Postoperative Peripheral Absolute Blood Lymphocyte-to-Monocyte Ratio Predicts Therapeutic Outcome After Pancreatic Resection in Patients with Pancreatic Adenocarcinoma

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Abstract. *Aim: The aim of this study was to evaluate the significance of postoperative peripheral absolute blood lymphocyte-to-monocyte (ALC/AMC) ratio in pancreatic resections for pancreatic carcinoma. Patients and Methods: One hundred eleven patients who underwent pancreatic resection for pancreatic carcinoma were included in this study. We retrospectively examined perioperative findings as predictors of therapeutic outcome and the relation between postoperative ALC/AMC ratio and recurrence rate as well as overall survival of the patients with pancreatic carcinoma. Results: In univariate analysis, advanced tumor-node-metastasis (TNM) classification (p=0.0002), intraoperative flesh-frozen plasma (FFP) transfusion (p=0.0395), increased in preoperative serum carbohydrate antigen 19-9 (CA19-9) (p=0.0051) and lower postoperative ALC/AMC ratio (p=0.0007) were positively associated with poor disease-free survival. Advanced TNM classification (p=0.0008), intraoperative FFP transfusion (p=0.0343), elevated postoperative serum C-reactive protein (CRP) (p=0.0165) and lower postoperative ALC/AMC ratio (p=0.0029), as well as decreased preoperative lymphocyte counts (p=0.0248) were positively associated with poor overall survival. In multivariate analysis, advanced TNM classification (p=0.007), intraoperative FFP transfusion (p=0.0197), increase in preoperative serum CA19-9 (p=0.0075) and lower postoperative ALC/AMC ratio (p=0.0051) were independent factors for poor disease-free survival. Advanced TNM classification (p=0.0083), lower postoperative ALC/AMC ratio (p=0.0070) and elevated postoperative serum CRP (p=0.0094) were independent factors for poor overall survival. Conclusion: Lower postoperative peripheral ALC/AMC ratio may have a negative impact on recurrence and overall survival after pancreatic resection for pancreatic carcinoma.*

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Pancreatic carcinoma is one of the most fatal malignant cancers worldwide (1). Surgical pancreatic resection is the only curative treatment for pancreatic carcinoma. However, the overall survival rate of patients with curative surgical resection against pancreatic carcinoma still remains poor despite improvements in surgical techniques, instruments and postoperative management (2, 3). Most investigators agree that small tumor size, absence of lymph node involvement, a curative (R0) resection and the absence of adjuvant chemotherapy are significant better prognostic factors for long-term survival in patients with resected pancreatic carcinoma (4, 5).

Prediction of cancer-specific survival by evaluation of perioperative immunonutritional status can be useful in the search for a strategy to improve cancer-specific survival. Recent studies suggest that preoperative immunosuppression in patients with cancers may contribute to cancer development (6, 7). Several studies have indicated that elevated preoperative neutrophil-to-lymphocyte ratio, decreased preoperative lymphocyte count, increased preoperative serum C-reactive protein (CRP) and intraoperative fresh-frozen plasma (FFP) transfusion are related to poor prognosis in patients with operable pancreatic cancer (8-11). However, the relationship between postoperative immune suppression and cancer recurrence as well as cancer-specific survival is still unclear. Therefore, we hypothesized that perioperative immune response might be one of the predictors of tumor recurrence and survival in patients with pancreatic carcinoma after pancreatic resection. In the present study, we retrospectively investigated perioperative findings as predictors of therapeutic outcome, the relation between postoperative peripheral absolute blood lymphocyte-to-monocyte (ALC/AMC) ratio and disease-free survival, as well as overall survival in patients with pancreatic carcinoma after pancreatic resection.

Patients and Methods

Patients' characteristics and classification into groups of study. Between January 2004 and December 2012, 120 patients underwent surgical resection for pancreatic carcinoma in the Department of Surgery, Jikei University Hospital, Tokyo, Japan. Of these, 9 patients were excluded because of loss to follow up, leaving the remaining 111 patients for this study. The patients with pancreatic carcinoma underwent pancreaticoduodenectomy (PD) (N=73), distal pancreatectomy (DP) (N=33), middle pancreatectomy (MP) (N=2) and total pancreatectomy (TP) (N=3). Tumor-Nodes-Metastasis (TNM) staging was based on the sixth Japanese edition of the General Rules for the Study of Pancreatic Cancer in 2009 (12) and the patients were staged as follows: 0 (8 patients), I (6 patients) II (18 patients), III (51 patients) and IV (28 patients). Postoperatively, the patients received adjuvant chemotherapy after pancreatic resection for pancreatic carcinoma, based on gemcitabine or S-1, excluding the patients diagnosed as stage 0 or those who refused treatment. After June 2011, almost of patients received adjuvant chemotherapy using gemcitabine and intra-arterial transfusion of nafamostat mesilate, which are now ongoing a phase II clinical trial for patients with pancreatic cancer after pancreatic resection in our hospital (13). Hemogram and chemistry profile were routinely measured for each patient preoperatively and on postoperative day (POD) 1. Tumor markers were measured preoperatively. Absolute white blood cell counts (WBC), lymphocytes and monocytes were routinely determined in peripheral venous blood samples.

For the assessment of postoperative immune response using postoperative peripheral blood lymphocyte-to-monocyte ratio, patients were classified into two groups according to age (≥60 or <60 years), type of disease (head of pancreas or body or tail of pancreas), postoperative day (≥30 or <30 days), TNM classification (Stage 0, I and II or Stage III and IV), resection of margin (R0 or R1, R2), duration of operation (≥500 or <500 min), intraoperative blood loss (≥800 or <800 ml), body mass index (BMI; ≥25 or <25 kg/m^2), texture of the pancreatic parenchyma (soft pancreas or hard pancreas), preoperative serum carcinoembryonic antigen (CEA) level (≥10 or <10 ng/ml), preoperative carbohydrate antigen 19-9 (CA19-9) level (≥200 or <200 U/ml), preoperative WBC (≥5,000 or <5,000/μl), postoperative WBC (≥10,000 or <10,000/μl), preoperative serum CRP level (≥1.0 or <1.0 mg/dl), postoperative serum CRP levels (≥10 or <10 mg/dl) and postoperative ALC/AMC ratio (≥2 or <2 times). Then, we investigated the relation between clinical variables and disease-free or overall survival after pancreatic resection in patients with pancreatic cancer by univariate and multivariate analyses. The factors included the following 25 factors: age, gender, location of pancreatic carcinoma, postoperative hospital day, TNM classification based on tumor pathology, resection margin, duration of operation, intraoperative blood loss, combined resection of the portal vein or other organs excluding the spleen, surgical site infection, postoperative pulmonary complications, postoperative pancreatic fistula, BMI, diabetes mellitus, texture of the pancreatic parenchyma, intraoperative transfusion of red blood cell concentrate (RCC) or FFP, preoperative serum CEA, preoperative serum CA19-9, pre- or postoperative WBC, pre- or postoperative serum CRP and postoperative ALC/AMC ratio.

Next, we analyzed patients' characteristics in relation to postoperative ALC/AMC ratio, using the following 24 factors: age, gender, location of pancreatic carcinoma, postoperative hospital day, TNM classification based on tumor pathology, resection margin, duration of operation, intraoperative blood loss, combined resection of the portal vein or other organs excluding the spleen, surgical site infection, postoperative pulmonary complications, postoperative pancreatic fistula, BMI, diabetes mellitus, texture of the pancreatic parenchyma, intraoperative transfusion of RCC or FFP, preoperative serum CEA, preoperative serum CA19-9, pre- or postoperative WBC and pre- or postoperative serum.

Recurrence of pancreatic cancer was defined as newly-detected hypovascular abdominal or extra-abdominal tumors by computed tomography (CT), magnetic resonance image (MRI), with or without an increase in tumor markers. For recurrence of pancreatic cancer, chemotherapies or conversion to other chemotherapy were given based on performance status. For patients with poor performance status or refusal, best supportive care was given.

Pulmonary complications were defined as postoperative pneumonia; postoperative respiratory failure with pyrexia, dyspenia and a pulmonary infiltrate on chest X-ray; or pleural effusion that required thoracentesis. Pancreatic fistula was determined by the guideline of the International Study Group on Pancreatic Fistula (ISGPF) (14). Pancreatic fistula is classified into three categories by ISGPF as follows: transient pancreatic fistula (no clinical impact) (grade A); requiring a change in management or adjustment in the clinical pathway (grade B); requiring a major change in clinical management or deviation from the normal clinical pathway (grade C). Combined grade B and grade C is defined as "postoperative clinical pancreatic fistula".

This study was approved by the Ethics Committee of Jikei University School of Medicine (Number: 21-121).

Statistical analysis. Data were expressed as a mean±standard deviation (SD). Univariate analyses were performed using the log-rank test, Mann-Whitney's *U*-test and Chi-square test. Multivariate analyses were performed using the Cox proportional regression model. All *p*-values were considered statistically significant when the association probability was less than 0.05.

Results

Univariate and multivariate analysis of disease-free survival and overall survival after pancreatic resection and clinical variable. Table I lists the relationship between the clinical variables and disease-free survival as well as overall survival after pancreatic resection in patients with pancreatic carcinoma. On univariate analysis, worse disease-free survival was positively-correlated with advanced TNM classification (p=0.0002), intraoperative FFP transfusion (p=0.0395), increased preoperative serum CA19-9 (p=0.0051) and lower postoperative ALC/AMC ratio (p=0.0007, Figure 1A). Worse overall survival was positively-correlated with advanced TNM classification (p=0.0008), intraoperative FFP transfusion (p=0.0343), elevated postoperative serum CRP (p=0.0165) and lower postoperative ALC/AMC ratio (p=0.0029, Figure. 1B).

On multivariate analysis, advanced TNM classification (p=0.007), intraoperative FFP transfusion (p=0.0197), increased preoperative serum CA19-9 (p=0.0075) and lower postoperative ALC/AMC ratio (p=0.0051) were independent predictors of disease-free survival (Table II). In overall survival, advanced TNM classification (p=0.0083), lower postoperative ALC/AMC ratio (p=0.0070) and elevated postoperative serum CRP (p=0.0094) were independent predictors (Table III).

Table I. *Univariate analysis of disease-free and overall survival after pancreatic resection.*

Factor	N	Disease-free survival		Overall survival	
		Median (years)	*p*-Value	Median (years)	*p*-Value
Age					
<60 years	24	1.528	0.0721	3.334	0.1990
≥60 years	87	1.479		2.951	
Gender					
Male	68	1.507	0.6903	3.230	0.8997
Female	43	1.340		3.334	
Location of pancreatic carcinoma					
Head	79	1.430	0.9155	3.071	0.1922
Body or Tail	32	2.468		3.923	
Postoperative hospital day					
<30 days	79	1.433	0.5539	3.334	0.9512
≥30 days	32	1.507		3.244	
TNM classification					
Stage 0, I or II	32	3.715	0.0002		0.0008
Stage III or IV	79	1.241		2.951	
Resection margin					
R0	83	1.433	0.1947	3.244	0.2836
R1 or 2	28	1.479		3.162	
Duration of operation					
<500 min	56	1.573	0.6338	3.600	0.6535
≥500 min	55	1.348		3.244	
Blood loss					
<800 ml	55	1.351	0.3776	3.071	0.0637
≥800 ml	56	1.521		3.334	
Combined resection					
Present	27	1.373	0.1447	3.005	0.0628
Absent	84	1.523		3.868	
Surgical site infection					
Present	16	0.981	0.2161	2.942	0.1552
Absent	95	1.521		3.244	
Pulmonary complications					
Present	15	1.310	0.7732	2.510	0.1184
Absent	96	1.523		3.600	
Pancreatic fistula (B or C)					
Present	21	1.748	0.7411	3.784	0.3220
Absent	90	1.430		3.071	
Body mass index					
<25 kg/m^2	92	1.430	0.0956	3.600	0.3303
≥25 kg/m^2	19	3.348		3.230	
Diabete mellitus					
Present	37	1.479	0.9666	2.921	0.4772
Absent	74	1.430		30334	
Texture of pancreatic parenchyma					
Soft	71	1.479	0.9988	3.315	0.0865
Hard	40	1.523		3.230	
Intraoperative RCC transfusion					
Present	28	1.430	0.9912	3.244	0.6227
Absent	83	1.507		3.600	
Intraoperative FFP transfusion					
Present	12	0.962	0.0395	2.775	0.0343
Absent	99	1.523		3.600	
Preoperative serum CEA					
<10 ng/ml	99	1.507	0.4724	3.230	0.8630
≥10 ng/ml	12	0.912		3.334	
Preoperative serum CA19-9					
<200 U/ml	78	1.521	0.0051	3.868	0.1011
≥200 U/ml	33	1.310		3.005	
Preoperative WBC					
<5,000/μl	41	1.430	0.4086	3.060	0.2548
≥5,000/μl	70	1.479		3.600	
Preoperative serum CRP					
<1.0 mg/dl	94	1.507	0.9820	3.230	0.8958
≥1.0 mg/dl	17	1.030		3.315	
Postoperative WBC					
<10,000/μl	44	1.616	0.4104	3.060	0.9481
≥10,000/μl	67	1.430		3.315	
Postoperative serum CRP					
<10 mg/dl	84	1.252	0.1373	3.060	0.0165
≥10 mg/dl	27	2.266		4.041	
Postoperative serum lymphocyte/monocyte ratio					
<2 times	53	1.153	0.0007	2.942	0.0029
≥2 times	58	1.748		3.600	

RCC, Red blood cell concentrate; FFP, fresh frozen plasma; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; WBC, white blood cell count; CRP, C-reactive protein.

Association between clinical variable and postoperative serum lymphocyte-to-monocyte ratio. Table IV lists the relationship between clinical variables and postoperative ALC/AMC ratio. On univariate analysis, the lower postoperative ALC/AMC ratio group was positively correlated with elevated postoperative WBC (p=0.0021).

Discussion

Pathogenesis and cancer-specific survival after pancreatic resection are thought to be influenced by a deficiency of host immunity. Several investigators have reported the relation between pre- and post-operative immunological findings and

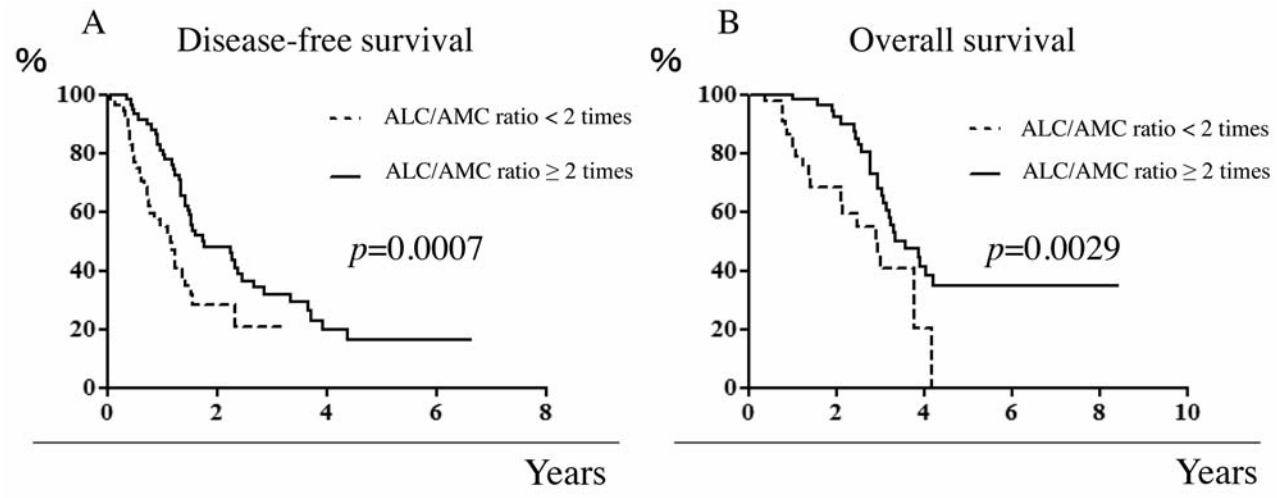

Figure 1. *Lower postoperative peripheral ALC/AMC ratio was associated with worse disease-free survival (1A, p=0.0051) and overall survival (1B, p=0.0029).*

Table II. *Multivariate analysis of disease-free survival after pancreatic resection.*

Factor		Odds ratio (95% CI)	*p*-Value
TNM classification	Stage III and IV	2.326 (1.251-4.326)	0.0076
Intraoperative FFP transfusion	Present	2.213 (1.135-4.314)	0.0197
Postoperative serum Lymphocyte/monocyte ratio	<2 times	2.051 (1.241-3.390)	0.0051
Preoperative serum CA19-9	≥200 U/ml	1.990 (1.202-3.297)	0.0075

FFP: Fresh frozen plasma; CA19-9: carbohydrate antigen 19-9; CI: confidence interval.

Table III. *Multivariate analysis of overall after pancreatic resection.*

Factor		Odds ratio (95% CI)	*p*-Value
TNM classification	Stage III and IV	3.291 (1.359-7.968)	0.0083
Intraoperative FFP transfusion	Present	2.021 (0.866-4.716)	0.1037
Postoperative serum Lymphocyte/monocyte ratio	<2 times	2.414 (1.273-4.579)	0.0070
Postoperative serum CRP	<10 mg/dl	2.557 (1.259-5.195)	0.0094

CRP: C-reactive protein; CI: confidence interval.

tumor recurrence as well as prognosis in patients with various malignant tumors (6-11, 15). Elias *et al.* (16) analyzed mononuclear cell percentages in 55 patients with epidermoid carcinoma of the head and neck and found that high lymphocyte and low monocyte percentages (<10%) correlated with early-stage disease and were associated with better prognosis. For monocyte count, increased preoperative peripheral blood monocyte count (>300/mm^3) negatively correlated with disease-free survival in patients with hepatocellular carcinoma (17) and with overall survival in patients with colorectal liver metastasis (18).

Previously, several investigators reported ALC/AMC ratio at diagnosis was a representative and surrogate biomarker of host immunity against tumor microenvironment as well as a prognostic factor for survival in patients with lymphomas (19, 20). Lymphopenia is thought to be a marker of immune suppression, and monocyte regarded as a surrogate marker of the tumor microenvironment (21, 22). However, the role of

Table IV. *Univariate analysis of patient's characteristics in relation to postoperative serum lymphocyte/monocyte ratio.*

Factor		Postoperative serum lymphocyte/monocyte ratio		*p*-Value
		≥2 times (n=58)	<2 times (n=53)	
Age	Years	68.8±8.6	64.3±13.2	0.1742
Gender	Male:Female	32:26	36:17	0.2363
Location	Head:Body or Tail	42:16	37:16	0.9247
Postoperative day	Days	32.2±49.0	24.4±13.2	0.2839
TNM classification	Stage 0, I or II:III or IV	20:38	12:41	0.2429
Resection margin	R0:R1 or R2	43:15	40:13	0.9999
Duration of operation	min	500.2±137.2	521.2±144.2	0.3855
Intraoperative blood loss	ml	1,832.1±5,076.1	1,036.4±778.3	0.6751
Combined resection	Present:Absent	15:43	12:41	0.8606
Surgical site infection	Present:Absent	2:56	14:39	0.0015
Pulmonary complications	Present:Absent	7:51	8:45	0.8491
Pancreatic fistula	Present:Absent	9:49	12:41	0.4735
Body-mass index	≥25 kg/m^2:<25 kg/m^2	9:49	10:43	0.8273
Diabetes mellitus	Present:Absent	22:36	15:38	0.3815
Texture of pancreatic parenchyma	Soft:Hard	38:20	33:20	0.8725
Intraoperative RCC transfusion	Present:Absent	16:42	12:41	0.7022
Intraoperative FFP transfusion	Present:Absent	7:51	5:48	0.8860
Preoperative serum CEA	ng/ml	5.37±4.24	10.0±38.7	0.9553
Preoperative serum CA19-9	U/ml	273.6±533.6	216.7±312.1	0.9154
Preoperative WBC	/μl	5,770.7±2,462.7	5,809.2±2,061.3	0.6304
Preoperative serum CRP	mg/dl	0.792±2.30	2.17±10.8	0.7454
Postoperative WBC	/μl	10,025.9±3,328.9	12,084.9±3,203.4	0.0021
Postoperative serum CRP	mg/dl	8.26±3.68	8.70±3.19	0.4982

CC, Red blood cell concentrate; FFP, fresh frozen plasma; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; WBC, white blood cell count; CRP, C-reactive protein.

postoperative ALC/AMC ratio is unknown in patients with operable solid tumors. To our knowledge, this is the first report in which postoperative ALC/AMC ratio appears to be an independent risk factor of disease-free as well as overall survival in patients with operable pancreatic cancer after pancreatic resection. Biological reasons for the relationship between lower postoperative ALC/AMC ratio and poor prognosis in patients with resected pancreatic carcinoma include the ability of pancreatic carcinoma cells to escape host immune surveillance by inducing immunosuppression. Several investigators reported that the number of forkhead box P3 (FOXP3$^+$), CD4$^+$ and/or CD25$^+$ regulatory T (Treg)-cells in peripheral blood and/or tumors are increased, and that elevated Treg count after surgery was a poor prognostic factor of patients with pancreatic carcinoma. Actually, a reduced number of cytotoxic CD8$^+$ cells or increased number of Treg cells in peripheral blood and/or tumors were correlated with a worse prognosis in patients with pancreatic carcinoma because Treg cells inhibited the proliferation and tumor-infiltration of CD4$^+$ and CD8$^+$ lymphocytes (7, 23). On the other hand, the monocyte subset in peripheral blood includes the dendritic cell (DC) population. Some investigators have shown that DCs with regulatory function (regulatory DCs) cause immunosuppression by activated and differentiated Treg cells in patients with malignant tumor (24). Therefore, postoperative immunological and inflammatory status in patients with pancreatic carcinoma is one of the most important factors for tumor recurrence and patients' prognosis. In the present study, postoperative ALC/AMC ratio was shown to be an independent prognostic factor of both disease-free and overall survival in patients with pancreatic carcinoma after pancreatic resection. Because postoperative decrease of lymphocyte counts or increase of monocyte counts also may reflect immunological and inflammatory status of patients, and may correlate with prognosis after pancreatic resection for pancreatic carcinoma. Patients' risk stratification using postoperative ALC/AMC ratio is easy because it is routinely examined in perioperative patients' management. Further investigation to clarify the relationship between immunosuppressive mechanisms caused by postoperative ALC/AMC ratio and tumor progression is needed.

Conclusion

Lower postoperative peripheral ALC/AMC ratio may have a negative impact on recurrence and overall survival after pancreatic resection for pancreatic carcinoma.

Conflicts of Interest

None declared.

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