13	(0.3371-17.65)			
Blood loss (g)					
≥1,000	10	0.2216	0.1546		
<1,000	20	(0.0278-1.765)			
Postoperative complications					
Present	19	0.2005	0.1204		
Absent	11	(0.0264-1.523)			
T Factor					
pT3 or pT4	11	6.673	0.0752		
pT1 or pT2	19	(0.8248-53.99)			
Lymph node metastasis					
pN2 or pN3	3	947.0	0.0006	12.460	0.0411
pN0 or pN1	27	(18.99-47,237)		(1.106-140.3)	
Pre-operative biliary drainage					
Present	11	7.133	0.0672		
Absent	19	(0.8701-58.48)			
Glasgow prognostic score					
1 or 2	7	44.99	0.0034	11.364	0.0484
0	23	(3.524-574.4)		(1.017-126.9)	

T Factor, Tumor factor based on tumor pathology; CI, confidence interval.

Table IV. *Univariate analysis of clinicopathological variables in relation to Glasgow prognostic score after elective pancreaticoduodenectomy for carcinoma of the ampulla of Vater.*

Factor	Glasgow prognostic score		*p*-Value (univariate)
	0 (n=23)	1 or 2 (n=7)	
Age (years)	62.7±9.0	66.0±7.6*	0.3803
Gender (male:female)	15:8	5:2	0.7602
Body mass índex (kg/m^2)	21.9±2.8	21.9±2.4	0.9599
Duration of operation (min)	477.6±92.2	501.7±68.5	0.5294
Blood loss (g)	864.0±562.9	818.7±322.3	0.8420
Postoperative complications (present:absent)	16:7	3:4	0.1992
T Factor (pT1 or pT2:pT3 or pT4)	18:5	1:6	0.0021
Lymph node metastasis (pN0 or pN1:pN2 or pN3)	21:2	6:1	0.6660
Preoperative biliary drainage (present:absent)	7:16	4:3	0.1992

T Factor, Tumor factor based on tumor pathology; *mean±SD.

preoperative serum CRP and albumin concentration, which are routine examinations for perioperative patient management. GPS is, therefore, useful for identification of patients at risk of poor therapeutic outcome.

Conclusion

In conclusion, the GPS upon diagnosis for patients with carcinoma of the ampulla of Vater was found to be an independent and significant predictor in overall survival after elective pancreaticoduodenectomy. Measurement of the GPS may help decision making in the postoperative management of patients with carcinoma of the ampulla of Vater.

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