Original Article/Pancreas

Combined preoperative platelet-to-lymphocyte ratio and serum carbohydrate antigen 19–9 level as a prognostic factor in patients with resected pancreatic cancer

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ABSTRACT

Background: Carbohydrate antigen 19–9 (CA19-9) is the most frequently used tumor marker and serves as a prognostic indicator in patients with pancreatic cancer (PC). The platelet-to-lymphocyte ratio (PLR) is thought to be an inflammation-related serum marker. An elevated PLR represents increased inflammatory status and is associated with poor prognosis in patients with various cancers including PC.
Methods: This study involved 103 patients with a histopathological diagnosis of pancreatic ductal adenocarcinoma who underwent pancreatectomy. The patients were assessed to determine the prognostic significance of the combination of the PLR and CA19-9 level.
Results: Based on the receiver operating characteristic analysis results, the patients were divided into PLR_{High} (PLR $\geq$ 129.1) and PLR_{Low} (PLR < 129.1) groups and into $CA19-9_{High}$ (CA19-9 $\geq$ 74.0 U/mL) and $CA19-9_{Low}$ (CA19-9 < 74.0 U/mL) groups. The cumulative 5-year overall survival (OS) and disease-specific survival (DSS) rates significantly differed by both the PLR (PLR_{High} group: 19.5% and 22.9%; PLR_{Low} group: 39.1% and 45.9%) and CA19-9 ($CA19-9_{High}$ group: 19.1% and 25.6%; $CA19-9_{Low}$ group: 41.0% and 41.0%). We then divided the patients into Groups A ($PLR_{Low}/CA19-9_{Low}$), B ($PLR_{Low}/CA19-9_{High}$ or $PLR_{High}/CA19-9_{Low}$), and C ($PLR_{High}/CA19-9_{High}$). The cumulative 5-year OS rates in Groups A, B, and C were 44.0%, 31.9%, and 11.9%, respectively ($P=0.002$). The cumulative 5-year DSS rates in Groups A, B, and C were 47.7%, 36.4%, and 16.8%, respectively ($P=0.002$). Multivariate analysis revealed that the combination of the PLR and CA19-9 was an independent prognostic factor in patients with resected PC.
Conclusions: The combination of the PLR and CA19-9 is useful for predicting the prognosis of patients with resected PC.

Introduction

Pancreatectomy with regional lymph node dissection is the mainstay curative treatment for pancreatic cancer (PC). However, the survival of patients with PC after macroscopically curative resection remains low (5-year survival rate of 20.7%–23.9%, median survival duration of 22.3–23.6 months) even after administration of adjuvant chemotherapy using gemcitabine [1–3]. A recent study showed that the 5-year overall survival (OS) rate of patients with stage I to III PC with no local residual or microscopic residual tumor after pancreatectomy with regional lymph node dissection improved up to 44.1% by using S-1 as adjuvant chemotherapy [4]. Thus, identifying and carefully monitoring patients with PC with a high possibility of recurrence after curative pancreatectomy is important in improving their prognoses. To this end, reliable prognostic indicators for PC are indispensable. Serum tumor markers are easy to measure and useful for establishing a diagnosis, predicting survival rates, and monitoring recurrence; the tumor marker most commonly used for patients with PC is carbohydrate antigen 19–9 (CA19-9) [5,6].

CA19-9 is a modified Lewis (a) blood group antigen and is currently recommended for clinical use by the National Comprehensive Cancer Network guidelines for PC. Several reports have described the usefulness of CA19-9 for diagnosis in symptomatic patients or for monitoring therapy and as a prognostic factor for PC [5,6]. However, approximately 20% of patients with PC have a normal serum CA19-9 level preoperatively [7]. Therefore, a more sensitive marker is needed to improve the prognosis of patients with PC.

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Although CA19-9 is mainly derived from the cancer itself, numerous studies have demonstrated that some patient-related factors reflecting inflammation, malnutrition, and the immune status of patients are closely associated with the outcome of various cancers. Among these patient-related factors, a close correlation between inflammation and cancer has long been known. Virchow first discovered the correlation between inflammation and malignant tumors in 1863 [8]. Since then, it has become widely accepted that inflammation plays a role in tumor pathogenesis and that an inflammatory microenvironment is an essential component of all tumors [9]. Some serum markers reflect a patient's inflammatory status, such as the neutrophil count, platelet count, and C-reactive protein level. These serum parameters can be easily measured by blood analysis and are frequently used in routine clinical practice. These inflammation-related serum markers have recently been used to develop new prognostic indicators in patients with cancer. The platelet-to-lymphocyte ratio (PLR) is one of these markers and has been shown to be a useful prognostic indicator in patients with various types of cancers, including PC [10–14].

The differences in the origins of the PLR and the serum CA19-9 level have allowed us to speculate that combining the PLR and serum CA19-9 level might be superior to using only the PLR or serum CA19-9 level in predicting the prognosis in patients with PC. To the best of our knowledge, no reports have described the prognostic significance of the combination of the PLR and serum CA19-9 level in patients with cancer including PC. Therefore, this study aimed to evaluate the prognostic significance of the combination of the PLR and serum CA19-9 level in patients with PC.

Methods

Patients

This study was based on a retrospective analysis of 103 patients with a histopathological diagnosis of pancreatic ductal adenocarcinoma who underwent pancreatectomy at Tottori University Hospital from January 2005 to December 2016. All patients underwent either pancreatoduodenectomy, distal pancreatectomy, or total pancreatectomy with regional lymphadenectomy. Among the 103 patients included in this study, 1 patient underwent R2 resection and 3 patients had distant metastasis (para-aortic lymph node metastasis, $n = 2$; peritoneal metastasis, $n = 1$). Fifty-seven patients (55.3%) underwent adjuvant chemotherapy after the operation (gemcitabine, $n = 19$; S-1, $n = 36$; uracil-tegafur, $n = 2$). The patients were periodically checked for early recurrence by diagnostic imaging, such as ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET). Causes of death and patterns of recurrence were determined by reviewing the medical records (including the laboratory data and US, CT, MRI, and PET findings) or by direct inquiry with family members. Clinicopathologic data, such as age, sex, tumor localization, primary tumor size, lymph node metastasis, lymphatic involvement, vascular involvement, perineural invasion, and adjuvant chemotherapy, were obtained from the database. Pathological classification of the primary tumor, lymph node metastasis, distant metastasis, and histological grading were determined according to the 7th edition of the Union for International Union Against Cancer classification system of TNM [15]. Lymphatic vessel invasion, blood vessel invasion, and perineural invasion were determined according to the General Rules for the Study of Pancreatic Cancer, 7th edition, by the Japan Pancreas Society [16]. We also collected data regarding the serum CA 19–9 level, peripheral lymphocyte count, and peripheral platelet count from blood tests performed preoperatively (within 1 month before the operation) and as indicated in the patients' records. The PLR was calculated by dividing the peripheral platelet count by the peripheral lymphocyte count.

Statistical analysis

Continuous variables were compared using the Mann–Whitney U test. Optimal cutoff values and areas under the curve (AUCs) for the PLR and serum CA19-9 level with respect to the 5-year OS rate were calculated using receiver operating characteristic (ROC) analysis. Survival curves were constructed by the Kaplan–Meier method, and the prognostic differences among survival curves were examined with log-rank tests. Univariate and multivariate analysis of factors considered prognostic of OS were performed using Cox's proportional hazards model. The covariates included in univariate analysis were age, tumor size, tumor location, histological grading, lymph node involvement, lymphatic vessel invasion, blood vessel invasion, perineural invasion, serum bilirubin level, adjuvant chemotherapy, bile drainage, and the combination of the PLR and serum CA19-9 level. The covariates with $P < 0.1$ in univariate analysis were included in multivariate analysis. A P value of < 0.05 was considered significant. All statistical analyses were performed using SPSS software (SPSS for Windows Version 24; IBM Corp., Armonk, NY, USA).

Results

The mean PLR and serum CA19-9 level were 149.2 ± 68.6 and 309.2 ± 617.3 U/mL, respectively. There was no significant correlation between the PLR and serum CA19-9 level (Fig. 1).

The correlations of PLR and serum CA19-9 level to clinicopathological variables are shown in Table 1. Patients with larger tumors (≥ 29.4 mm), those with a tumor located in the pancreas head, and those with lymph node metastasis had a significantly higher PLR than patients with smaller tumors ($P = 0.002$), those with a tumor located in the pancreas body and tail ($P = 0.021$), and those without lymph node metastasis ($P = 0.010$), respectively. Patients with lymph node metastasis and those with lymphatic vessel invasion had a significantly higher serum CA19-9 level than those without lymph node metastasis ($P = 0.003$) and those without lymphatic vessel invasion ($P = 0.022$), respectively.

ROC analysis with respect to the 5-year OS rate indicated that the highest Youden indices (sensitivity + specificity − 1) with
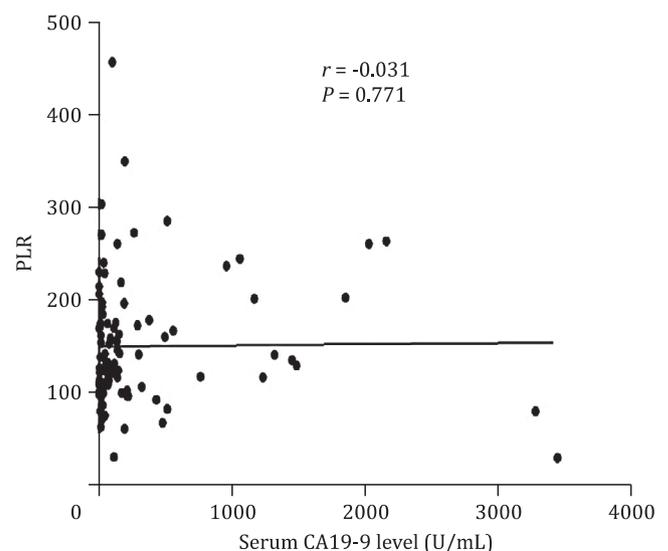

Fig. 1. The correlation between the PLR and serum CA19-9 level. PLR: platelet-to-lymphocyte ratio; CA19-9: carbohydrate antigen 19–9.

Table 1

Correlations of PLR and serum CA19-9 level to clinicopathological variables in patients with resected pancreatic cancer.

Variables	PLR	P value	CA19-9 (U/mL)	P value
Age (yr)		0.351		0.745
<70 ($n = 42$)	141.3 ± 57.6		277.6 ± 588.9	
≥70 ($n = 61$)	154.5 ± 75.2		330.1 ± 640.0	
Sex		0.187		0.940
Male ($n = 64$)	140.8 ± 61.2		315.1 ± 605.7	
Female ($n = 39$)	162.9 ± 78.1		299.4 ± 643.8	
Tumor size (mm)[a]		**0.002**		0.762
<29.4 ($n = 54$)	131.1 ± 53.8		307.1 ± 678.3	
≥29.4 ($n = 47$)	170.9 ± 75.1		303.9 ± 551.3	
Tumor localization		**0.021**		0.071
Head ($n = 66$)	159.6 ± 68.0		376.8 ± 639.2	
Body and tail ($n = 37$)	130.5 ± 66.4		188.6 ± 564.4	
Histological grading[b]		0.557		0.364
G1 ($n = 51$)	148.5 ± 76.0		247.1 ± 564.1	
G2-4 ($n = 52$)	149.8 ± 61.1		370.0 ± 665.2	
Lymph node metastasis		**0.010**		**0.003**
Absent ($n = 43$)	133.6 ± 66.4		153.3 ± 356.6	
Present ($n = 60$)	160.3 ± 68.4		420.9 ± 733.4	
Lymphatic vessel invasion[c]		0.905		**0.022**
0/1 ($n = 52$)	155.8 ± 77.8		196.4 ± 411.0	
2/3 ($n = 51$)	142.4 ± 57.6		424.2 ± 760.5	
Blood vessel invasion[d]		0.356		0.516
0/1 ($n = 50$)	141.3 ± 54.4		250.0 ± 421.0	
2/3 ($n = 53$)	156.6 ± 79.5		365.0 ± 757.5	
Perineural invasion[e]		0.242		0.604
0/1 ($n = 24$)	137.8 ± 65.1		134.5 ± 216.0	
2/3 ($n = 79$)	152.6 ± 69.6		362.3 ± 687.2	
Adjuvant chemotherapy		0.053		0.652
Absent ($n = 47$)	137.2 ± 68.8		357.2 ± 777.3	
Present ($n = 56$)	159.2 ± 67.3		268.6 ± 444.7	

[a] Data not available for two patients.
[b] G1, well-differentiated; G2, moderately differentiated; G3, poorly differentiated; G4, undifferentiated.
[c] Grade of lymphatic vessel invasion.
[d] Grade of vessel invasion.
[e] Grade of perineural invasion. PLR: platelet-to-lymphocyte ratio; CA19-9: carbohydrate antigen 19–9.

the optimal cutoff values were as follows: PLR, 129.1 ($P = 0.32$; AUC, 0.560; 95% confidence interval [CI], 0.444–0.676) and CA19-9, 74.0 U/mL ($P = 0.005$; AUC, 0.667; 95% CI, 0.560–0.775). Based on these results, the patients were subgrouped as follows: PLR$_{High}$ (PLR ≥ 129.1; $n = 55$) or PLR$_{Low}$ (PLR < 129.1; $n = 48$) and CA19-9$_{High}$ (CA19-9 ≥ 74.0 U/mL; $n = 51$) or CA19-9$_{Low}$ (CA19-9 < 74.0 U/mL; $n = 52$). The cumulative 5-year OS rates differed significantly between the PLR$_{High}$ group (19.5%) and the PLR$_{Low}$ group (39.1%, $P = 0.049$) (Fig. 2A) and between the CA19-9$_{High}$ group (19.1%) and CA19-9$_{Low}$ group (41.0%, $P = 0.003$) (Fig. 3A). The cumulative 5-year disease-specific survival (DSS) rates also differed significantly between the PLR$_{High}$ group (22.9%) and the PLR$_{Low}$ group (45.9%, $P = 0.012$) (Fig. 2B) and between the CA19-9$_{High}$ group (25.6%) and CA19-9$_{Low}$ group (41.0%, $P = 0.009$) (Fig. 3B).

The patients were then divided into the following three groups: Group A comprised those in the PLR$_{Low}$ and CA19-9$_{Low}$ groups ($n = 29$), Group B comprised those in either the PLR$_{High}$ and CA19-9$_{Low}$ or PLR$_{Low}$ and CA19-9$_{High}$ groups ($n = 41$), and Group C comprised those in the PLR$_{High}$ and CA19-9$_{High}$ groups ($n = 33$). The cumulative 5-year OS rates were 44.0%, 31.9%, and 11.9% in Groups A, B, and C, respectively, and the difference was statistically significant ($P = 0.002$) (Fig. 4A). Furthermore, the cumulative DSS rates were 47.7%, 36.4%, and 16.8% in Groups A, B, and C, respectively, and the difference was also statistically significant ($P = 0.002$) (Fig. 4B).

Univariate analysis indicated that lymph node metastasis, lymphatic vessel invasion, perineural invasion, and the combination of PLR and serum CA19-9 level were significantly associated with OS (Table 2). We next included covariates with $P < 0.1$ in univariate analysis into the multivariate analysis. Multivariate analysis revealed that the combination of the PLR and serum CA19-9

level (HR=1.711; 95% CI: 1.035–2.829) was an independent prognostic factor along with lymph node metastasis (HR=2.333; 95% CI: 1.305–4.171), and lymphatic vessel invasion (HR=2.049; 95% CI: 1.195–3.512) in patients with resected PC (Table 2).

Discussion

In this study, we first demonstrated that the PLR was closely associated with the prognosis of patients with resectable PC. The PLR consists of the peripheral platelet count and lymphocyte count and is considered to be an inflammatory indicator. A high PLR reflects an increased platelet count. Thrombocytosis is detected in 10% to 57% of patients with malignancy because many types of neoplastic cells stimulate platelet activation [17]. One of the mechanisms responsible for thrombocytosis might be the secretion of factors such as interleukin-6 (IL-6) and vascular endothelial growth factor (VEGF) by the cancer cells themselves and the cancer microenvironment. IL-6 has an important role in reactive thrombocytosis based on its cell-proliferative effect because it triggers the differentiation of megakaryocytes to platelets in the bone marrow [18,19]. VEGF also stimulates the differentiation of megakaryocytes to platelets [20]. Studies have shown that the serum concentrations of IL-6 and VEGF are significantly higher in patients with PC than in healthy subjects [21,22]. Both IL-6 and VEGF are associated with the prognosis of patients with various types of cancers including PC [23,24]. Therefore, thrombocytosis indirectly reflects tumor progression. Furthermore, platelets themselves have a direct effect on cancer progression by interacting with malignant cells to promote metastasis [25]. They also enhance the sequestration, adherence, and penetration of malignant cells through the endothelium, prevent the immune system
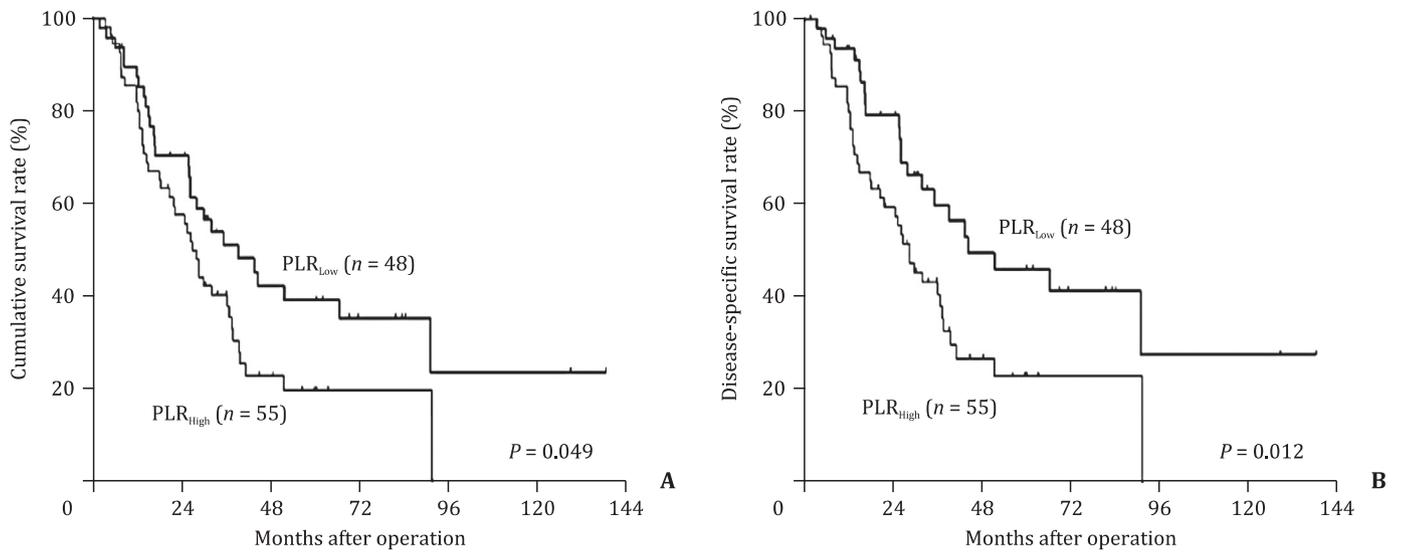
Fig. 2. Overall survival curve **(A)** and disease-specific survival curve **(B)** according to the PLR. PLR: platelet-to-lymphocyte ratio.
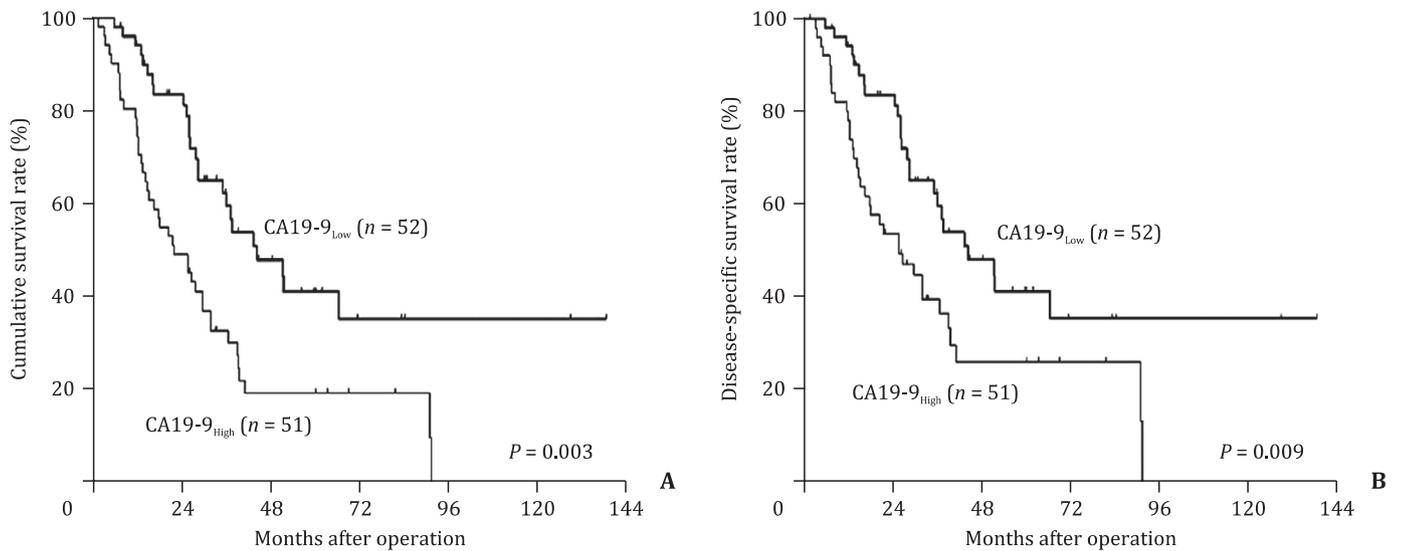

Fig. 3. Overall survival curve **(A)** and disease-specific survival curve **(B)** according to the serum CA19-9 level. CA19-9: carbohydrate antigen 19–9.
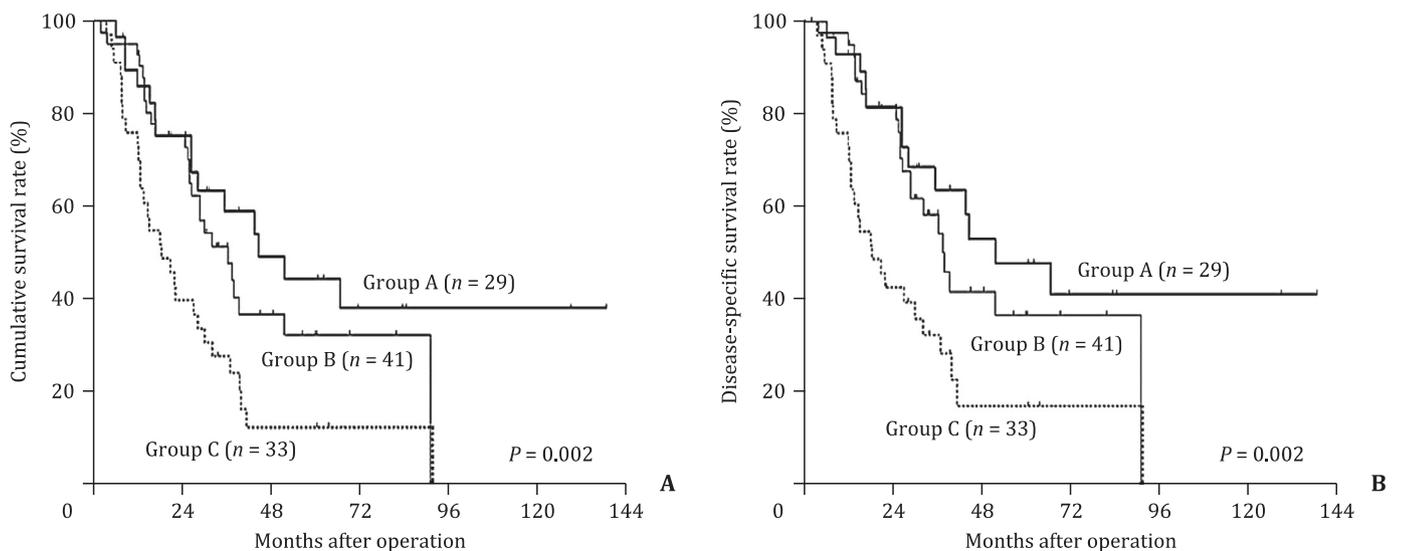

Fig. 4. Overall survival curve **(A)** and disease-specific survival curve **(B)** according to combination of PLR and serum CA19-9 level. PLR: platelet-to-lymphocyte ratio; CA19-9: carbohydrate antigen 19–9.

Table 2
Univariate and multivariate analyses of prognostic factors for overall survival in patients with resected pancreatic cancer.

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age (yr, ≥ 70 vs < 70)	1.369	0.838–2.238	0.210			
Primary tumor size (mm, ≥ 29.4 vs < 29.4)	1.467	0.903–2.383	0.121			
Tumor location (head vs body and tail)	1.200	0.733–1.965	0.468			
Histological grading (G1 vs G2-4)	1.461	0.905–2.359	0.120			
Lymph node metastasis (present vs absent)	3.645	2.125–6.251	**<0.001**	2.333	1.305–4.171	**0.004**
Lymphatic vessel invasion (0/1 vs 2/3)	2.697	1.638–4.440	**<0.001**	2.049	1.195–3.512	**0.009**
Blood vessel invasion (0/1 vs 2/3)	1.510	0.937–2.433	0.091	1.454	0.889–2.377	0.135
Perineural invasion (0/1 vs 2/3)	2.842	1.450–5.572	**0.002**	0.629	0.308–1.283	0.202
Serum bilirubin (mg/dL, ≥ 1.0 vs < 1.0)	1.434	0.842–2.441	0.184			
Bile drainage (present vs absent)	1.399	0.848–2.307	0.189			
Adjuvant chemotherapy (present vs absent)	0.819	0.509–1.315	0.408			
Combination of PLR and serum CA19-9 level (Group C vs other)	2.454	1.518–3.966	**<0.001**	1.711	1.035–2.829	**0.036**

HR: hazard ratio; 95% CI: 95% confidence interval; PLR: platelet-to-lymphocyte ratio; CA19-9: carbohydrate antigen 19–9. G1: well-differentiated; Group C: PLR_{High} / $CA19-9_{High}$.

Table 3
Summary of published studies that determined prognostic significance of preoperative platelet-to-lymphocyte ratio in patients with pancreatic cancer.

Studies	Year	No. of patients	Study design	Cutoff value	Survival outcome	Statistical significance
Advanced pancreatic cancer						
Martin et al. [36]	2014	124	Retrospective	200	OS	Present
Qi et al. [37]	2015	211	Retrospective	126	OS	Present
Kou et al. [38]	2016	306	Retrospective	150	OS	Absent
Lee et al. [39]	2018	497	Retrospective	149	OS	Present
Resected pancreatic cancer						
Smith et al. [40]	2009	110	Retrospective	150	OS	Present
Shirai et al. [41]	2015	131	Retrospective	150	OS	Present
Asari et al. [42]	2016	184	Retrospective	225	OS	Present
Watanabe et al. [43]	2016	46	Retrospective	200	OS	Present
Yamada et al. [44]	2016	379	Retrospective	150	OS	Absent
Our study		103	Retrospective	129.1	OS	Present

from clearing tumor cells from the circulatory system [26], and are the source of thymidine phosphorylase/platelet-derived endothelial cell growth factor, which has both mitogenic and angiogenic activity [27]. These observations can account for the association of reactive thrombocytosis with survival in patients undergoing surgery for several types of cancer including PC.

A high PLR also reflects a decreased lymphocyte count. Lymphopenia is frequently observed in patients with advanced cancer, and a decreased preoperative lymphocyte count is related to a poor prognosis in patients with PC [28], esophageal cancer [29], renal cancer [30], and sarcoma and lymphoma [31]. Lymphocytes include CD4$^+$ and CD8$^+$ *T* cells, natural killer cells, natural killer T cells, gamma-delta T cells, and B cells, which exhibit anti-cancer activities. Niccolai et al. demonstrated that peripheral α-enolase-specific T cells mirrored the intratumoral immune response and that their presence was a potential prognostic factor for PC [32]. Furthermore, Xu et al. demonstrated that peripheral CD19$^+$ *B* cells and CD8$^+$CD28$^+$ *T* cells were independent predictors of the OS of patients with PC [33]. It is likely that a decreased lymphocyte count is closely associated with decreases in these cell counts, which results in a poor prognosis. Therefore, the peripheral lymphocyte count might be a good indicator of a patient's immune status against PC cells.

The lymphocyte count also reflects patients' nutritional status, which is associated with their prognoses. For instance, Onodera's prognostic nutritional index is a simple nutritional index calculated by the serum albumin level and total lymphocyte count [34]. The preoperative prognostic nutritional index has been proposed as a predictor of the prognosis for patients with PC [35]. Therefore, the results we observed in the current study might be associated with not only immunity but also the nutritional status.

In the current study, we demonstrated the close correlation between PLR and prognosis in resected PC. However, most patients with PC were diagnosed at advanced stage and were not candidates for curative resection. Therefore, it is also important to determine the prognostic significance of PLR in patients with advanced PC. Table 3 shows the summary of 4 previous reports that determined the correlation between PLR and prognosis in patients with advanced PC [36–39]. Among them 3 reports showed that the high PLR level is significantly associated with poor prognosis in advanced PC patients. Therefore, PLR is also useful in predicting the prognosis of patients with advanced PC.

CA19-9 is the most frequently used tumor marker in patients with PC and is reportedly a useful prognostic indicator. CA19-9 is mainly derived from the cancers themselves, whereas the PLR is a patient-related indicator that is considered to reflect the patient's inflammation, immunity, and nutritional status. Importantly, there was no significant correlation between the PLR and serum CA19-9 level in the current study. The difference in origin and the lack of a significant correlation between the PLR and serum CA19-9 level encourage us to determine the prognostic significance of the combination of the PLR and serum CA19-9 level. Our results demonstrated that the prognosis of patients in the PLR_{High} and $CA19-9_{High}$ group was extremely low. Furthermore, the multivariate analysis revealed that the combination of the PLR and serum CA19-9 level was an independent prognostic indicator, indicating its usefulness as a prognostic indicator in patients with PC.

This study has a few limitations. First, it was a retrospective analysis, which should generate some bias. Second, a few patients developed obstructive cholangitis before the operation. Therefore, we cannot rule out the possibility that inflammation induced by obstructive cholangitis affected the results. Third, there are some

studies indicating that high PLR was associated with poor prognosis in patients with resected PC [40–44]. The cutoff values of PLR used in previous studies are higher than that used in our study (Table 3). Optimal cutoff value of PLR remains unclear due to the small number of studies demonstrating the prognostic significance of PLR in PC patients. Therefore, a large-scale study is needed before PLR can be used in the routine clinical evaluation of PC patients.

In conclusion, the combination of the PLR and serum CA19-9 level appear to be useful in predicting the prognosis of patients with PC. Because evaluation of the PLR and serum CA19-9 level is a quick, easy, and noninvasive assay, the combination of these two parameters could be an inexpensive and practical biomarker for the prognosis of patients with PC in routine clinical settings.

Contributors

ST proposed the study. ST and SH performed the research and wrote the first draft. ST and AM collected and analyzed the data. All authors contributed to the design and interpretation of the study and to further drafts. SH and FY are the guarantors.

Funding

Ethical approval

This study was approved by the Institutional Review Board of our institution in accordance with the ethical standards laid down in the 1964 *Declaration of Helsinki* and its later amendments (17A135).

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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