Keywords: Pancreas cancer, C-reactive protein, albumin

INTRODUCTION

The prognosis of patients with pancreatic ductal adenocarcinoma (PDAC) is extremely poor. Despite the development of surgical techniques and perioperative chemotherapy, the 5-year survival rate is 8% in the United States (1). PDAC is also the fifth most common cause of cancer death in Japan (2). The frequency of postoperative recurrence remains high in patients with PDAC (3); therefore, a novel prognostic marker to predict recurrence is required.

Nowadays, tumour-related pathological factors have been identified as predictive markers in patients with PDAC, including tumour stage, lymph node metastasis, vascular and lymphatic invasion and perineural invasion. Several predictive markers based on preoperative systemic inflammation and nutritional status such as the neutrophil–lymphocyte ratio (NLR), platelet–lymphocyte ratio (PLR), modified Glasgow prognostic score (mGPS), and prognostic index (PNI) were reported in lung cancer (4), hepatocellular carcinoma (5), melanoma (6), renal cell carcinoma (7), gastric cancer (8), intrahepatic cholangiocarcinoma (9) and colorectal cancer (10). These factors has been reported as useful biomarker to predict the prognosis in PDAC (11, 12).

C-reactive protein (CRP) to albumin ratio is based on two acute inflammatory protein (13). The CRP–albumin ratio (CAR) was reported as a prognostic factor of resectable hepatocellular carcinoma, colorectal cancer, oesophageal cancer, gastric cancer, renal cancer, and pancreatic cancer (14-18).

The aim of this study was to analyse and validate the significance of CAR in resectable pancreatic cancer at our hospital.

PATIENTS AND METHODS

One hundred sixty-three patients who underwent curative surgical resection for PDAC during 2004 to 2018 at the University of Tokushima Hospital were enrolled in this retrospective study. Fourteen patients were excluded because of non-curative resection. All the patients had PDAC proven histologically. Finally, 149 patients were analysed in this study. Laboratory data including serum CRP and albumin were collected within 1 month before surgery. Patients were followed up monthly for tumour markers including CEA and CA19-9 and underwent computed tomography every 4–6 months. When recurrence was suspected, precise diagnostic imaging studies including positron emission tomography were performed. After confirmation of recurrent pancreatic cancer, systemic chemotherapy, radiation therapy, or best supportive care were indicated. The clinicopathological characteristics of the patients are shown in Table 1. All patients signed informed consent for this study, which was approved by the clinical ethics committee at our institution (#3362).

The NLR, PNI, PLR, and mGPS were calculated with cutoff values of 3, 45, 150, and 1, respectively. The CAR was also calculated. To determine the appropriate cutoff value of CAR, receiver operation characteristic (ROC) curve analysis was performed. The cutoff value of CAR was 0.06 and the AUC value was 0.54223.

Statistical analysis

Statistical comparisons for significance were made using chi-squared test or Fisher’s exact test with one degree of freedom, as appropriate. Cumulative patient survival and recurrence-free survival were determined using the Kaplan–Meier method with a log-rank test. Univariate and multivariate analyses were performed using a Cox proportional hazard model. A P-value of less than 0.05 was considered statistically significant. Statistical analysis was performed with JMP 14 software (SAS Institute, Cary, NC, USA).
RESULTS

Comparison of prognostic factors for overall survival (OS) in patients with surgical resection for PDAC

The OS rate was significantly worse in patients with a high CAR compared with those with a low CAR (Figure 1A). The prognostic factors for OS in patients with surgical resection for PDAC is shown in Table 2. In the univariate analysis, seven factors were independent prognostic factors for OS including CAR (HR 2.826, 95% CI 1.720–4.645, \( P < 0.001 \)), PNI (HR 2.250, 95% CI 1.384–3.645, \( P = 0.0007 \)), PLR (HR 1.643, 95% CI 1.022–2.684, \( P = 0.0045 \)), CA19-9 (HR 2.085, 95% CI 1.314–3.311, \( P = 0.0013 \)), adjuvant chemotherapy (HR 2.208, 95% CI 1.700–5.114, \( P = 0.0001 \)), T3+4 (HR 2.873, 95% CI 1.232–2.966, \( P = 0.0095 \)). In the multivariate analysis of these seven factors, three factors were independent prognostic factors for OS including CAR (HR 2.668, 95% CI 1.523–4.673), CA19-9 (HR 2.011, 95% CI 1.213–3.334), and adjuvant chemotherapy (HR 2.231, CI 1.379–3.609).

Comparison of prognostic factors for disease-free survival (DFS) in patients with surgical resection for PDAC

The DFS rate was significantly worse in patients with a high CAR compared with those with a low CAR (Figure 1B). The prognostic factors for DFS with surgical resection for PDAC are shown in Table 3. In the univariate analysis, five factors were independent prognostic factors for DFS including CAR (HR 2.826, 95% CI 1.720–4.645, \( P < 0.001 \)), PNI (HR 1.643, 95% CI 1.022–2.684, \( P = 0.0045 \)), CA19-9 (HR 2.085, 95% CI 1.314–3.311, \( P = 0.0013 \)), adjuvant chemotherapy (HR 2.208, 95% CI 1.700–5.114, \( P = 0.0001 \)), T3+4 (HR 2.873, 95% CI 1.232–2.966, \( P = 0.0095 \)). In the multivariate analysis of these five factors, three factors were independent prognostic factors for DFS including CAR (HR 2.668, 95% CI 1.523–4.673, \( P = 0.0013 \)), CA19-9 (HR 2.011, 95% CI 1.213–3.334), and adjuvant chemotherapy (HR 2.231, CI 1.379–3.609).
Clinicopathological features according to the CAR

Clinicopathological factors were compared between the high CAR and low CAR groups in Table 4. The high CAR group was correlated with higher CRP, lower serum albumin, higher serum fibrinogen, low LCR, high NLR, low PNI and high mGPS. In the tumour-related factors, the high CAR group was significantly associated with T (3+4). Also, the high CAR group showed an association with portal vein resection and adjuvant chemotherapy but this was not significant. The other factors showed no significant difference between these two groups.

Table 2. OS related variables

| Factor          | Univariate p-value | HR (95% CI)       | Multivariate p-value | HR (95% CI)       |
|-----------------|--------------------|-------------------|----------------------|-------------------|
| CAR             | < 0.06/ ≥ 0.06     | 0.0001            | 2.826 (1.720-4.645)  | 0.0006            | 2.668 (1.523-4.672) |
| LCR             | < 15000/ ≥ 15000   | 0.0505            | 1.593 (0.390-1.007)  |                   |                   |
| NLR             | < 3/ ≥ 3           | 0.941             | 1.021 (0.603-1.672)  |                   |                   |
| PNI             | < 45/ ≥ 45         | 0.0007            | 2.250 (1.384-3.645)  | 0.3571            | 1.282 (0.755-2.175) |
| PLR             | < 150/ ≥ 150       | 0.0045            | 1.643 (1.022-2.684)  | 0.6254            | 1.139 (0.675-1.923) |
| mGPS            | 0/ ≥ 1,2           | 0.6799            | 2.270 (0.806-5.190)  |                   |                   |
| Gender          | Female/male        | 0.7023            | 1.315 (0.829-2.087)  |                   |                   |
| Age             | < 70/ ≥ 70         | 0.1558            | 1.391 (0.874-2.201)  |                   |                   |
| BMI kg/m²       | < 25/ ≥ 25         | 0.5203            | 1.216 (0.639-2.143)  |                   |                   |
| CEA ng/ml       | < 5/ ≥ 5           | 0.5878            | 1.203 (0.578-2.248)  |                   |                   |
| CA19-9 U/ml     | < 300/ ≥ 300       | 0.0013            | 2.085 (1.314-3.311)  | 0.0068            | 2.011 (1.213-3.334) |
| Resection type  | PD/DP/TP           | 0.4474            | 1.190 (0.726-1.951)  |                   |                   |
| PV resection    | No/yes             | 0.4731            | 1.310 (0.575-2.600)  |                   |                   |
| NAC(−)          | No/yes             | 0.9223            | 1.039 (0.433-2.116)  |                   |                   |
| AC(−)           | No/yes             | 0.0022            | 2.208 (1.396-3.491)  | 0.0011            | 2.231 (1.379-3.609) |
| T(3+4)          | No/yes             | < 0.001           | 2.873 (1.700-5.114)  | 0.0870            | 1.539 (0.906-3.166) |
| N(+)            | No/yes             | 0.0095            | 1.846 (1.143-2.945)  | 0.0087            | 1.693 (0.906-3.166) |

Table 3. DFS related variables

| Factor          | Univariate p-value | HR (95% CI)       | Multivariate p-value | HR (95% CI)       |
|-----------------|--------------------|-------------------|----------------------|-------------------|
| CAR             | < 0.06/ ≥ 0.06     | 0.0001            | 2.826 (1.720-4.645)  | 0.0103            | 1.990 (1.198-3.307) |
| LCR             | < 15000/ ≥ 15000   | 0.0030            | 1.843 (0.357-8.022)  |                   |                   |
| NLR             | < 3/ ≥ 3           | 0.3812            | 1.176 (0.759-1.792)  |                   |                   |
| PNI             | < 45/ ≥ 45         | 0.0308            | 1.542 (1.008-2.340)  | 0.6387            | 1.113 (0.708-1.735) |
| PLR             | < 150/ ≥ 150       | 0.2235            | 1.270 (0.840-1.928)  |                   |                   |
| mGPS (0/1+2)    | 0/ ≥ 1,2           | 0.0529            | 1.956 (0.662-6.462)  |                   |                   |
| Gender (F/M)    | Female/male        | 0.9196            | 1.040 (0.698-1.553)  |                   |                   |
| Age > 70        | < 70/ ≥ 70         | 0.4904            | 1.176 (0.780-1.759)  |                   |                   |
| BMI > 25 kg/m²  | < 25/ ≥ 25         | 0.3700            | 1.285 (0.729-2.158)  |                   |                   |
| CEA > 5 ng/ml   | < 5/ ≥ 5           | 0.1032            | 1.604 (0.866-2.713)  |                   |                   |
| CA19-9 > 300 U/ml | < 300/ ≥ 300    | 0.0031            | 1.864 (1.239-2.797)  | 0.0083            | 1.802 (1.166-2.776) |
| PD/DP/TP        | PD/DP/TP           | 0.4415            | 1.322 (0.850-2.058)  |                   |                   |
| PV resection    | No/yes             | 0.1937            | 1.466 (0.809-2.478)  |                   |                   |
| NAC(−)          | No/yes             | 0.4155            | 1.306 (0.709-2.405)  |                   |                   |
| AC(−)           | No/yes             | 0.0020            | 1.884 (1.257-2.824)  | 0.0032            | 1.884 (1.245-2.851) |
| T(3+4)          | No/yes             | 0.0032            | 1.890 (1.232-2.966)  | 0.0646            | 1.548 (0.974-2.514) |
| N(+)            | No/yes             | 0.0561            | 1.494 (0.979-2.252)  |                   |                   |
DISCUSSION

In this study, OS and DFS were significantly worse in patients with resectable PDAC and a high CAR of > 0.06. The CAR was an independent prognostic factor for OS and DFS in the multivariate analysis. To the best of our knowledge, no study has compared other prognostic markers such as lymphocyte to CRP ratio (LCR), NLR, PNI, PLR, and mGPS in patients with resectable PDAC.

In our study, the higher value of CAR was correlated with other prognostic markers which calculated with CRP and serum albumin and it was statistically superior to the other prognostic markers. The higher value of CAR was also correlated with higher T factor which reflected in local advancement of the pancreatic cancer.

The precise mechanism of the relation between the CAR and prognosis in patients with resectable PDAC has not been fully elucidated yet. Several possible mechanism has been reported in basic research articles. Mantovani A et al. reported that the migration, invasion, and metastasis of cancer cells could contribute to the inflammation through the activation of several chemokines such as CXCR4 and its ligand CXCL12 (19); as a result, the CRP reflects a cancer-specific inflammatory response to tumour necrosis or local tissue damage and indicates a favourable environment for the establishment and growth of distant metastasis. Yang J et al. also reported that CRP binding activated Fc receptors and stimulated the P38/AKT, ERK, and NFkB pathways and inhibited caspase cascade activation induced. CRP also enhanced myeloma cell secretion of IL-6 and IL-6-protected myeloma cells resulting from chemotheraphy drug-induced apoptosis. Therefore CRP could be one of the candidate of new therapeutic approach for cancer in basic research (20).

On the other hand, serum albumin level is low in patients with PDAC especially in the perioperative period because of malnutrition and cachexia. Improvement of perioperative immune-nutritional status reduced post-operative inflammation (21, 22). Poor nutritional state in pancreatic surgery has been reported to be associated with worse postoperative survival (11). Therefore, the CAR calculated with two critical factors could represent the inflammation and nutritional status of PDAC patients.

Recently, CAR was also reported as one of the poor prognostic marker not only in solid cancer but also hematologic cancer such as malignant lymphoma (23). Moreover, Araki T et al. reported that evaluation of CAR could predict therapeutic response to immune check point inhibitor such as nivolumab (24).

There were several limitations to this study. This study was retrospective and the sample size was relatively small. Further studies using a larger sample size and a prospective approach or propensity score matching are required.

In conclusion, the preoperative CAR is a poor prognostic factor in patients with resectable PDAC. CAR can be simply calculated using preoperative serum CRP and albumin and reflects local inflammation caused by invasion of PDAC.

COMPETING INTERESTS

The authors declare that they have no competing interests.

ACKNOWLEDGEMENTS

We thank H. Nikki March, PhD, from Edanz Group (https://en-author-services.edanzgroup.com/ac) for editing a draft of this manuscript.

REFERENCES

1. Siegel RL, Miller KD, Jemal A: Cancer statistics, 2018. CA Cancer J Clin 68(1): 7-30, 2018

2. Inoue D, Ozaka M, Matsuyama M, Yamada I, Takano K, Saiura A, Ishii H: Prognostic value of neutrophil-lymphocyte ratio and level of C-reactive protein in a large cohort of pancreatic cancer patients: a retrospective study in a single institute in Japan. Jpn J Clin Oncol 45(1): 61-6, 2015

3. Doi R, Imamura M, Hosotani R, Imaizumi T, Hatori T, Takasaki K, Furukoshi A, Wakisagi H, Asano T, Hishimura S: Surgery versus radiochemotherapy for resectable locally invasive pancreatic cancer: final results of a randomized multi-institutional trial. Surgery today 38(11): 1021-8, 2008

4. Forrest LM, McMillan DC, McArdle CS, Angerson WJ, Dunlop DJ: Comparison of an inflammation-based prognostic score (GPS) with performance status (ECOG) in patients receiving platinum-based chemotherapy for inoperable non-small-cell lung cancer. British Journal of Cancer 90(9): 1704-6, 2004

5. Hashimoto K, Ikeda Y, Kornaga D, Tanoue K, Hamatake M, Kawasaki K, Yamada T, Iwatani Y, Akazawa K, Takenaka K: The impact of preoperative serum C-reactive protein on the prognosis of patients with hepatocellular carcinoma. Cancer 103(9): 1856-64, 2005

6. Schmidt H, Suci S, Punt CJ, Gore M, Kruit W, Patel P, Lienard D, von der Maase H, Eggermont AM, Keilholz U: Pretreatment levels of peripheral neutrophils and leucocytes as independent predictors of overall survival in patients with American Joint Committee on Cancer Stage IV Melanoma: results of the EORTC 18951 Biochemotherapy Trial. Journal of Clinical Oncology: official journal of the
American Society of Clinical Oncology 25(12) : 1562-9, 2007
7. Karakiewicz PI, Hutterer GC, Trinh QD, Jeldres C, Perrotte P, Gallina A, Tostain J, Patard JJ: C-reactive protein is an informative predictor of renal cell carcinoma-specific mortality: a European study of 313 patients. Cancer 110(6) : 1241-7, 2007
8. Lee S, Oh SY, Kim SH, Lee JH, Kim MC, Kim KH, Kim HJ: Prognostic significance of neutrophil lymphocyte ratio and platelet lymphocyte ratio in advanced gastric cancer patients treated with FOLFOX chemotherapy. BMC Cancer 13 : 350, 2013
9. Noguchi D, Kuriyama N, Nakagawa Y, Maeda K, Shinkai T, Gyoten K, Hayasaki A, Fujii T, Iizawa Y, Tanemura A: The prognostic impact of lymphocyte-to-C-reactive protein score in patients undergoing surgical resection for intrahepatic cholangiocarcinoma: A comparative study of major representative inflammatory/immunonutritional markers. PloS one 16(1) : e0245946, 2021
10. Shafique K, Proctor MJ, McMillan DC, Leung H, Smith K, Sloan B, Morrison DS: The modified Glasgow prognostic score in prostate cancer: results from a retrospective clinical series of 744 patients. BMC Cancer 13 : 292, 2013
11. Kanda M, Fujii T, Kodera Y, Nagai S, Takeda S, Nakao A: Nutritional predictors of postoperative outcome in pancreatic cancer. The British journal of surgery 98(2) : 268-74, 2011
12. Sierzega M, Lenart M, Rutkowska M, Surman M, Mytar B, Matyja A, Siedlar M, Kulig J: Preoperative Neutrophil-Lymphocyte and Lymphocyte-Monocyte Ratios Reflect Immune Cell Population Rearrangement in Resectable Pancreatic Cancer. Annals of surgical oncology 24(3) : 808-15, 2017
13. Yamada S, Fuji T, Yabusaki N, Murotani K, Iwata N, Kanda M, Tanaka C, Nakayama G, Sugimoto H, Koike M: Clinical Implication of Inflammation-Based Prognostic Score in Pancreatic Cancer: Glasgow Prognostic Score Is the Most Reliable Parameter. Medicine (Baltimore) 95(18) : e3582, 2016
14. Haruki K, Shibata H, Fujiwara Y, Furukawa K, Wakiyama S, Ogawa M, Ishida Y, Misawa T, Yanaga K: Perioperative change in peripheral blood monocyte count may predict prognosis in patients with colorectal liver metastasis after hepatic resection. Journal of surgical oncology 2012.
15. Ishizuka M, Nagata H, Takagi K, Iwasaki Y, Shibuya N, Kubota K: Clinical Significance of the C-Reactive Protein to Albumin Ratio for Survival After Surgery for Colorectal Cancer. Annals of surgical oncology 23(3) : 900-907, 2016
16. Kinoshita A, Onoda H, Imai N, Iwaku A, Oishi M, Tanaka K, Fushiyama N, Koike K, Nishino H, Matsuishima M: The C-reactive protein/albumin ratio, a novel inflammation-based prognostic score, predicts outcomes in patients with hepatocellular carcinoma. Annals of surgical oncology 22(3) : 803-810, 2015
17. Liu X, Sun X, Liu J, Kong P, Chen S, Zhan Y, Xu D: Preoperative C-Reactive Protein/Albumin Ratio Predicts Prognosis of Patients after Curative Resection for Gastric Cancer. Transl Oncol 8(4) : 339-345, 2015
18. Wei XL, Wang FH, Zhang DS, Qiu MZ, Ren C, Jin Y, Zhou YX, Wang DS, He MM, Bai L: A novel inflammation-based prognostic score in esophageal squamous cell carcinoma: the C-reactive protein/albumin ratio. BMC Cancer 15 : 350, 2015
19. Lim JE, Chien MW, Earle CC: Prognostic factors following curative resection for pancreatic adenocarcinoma: a population-based, linked database analysis of 396 patients. Annals of surgery 237(1) : 74-85, 2003
20. Jung J, Lee H, Heo JY, Chang MH, Lee E, Park WS, Park JH, Eom HS: High level of pre-treatment C-reactive protein to albumin ratio predicts inferior prognosis in diffuse large B-cell lymphoma. Scien Rep 11(1) : 2674, 2021
21. Araki T, Tateishi K, Tonehara K, Hirota S, Komatsu M, Yamamoto M, Kanda S, Kuraishi M, Hanaoka M, Koizumi T: Clinical utility of the C-reactive protein: albumin ratio in non-small cell lung cancer patients treated with nivolumab. Thorac Cancer 2021.
22. Mantovani A, Allavena P, Sica A, Balkwill F: Cancer-related inflammation. Nature 454(7203) : 436-444, 2008
23. Yang J, Wenzeman M, Zhang X, Lin P, Wang M, Qian J, Wan B, Kwak LW, Yu L, Yi Q: Human C-reactive protein binds activating Fcgamma receptors and protects myeloma tumor cells from apoptosis. Cancer cell 12(3) : 252-265, 2007
24. Bozzetti F, Mariani L: Perioperative nutritional support of patients undergoing pancreatic surgery in the age of ERAS. Nutrition 30(11-12) : 1267-1271, 2014