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Simple prognostic markers for optimal treatment of patients with unresectable pancreatic cancer

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Abstract

Most patients with pancreatic cancer are ineligible for curative resection at diagnosis, resulting in poor prognosis. This study aimed to evaluate the prognostic factors in patients with unresectable pancreatic cancer.

We retrospectively collected clinical data from 196 patients with unresectable pancreatic cancer who received palliative chemotherapy (N = 153) or palliative care alone (N = 43) from January 2011 to December 2013. Patients' background data and overall survival were analyzed using the Cox proportional hazard regression model.

In patients receiving palliative chemotherapy (gemcitabine-based regimen, 88.2%) and palliative care alone, the median (range) ages were 68 (43–91) and 78 (53–90) years, and metastatic diseases were present in 80% (N = 123) and 86% (N = 37), respectively. Multivariate analysis in the palliative chemotherapy patients showed that liver metastasis (hazard ratio [HR] 2.25, 95% confidence interval [CI] 1.58–3.20, $P < .001$), neutrophil-to-lymphocyte ratio (>4.5 vs ≤4.5; HR 3.45, 95% CI 2.22–5.36, $P < .001$), and cancer antigen 19-9 (CA19-9) (≥900 vs <900 U/mL; HR 1.45, 95% CI 1.02–2.05, $P = .036$) were independent prognostic factors. In those receiving palliative care alone, lung (HR 3.27, 95% CI 1.46-7.35, p = 0.004) and peritoneum (HR 2.50, 95% CI 1.20–5.18, $P = .014$) metastases and the C-reactive protein-to-albumin ratio (≥1.3 vs <1.3; HR 3.33, 95% CI 1.51–7.35, $P = .003$) were independent prognostic factors. Furthermore, patients with multiple factors had worse prognosis in both groups. Median survival time of palliative chemotherapy patients with risk factors 0, 1, 2, and 3 were 13.1 (95% CI 8.0–16.9), 9.4 (95% CI 7.9–10.1), 6.6 (95% CI 4.9–7.8), and 2.5 (95% CI 1.7–4.0) months, respectively. Similarly, median survival time was 5.7 (95% CI 1.3 -8.0), 2.1 (95% CI 1.5–3.9), and 1.3 (95% CI 0.6–1.7) months, respectively, for palliative care alone patients with risk factor 0, 1, and 2 to 3.

Prognostic markers for pancreatic cancer were neutrophil-to-lymphocyte ratio, liver metastasis, and CA19-9 in patients undergoing palliative chemotherapy and C-reactive protein-to-albumin ratio and lung/peritoneum metastases in patients undergoing palliative care alone. These simple markers should be considered when explaining the prognosis and therapeutic options to patients.

Abbreviations: CA19-9 = cancer antigen 19-9, CAR = CRP-to-albumin ratio, CEA = carcinoembryonic antigen, CRP = C-reactive protein, ECOG = Eastern Cooperative Oncology Group, EPOCH = Ehime Pancreato-Cholangiology, HR = hazard ratio, MST = median survival times, NLR = neutrophil-to-lymphocyte ratio, OS = overall survival, PS = performance status, UICC = Union for International Carcinoembryonic Control.

Keywords: CAR, NLR, palliative treatment, pancreatic cancer, prognostic factor

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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1. Introduction

Pancreatic cancer has the worst prognosis among various cancers. Although surgical resection is the only curative treatment for pancreatic cancer, most patients are diagnosed at the advanced stages, and the overall survival (OS) is extremely poor.[1]

To identify prognostic factors for patients with pancreatic cancer who received palliative chemotherapy, many studies have been performed with many common factors reported, such as the Karnofsky performance status (PS) score, the Eastern Cooperative Oncology Group (ECOG) PS, hemoglobin levels, tumor burden, liver metastasis, cancer antigen 19-9 (CA 19-9) levels, and expression of B7H1 or B7H4.[2–4] There are many reports of managements for patients with cancer receiving palliative care alone, including various tumor types and affected organs.[5] To the best of our knowledge, however, there is no report on the prognostic factors for patients with pancreatic cancer with palliative care alone. Furthermore, recently reported independent prognostic factors using routinely measured blood tests include neutrophil count, lymphocyte %, and serum C-reactive protein (CRP) and albumin levels.[6–8] Emerging evidence suggests that cancer-associated inflammation and nutritional status play a critical role in tumor progression. Previous studies identified several inflammatory or nutritional biomarkers as prognostic factors for OS; for example, CRP, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio, and CRP-to-albumin ratio (CAR).[6–8]

Lack of easily assessable parameters in clinical practice in patients with pancreatic cancer leads to difficulty in treatment choice and prognostic guidance, especially for those who receive palliative care alone. Therefore, in the present study, the Ehime Pancreato-Cholangiology (EPOCH) Study Group, which is dedicated to clinical practice and research on pancreatic cancer,[1,9–11] investigated prognostic factors for palliative treatments of unresectable pancreatic cancer, using routinely measured blood tests in conjunction with imaging.

2. Methods

2.1. Patient population

The EPOCH Study Group, composed of Ehime University Hospital and its affiliated centers, retrospectively investigated the clinical data from patients consecutively diagnosed with pancreatic cancer between January 1, 2011, and December 31, 2013. Among 566 patients diagnosed with pancreatic cancer at seven institutes, 311 patients had unresectable advanced or metastatic pancreatic cancer and received palliative chemotherapy or palliative care alone. Treatment selection depended on various factors; age; general condition; and the thoughts of patients, his/her family members and the physicians. Excluding 115 patients with missing data, the data of 196 patients (36.7% of them from cancer center) were used for the analyses (153 patients receiving palliative chemotherapy and 43 patients receiving palliative care alone) (Fig. 1). Prognostic analyses were done separately in the following two groups: patients with palliative chemotherapy and those with palliative care alone. The diagnosis of pancreatic cancer was based on tumor markers, abdominal images (computed tomography and magnetic resonance imaging), and/or histological findings, as previously described.[1] The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the ethics committee of the Ehime University Graduate School of Medicine (approval number: 1204066). All subjects were assigned a numerical code that was used throughout the study, and all data were stored in a secure database to maintain anonymity. Consent for publication was not necessary due to the retrospective approach of the research.

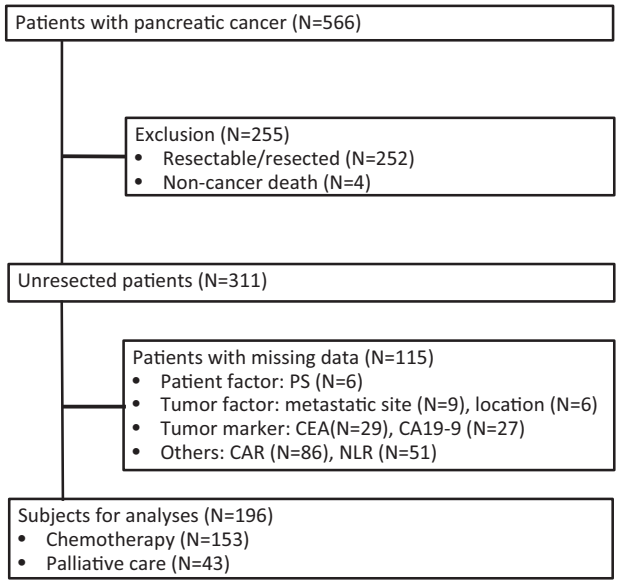

Figure 1. Flow chart of patient selection.

2.2. Data collection

Data regarding the potential prognostic factors were collected from medical records, including age, sex, ECOG PS, laboratory tests (counts of white blood cells, neutrophils, lymphocytes, and platelets; serum level of CRP, albumin, CA19-9, and carcinoembryonic antigen [CEA]) before initial treatment in the palliative chemotherapy group and at diagnosis in the palliative care alone group, tumor characteristics (Union for International Carcinoembryonic Control stage [7th edition], tumor location, distant metastasis [liver, lung, bone, peritoneum]), and survival time from diagnosis.

2.3. Statistical analyses

All statistical analyses were performed with EZR.[12] It is a modified version of the R commander designed to add statistical functions and is frequently used in biostatistics. For survival time analysis, the Kaplan-Meier method was used to estimate the survival curve, and the log-rank test was used to compare the survival curves between the two groups. The hazard ratio (HR) was calculated using the Cox proportional hazard regression model to adjust the covariates. For clinical use, the optimal cut-off values of continuous variables were determined, exploring various points (eg, mean, median, quantile, and nearest point of the receiver operating characteristics curve) and those deemed to be appropriate and clinically meaningful were used for analyses. All P values <0.05 were considered as significant in this study.

3. Results

3.1. Patient characteristics

Table 1 shows the patient background data in the palliative chemotherapy group and the palliative care alone group. In the

Table 1

Patients' characteristics.

	Chemotherapy (n = 153)	Palliative care (n = 43)	P*
Age, y	68 (43–91)	78 (53–90)	<.001
Sex, male/female	90 / 63	25 / 18	1
ECOG PS, 0/1 /2/3/4	83/58/10/2/0	18/15/3/6/1	.011
Stage, III/IV	30/123	6/37	.559
Tumor location, head/body—tail	75/78	16/27	.226
Metastasis			
Liver (%)	79 (52)	26 (61)	.387
Peritoneum (%)	49 (32)	20 (47)	.103
Lung (%)	29 (19)	14 (33)	.063
Bone (%)	4 (3)	5 (12)	.066
Neutrophil, /μL	4542 (1017–18,367)	5739 (1679–17,381)	.011
Lymphocyte, /μL	1407 (378–4902)	1216 (315–2836)	.013
Platelet, $\times 10^4$/μL	21 (7–46)	20 (8–44)	.572
Albumin, g/dL	4.1 (2.4–5.2)	3.6 (2.1–4.6)	<.001
CRP, mg/dL	0.48 (0.01–22)	1.93 (0.08–17)	<.001
NLR	3.0 (0.79–31)	4.8 (1.8–31)	<.001
CAR	0.12 (0.002–7.5)	0.6 (0.02–5.9)	<.001
PLR	142 (36–664)	167 (63–892)	<.001
CEA, ng/mL	6.3 (0.1–2367)	9.0 (1–670)	.857
CA19–9, <900/>900 U/Ml†	88/65	21/22	.385

The majority of data are shown as a median (range).
* χ^2 and Student *t* tests were used.
† Categorized because there are many values beyond measurement-limit.
CA19-9 = cancer antigen 19-9, CAR = CRP-to-albumin ratio, CEA = carcinoembryonic antigen, C1RP = C reactive protein, ECOG PS = Eastern Cooperative Oncology Group performance status, NLR = neutrophil-to-lymphocyte ratio, PLR = platelet-to-lymphocyte ratio.

palliative chemotherapy group, the median age was 68 (43–91) years, and 90 patients (59%) were male. The proportions of PS 0 or 1, stage IV, and tumor location-head were 92%, 80%, and 49%, respectively. The first-line chemotherapy regimens were gemcitabine (73%), S-1 (12%), gemcitabine plus S-1 (7%), gemcitabine plus radiation (4%), and others (4%) including gemcitabine plus erlotinib or plus investigational drugs. In the palliative care alone group, the median age was 78 (43–91) years, and 25 patients (58%) were male. The proportions of PS 0 or 1, stage IV, and tumor location-head were 77%, 86%, and 37%, respectively. Compared with the palliative chemotherapy group, the palliative care alone group was characterized by older age, poorer PS, and lower serum albumin, and higher serum CRP, NLR, CAR, and platelet-to-lymphocyte ratio. The median survival times (MST) were 8.0 (95% confidence interval [CI] 7.1–9.4) months in the palliative chemotherapy group and 2.0 (95% CI 1.5–2.8) months in the palliative care alone group. All patients died of pancreatic cancer.

3.2. Prognostic factors for patients receiving palliative chemotherapy

Table 2 shows the univariate and multivariate analyses in the palliative chemotherapy group. Cutoff values were retrieved from receiver-operating characteristic curve except for NLR and CA19-9. As for CA19-9, a cutoff at 900 U/mL was derived from the median value of the entire patients. Cutoff values of NLR had been extensively studied previously and set as 4.0 or 5.0. Thus, we chose 4.5 in our study. In the univariate analysis, the clinical factors significantly associated with worse OS were liver and peritoneal metastases. Regarding the blood markers, neutrophil counts, albumin levels, CRP levels, NLR, CAR, CEA, and CA19-9 were significantly associated with worse OS, whereas age, ECOG PS, and tumor location were not. In the multivariate analysis using these significant factors, liver metastasis (HR 2.25, 95% CI 1.58–3.20, $P < .001$), NLR (≥4.5 vs <4.5; HR 3.45, 95% CI 2.22–5.36, $P < .001$), and CA19-9 (≥900 vs <900 U/mL; HR 1.45, 95% CI 1.02–2.05, $P = .036$) were confirmed to be significantly and independently associated with decreased OS (Fig. 2A–C). Supplementary Table 1, http://links.lww.com/MD2/A591 shows the univariate and multivariate analyses in the

Table 2

Overall survival analyses using Cox proportional hazard model in patients with chemotherapy.

		Univariate analysis			Multivariate analysis		
Variable	Reference	Hazard ratio	95% confidence interval	P	Hazard ratio	95% confidence interval	P
Age ,y	<68	0.77	0.55–1.07	.12			
Sex	Female	1.18	0.84–1.66	.33			
ECOG PS	0/1	1.14	0.57–2.26	.72			
Tumor location	Head	1.20	0.86–1.68	.28			
Metastasis							
Liver	Absent	1.95	1.39–2.73	<.001	2.25	1.58–3.20	<.001
Lung	Absent	1.05	0.69–1.60	.81			
Bone	Absent	1.76	0.77–4.02	.18			
Peritoneum	Absent	1.49	1.05–2.18	.03			
Laboratory data							
Neutrophil (/μL)	<4500	0.65	0.47 – 0.91	.01			
Lymphocyte (/μL)	≥1514	1.03	0.74–1.45	.86			
Albumin, g/dL	≥4.0	1.40	1.00–1.97	.04			
CRP, mg/dL	<1.7	1.61	1.08–2.40	.02			
NLR	<4.5	2.97	1.96–4.49	<.001	3.45	2.22–5.36	<.001
CAR	<0.5	1.55	1.03–2.34	.04			
PLR ($\times 10^4$/μL)	<168	1.35	0.95–1.91	.10			
CEA, ng/mL	<5.0	1.52	1.08–2.13	.02			
CA19-9, U/mL	<900	1.72	1.23–2.41	.002	1.45	1.02–2.05	.036

CA19-9 = cancer antigen 19-9, CAR = CRP-to-albumin ratio, CEA = carcinoembryonic antigen, CRP = C reactive protein, ECOG PS = Eastern Cooperative Oncology Group performance status, NLR = neutrophil-to-lymphocyte ratio, PLR = platelet-to- lymphocyte ratio.

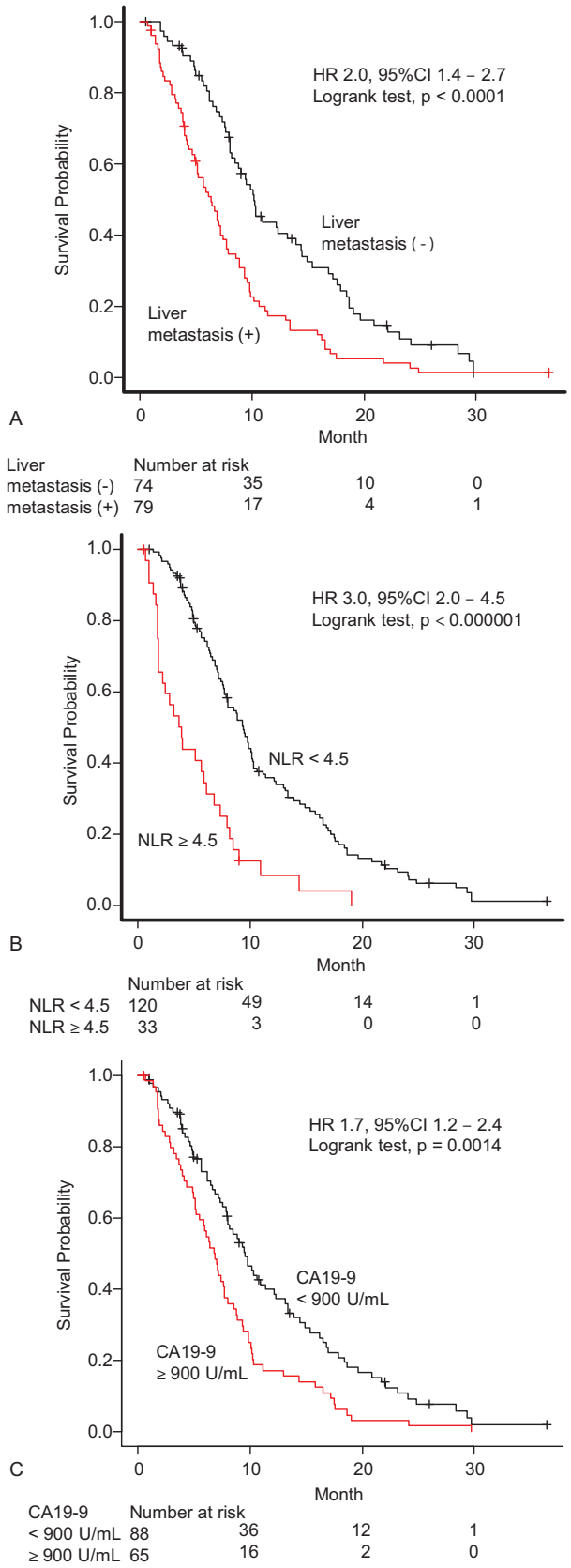

Figure 2. Survival curves according to the prognostic factors of patients treated with chemotherapy. (A) Liver metastasis, (B) NLR, and (C) CA19-9. NLR = neutrophil-to-lymphocyte ratio, CA19-9 = cancer antigen 19-9.

palliative chemotherapy group using continuous variables instead of categorical variables (Table 2), and NLR remained as a significant prognostic factor (HR 1.142, 95% CI 1.089–1.198, $P < .001$). The same analyses using continuous variables were carried out (see Table, Supplemental Content 1, http://links.lww.com/MD2/A591 which shows NLR remaining as a significant prognostic factor).

3.3. Prognostic factors for patients receiving palliative care alone

Table 3 shows the univariate and multivariate analyses in the palliative care alone group. In the univariate analysis, the clinical factors significantly associated with worse OS were PS and lung and peritoneum metastases. Regarding blood markers, CRP, CAR, CEA, and CA19-9 were significantly associated with worse OS. In the multivariate analysis using these significant factors, lung metastasis (HR 3.27, 95% CI 1.46–7.35, $P = .004$), peritoneum metastasis (HR 2.50, 95% CI 1.20–5.18, $P = .014$), and CAR (≥1.3 vs <1.3; HR 3.33, 95% CI 1.51–7.35, $P = .003$) were independent prognostic factors for OS (Fig. 3A–C). The same analyses using continuous variables were carried out (see Table, Supplemental Content 2, http://links.lww.com/MD2/A592 which shows CAR remaining as a significant prognostic factor).

3.4. Survival of patients with worse prognostic (risk) factors

Figure 4 shows survival curves of the patients according to number of prognostic factors. The MSTs were 13.1 (95% CI 8.0–16.9), 9.4 (95% CI 7.9–10.1), 6.6 (95% CI 4.9–7.8), and 2.5 (95% CI 1.7–4.0) months in the palliative chemotherapy patients with risk factor 0, 1, 2, and 3, respectively (Fig. 4A). The MSTs were 5.7 (95% CI 1.3–8.0), 2.1 (95% CI 1.5–3.9), and 1.3 (95% CI 0.6–1.7) months in the palliative care alone patients with risk factor 0, 1, and 2 to 3, respectively (Fig. 4B).

4. Discussion

This study identified simple prognostic factors to use separately in palliative chemotherapy and palliative care alone for patients with unresectable pancreatic cancer. The results were similar between the analysis using continuous and categorized variables. Patients with more prognostic factors showed worse OS in both patient groups. Liver metastasis, NLR, and CA19-9 have already been reported to be significant prognostic factors in patients who received systemic palliative chemotherapy in many large clinical trials worldwide.[13,14] A summary of the main reports sited here is shown in Table 4. We provide further evidence for this in the present study, using real-world samples in clinical practice. Moreover, the prognostic factors of lung/peritoneal metastases and CAR that were specific for palliative care alone of pancreatic cancer have been found in this study. Notably, these factors were different from those of the palliative chemotherapy group. This seems reasonable, because prognostic factors differ according to the disease progression status. For example, in the operable cases, tumor invasion depth and lymph node metastases are well known and proven pivotal factors for determining the clinical stage and estimating prognosis.[15,16] We should keep these in mind in routine daily medical work.

Table 3

Overall survival analyses using Cox proportional hazard model in patients with palliative care alone.

		Univariate analysis			Multivariate analysis		
Variable	**Reference**	**Hazard ratio**	**95% confidence interval**	***P***	**Hazard ratio**	**95% confidence interval**	***P***
Age, y	<76	1.43	0.72–2.84	.31			
Sex	Female	1.14	0.57–2.29	.71			
ECOG PS	0/1	2.31	1.05–5.05	.04			
Tumor location	Head	1.03	0.51–2.06	.94			
Metastasis							
Liver	Absent	1.14	0.55–2.36	.72			
Lung	Absent	2.36	1.08–5.14	.03	3.27	1.46–7.35	.004
Bone	Absent	1.92	0.72–5.09	.19			
Peritoneum	Absent	2.38	1.19–4.78	.02	2.50	1.20–5.18	.014
Laboratory data							
Neutrophil (/μL)	<6256	1.68	0.82–3.43	.16			
Lymphocyte (/μL)	≥1239	0.91	0.47–1.77	.78			
Albumin, g/dL	≥3.5	1.36	0.67–2.74	.40			
CRP, mg/dL	<3.8	3.03	1.43–6.40	.004			
NLR	<6.7	1.23	0.57–2.66	.59			
CAR	<1.3	2.92	1.38–6.18	.005	3.33	1.51–7.35	.003
PLR ($\times 10^4$/μL)	<222	1.40	0.67–2.89	.37			
CEA, ng/mL	<9	2.43	1.15–5.15	.02			
CA19-9, U/mL	<900	2.13	1.05–4.31	.04			

CA19-9 = cancer antigen 19-9, CAR = CRP-to-albumin ratio, CEA = carcinoembryonic antigen, CRP = C reactive protein, ECOG PS = Eastern Cooperative Oncology Group performance status, NLR = neutrophil-to-lymphocyte ratio, PLR = platelet-to- lymphocyte ratio.

Regarding the different metastatic sites identified between the palliative chemotherapy and palliative care alone groups, this might have been caused by the different status of tumor progression and tumor burden. The proportion of organ metastases was high in the palliative care alone group, compared with the palliative chemotherapy group. Lung metastasis generally occur late and involve liver and peritoneal metastases.[13,16] These may be the reasons why the different sites were chosen as the prognostic factors between the 2 groups.

NLR was the independent prognostic factor in the palliative chemotherapy group. The systemic inflammatory response from cancer cells is involved in cancer progression and malignant transformation. In pancreatic cancer, the tumor microenvironment stimulates extensive production of pro-inflammatory cytokines such as interleukin 2, 6, and 10, and growth factors such as vascular endothelial growth factor and fibroblast growth factors, promoting tumor proliferation and local fibrotic reaction.[17,18] These induce neutrophilia and CRP secretion and alter responses to hormones and chemotherapeutic agents. Elevated neutrophils are commonly accompanied by lymphocytopenia. Lymphocytopenia affects immune surveillance and lymphocyte-mediated immune responses to therapy. Immune cells that infiltrate into or around the tumor engage in dynamic and extensive cross-talk with cancer cells. A positive association between elevated NLR and poor prognosis has been reported in cancer-specific survival in patients with unresectable pancreatic cancer as well as other cancers.[19] Recently, NLR has been discussed as a response predictor to the immune checkpoint inhibitors in melanoma, non-small cell lung cancer, and kidney cancer.[20] These inflammatory and immune responses may influence the survival of patients who received palliative chemotherapy.

Nutritional status affects patients' general condition. Hypoalbuminemia, an indicator for chronic malnutrition, is a common complication in patients with advanced terminal cancer.[21,22] CRP, a marker of inflammation, is also correlated with survival outcomes in various cancers, including pancreatic cancer.[23–25] Therefore, CAR, a combined index of these two parameters, may be suitable for the survival prediction of extremely advanced pancreatic cancer. Indeed, we found CAR to be an independent prognostic factor for OS in patients receiving palliative care alone in this study.

Finally, the OS of patients having two risk factors in the palliative chemotherapy group was similar to that of patients without any risk factors in the palliative care group. Furthermore, patients having 3 risk factors in the chemotherapy group had a worse OS than patients in the palliative care group without any risk factors. This strongly suggests the importance of these factors in determining treatment choice.

There are some limitations to our study. Retrospective studies are characterized by inherent biases. In addition, our sample size was small and missing data was a huge issue. Therefore, our results should be further validated in the future. In previous reports, the cut-off values of NLR[26] and CAR[25] ranged widely. Our cutoff values were included within this range. A future study with a large sample size is required to determine the truly optimal cutoff value. The reasons for the selection of palliative chemotherapy or palliative care alone were unclear in this study. As we have previously reported, however, treatment selection depends on various factors based on age; patients' general condition; the relationship among the physician, patient, and his/her family; and the patients' own thoughts.[9] We also recognize that the data are old, and the studied patients might be an issue since no patient received nab-paclitaxel plus gemcitabine and FOLFILINOX; however, these had not yet been approved during the study period and recent studies including both regimens also showed similar results.[27,28] Nonetheless, our findings seem to mirror a real-world practice since various institutes (academic center, cancer center, and community hospital) were included in this study. Homogeneous patient population receiving similar

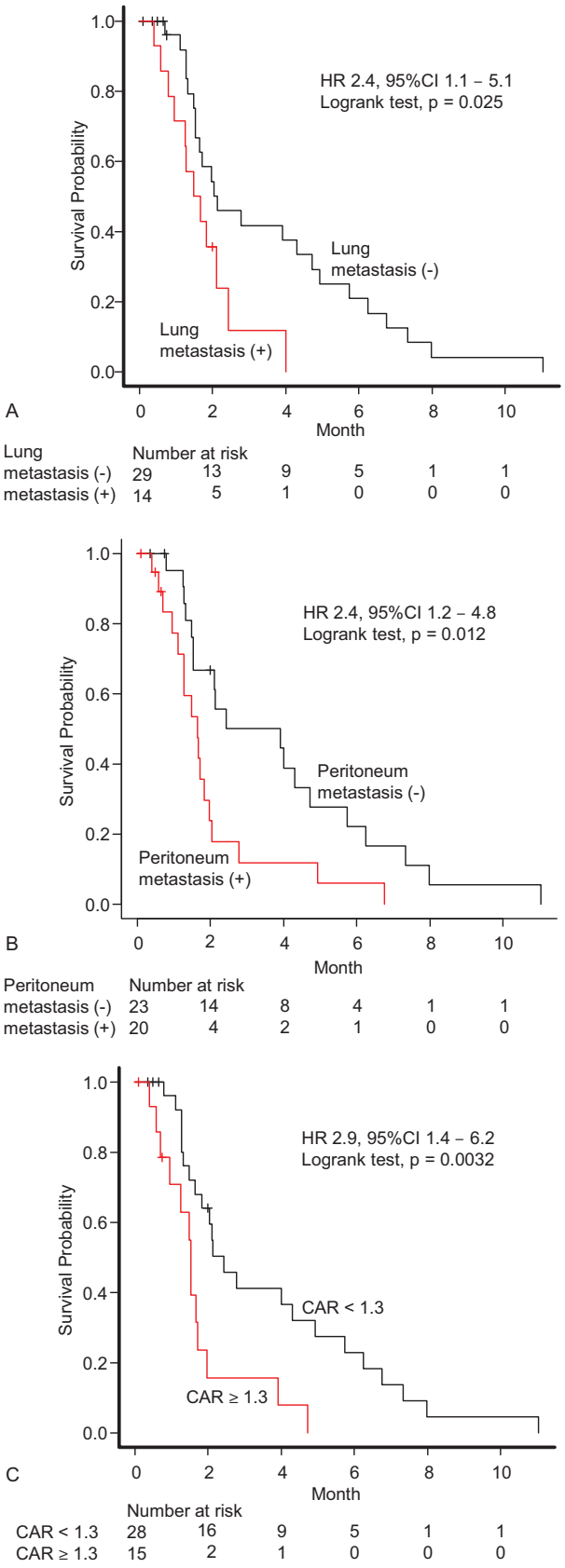

Figure 3. Survival curves according to the prognostic factors of patients treated with palliative care alone. (A) Lung metastasis, (B) Peritoneal metastasis, and (C) CAR. CAR = C-reactive protein-to-albumin ratio.

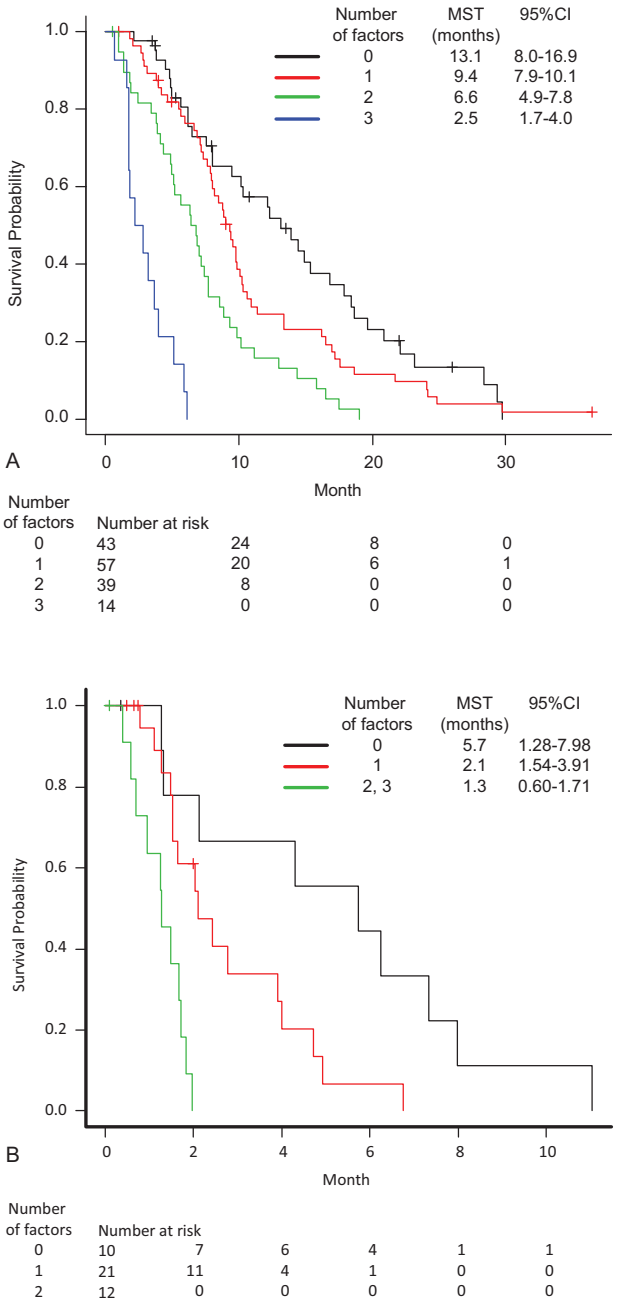

Figure 4. Survival of patients having worse prognostic (risk) factors. (A) Patients treated with chemotherapy. (B) Patients treated with palliative care alone.

chemotherapy (88.2% gemcitabine-based) regimen is another strength of this study. Moreover, this is the first study to show prognostic factors in patients with pancreatic cancer receiving palliative care alone. Therefore, our findings should be relevant.

In conclusion, NLR, liver metastasis, and CA19-9 for patients with advanced pancreatic cancer undergoing chemotherapy and CAR and lung/peritoneum metastases for patients with terminal pancreatic cancer undergoing palliative care were independent prognostic factors. These simple markers would be useful when physicians assess the prognosis and consider therapeutic options for patients with unresectable pancreatic cancer.

Table 4

Summary of previous reports about prognostic factors for advanced pancreatic cancer.

First author	Study design	Subjects	N	Prognostic factors for OS	Published year	Reference no.
Hamada et al[2]	Prospective	Gemcitabine-based chemotherapy for nonresectable stage III/IV	531	ECOG PS, tumor size, regional lymph node metastasis, distant metastasis	2014	2
Mitsunaga et al[8]	Retrospective Prospective	Advanced	280 141	CRP	2016	8
Allen et al[15]	Prospective	Resected	2318	Tumor size, nodal status	2017	15
Xue et al[19]	Retrospective	Palliative chemotherapy	252	Distant metastasis, recurrent tumor, NLR, CA19-9	2014	19
Szkandera et al[22]	Retrospective	Stage I-IV	474	Stage, tumor grade, chemotherapy, NLR	2014	22
Amano et al[23]	Prospective	Palliative-care cancer (hepatobiliary-pancreas)	1702 (343)	CRP for symptoms and ADL	2017	23
Fu et al[24]	Meta-analysis	Surgery/chemotherapy	2047 (7 studies)	CAR	2019	25

ADL = activity of daily life, CA19-9 = cancer antigen 19-9, CAR = CRP-to-albumin ratio, CRP = C-reactive protein, ECOG PS = Eastern Cooperative Oncology Group performance status, NLR = neutrophil-to-lymphocyte ratio, OS = overall survival.

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