Prognostic Nomogram for Patients With Unresectable Pancreatic Cancer Treated With Gemcitabine Plus Nab-paclitaxel or FOLFIRINOX: Real-world Results From a Multicenter Retrospective Study (NAPOLEON study).

Taro Shibuki

National Cancer Center-Hospital East: Kokuritsu Gan Center Higashi Byoin <https://orcid.org/0000-0001-7302-7691>

Toshihiko Mizuta

Fujikawa Hospital

Mototsugu Shimokawa

Yamaguchi University Graduate School of Medicine

Futa Koga

Saga Medical Center Koseikan

Yujiro Ueda

Japanese Red Cross Kumamoto Hospital

Junichi Nakazawa

Kagoshima City Hospital

Azusa Komori

Oita University Faculty of Medicine

Satoshi Otsu

Oita University Faculty of Medicine

Shiho Arima

Kagoshima University Graduate School of Medical and Dental Sciences

Masaru Fukahori

Kurume University School of Medicine

Akitaka Makiyama

Japan Community Healthcare Organization Kyushu Hospital

Hiroki Taguchi

Saiseikai Sendai Hospital

Takuya Honda

Nagasaki University Graduate School of Biomedical Sciences

Kenji Mitsugi

Hamanomachi Hospital

Kenta Nio

Sasebo Kyosai Hospital

Yasushi Ide

Karatsu Red Cross Hospital

Norio Ureshino

Saga Medical Center Koseikan

Tsuyoshi Shirakawa (✉ twriver1979@gmail.com)

Karatsu Higashi-matsuura Medical Association Center <https://orcid.org/0000-0002-9317-8216>

Taiga Otsuka

Saga Medical Center Koseikan

Research article

Keywords: unresectable pancreatic cancer, nomogram, prognosis, overall survival, chemotherapy

Posted Date: December 23rd, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-132462/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background No reliable nomogram has been developed until date for predicting the survival in patients with unresectable pancreatic cancer undergoing treatment with gemcitabine plus nab-paclitaxel (GnP) or FOLFIRINOX (FFX).

Methods This analysis was conducted using clinical data of patients with unresectable pancreatic cancer undergoing GnP or FFX treatment obtained from a multicenter study (NAPOLEON study). A Cox proportional hazards model was used to identify the independent prognostic factors. A nomogram to predict 6-, 12-, and 18-month survival probabilities was generated, validated by using the concordance index (C-index), and calibrated by the bootstrapping method. And then, we attempted risk stratification for survival by classifying the patients according to the sum of the scores on the nomogram (total nomogram points; TNP).

Results A total of 318 patients were enrolled. A prognostic nomogram was generated using data on the Eastern Cooperative Oncology Group performance status, liver metastasis, serum LDH, serum CRP, and serum CA19-9. The C-indexes of the nomogram were 0.77, 0.72 and 0.70 for 6-, 12-, and 18-month survival, respectively. The calibration plot showed optimal agreement at all points. Risk stratification based on tertiles of the TNP yielded clear separations of the survival curves. The median survival times in the low-, moderate-, and high-risk groups were 15.8, 12.8 and 7.8 months ($P < 0.05$), respectively.

Conclusions: Our nomogram is a convenient and inexpensive tool to accurately predict survival in patients with unresectable pancreatic cancer undergoing treatment with GnP or FFX, and will help clinicians in selecting appropriate therapeutic strategies for individualized management.

Introduction

Pancreatic cancer (PC) is the seventh leading cause of cancer-related death worldwide, and the fourth leading cause of cancer death in Japan [1, 2]. Although surgical resection is the only curative treatment for PC, only 15% of PC patients are suitable candidates for curative pancreatectomy, because most patients have either distant metastases or locoregional spread, including vascular invasion, even at diagnosis [3]. Palliative chemotherapy is used for patients diagnosed as having unresectable PC. Recently, great strides have been made in palliative chemotherapy for patients with metastatic PC due to development of the gemcitabine plus nab-paclitaxel (GnP) and FOLFIRINOX (fluorouracil, leucovorin, irinotecan, and oxaliplatin: FFX) regimens [4, 5]. However, the overall prognosis of PC remains unsatisfactory. The 5-year survival of patients with PC is a dismal 8% [6]. One of the reasons for the high mortality rate of PC patients may be the absence of a reliable method for prognosis determination and risk stratification. If the prognosis of PC patients could be evaluated more accurately, we could offer better therapeutic strategies and individualized treatments.

The American Joint Committee on Cancer (AJCC) TNM staging system, which is based on the tumor characteristics, and presence/absence of nodal and distant metastases, is currently the mainly used

system to predict survival in patients with cancers, including PC [7, 8]. Because patients with unresectable PC would be roughly classifiable as stage III or IV, the AJCC staging system is relatively difficult to discriminate for prediction of survival even in patients with the same AJCC stage [8]. Furthermore, it should be recognized that the AJCC TNM staging system only takes into account three tumor-related factors and not patient-specific factors such as the age, sex, race, and marital status, all of which are known to be associated with the survival in PC patients [7]. Therefore, an individualized, more accurate prognostic system is desirable.

A nomogram is a scoring and visualization tool of a multivariate predictive model, and is accepted as a reliable scale for more accurate survival prediction in individual patients as compared to the AJCC staging system [9–12]. However, to the best of our knowledge, no reliable nomogram has been developed yet for predicting survival in patients with unresectable PC undergoing treatment with GnP or FFX, which is currently recognized as the standard chemotherapy for these patients. In the present study, we attempted to develop a prognostic nomogram for patients with unresectable PC receiving GnP or FFX treatment, based on the real-world data.

Patients And Methods

Patients

This was a multicenter retrospective study of patients with unresectable or recurrent PC who underwent treatment with GnP or FFX at any of 14 centers in Kyushu, Japan (NAPOLEON study). We retrospectively reviewed the hospital medical records of the patients for the period between December 2013 and March 2017, and consecutive patients with locally advanced or metastatic PC were included. The following variables of the patients were investigated: the patient demographic characteristics (age, sex and body mass index), Eastern Cooperative Oncology Group performance status (ECOG PS), history of previous therapy (tumor resection and adjuvant chemotherapy), tumor size, tumor location (pancreatic head, body, or tail), tumor histology (adenocarcinoma, or not), sites of metastasis (liver, peritoneum, and/or lung), number of metastatic sites (one, or two or more), presence/absence of ascites, the AJCC TNM stage, and serum albumin, lactate dehydrogenase (LDH), C-reactive protein (CRP), carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) levels, and the first-line chemotherapy regimen used (GnP or FFX). This study was conducted with the approval of the institutional review board of each participating institution, and according to the principles laid down in the Declaration of Helsinki.

Treatment

All patients received either GnP or FFX as the first-line regimen. The GnP group consisted of patients who received nab-paclitaxel at the dose of 125 mg/m² given as a 30-minute intravenous infusion, followed by GEM at the dose of 1000 mg/m² given as a 30-minute intravenous infusion on days 1, 8, and 15, every 4 weeks [4]. The FFX group received either the original or the modified regimen. The original FFX regimen consists of a combination of oxaliplatin at the dose of 85 mg/m² given as a 2-hour intravenous infusion,

followed by l-leucovorin at the dose of 200 mg/m² given as a 2-hour intravenous infusion, with the addition, after 30 minutes, of irinotecan at the dose of 180 mg/m² given as a 90-minute intravenous infusion, followed by fluorouracil at the dose of 400 mg/m² given as an intravenous bolus injection, followed by a continuous intravenous fluorouracil infusion at 2400 mg/m² over a 46-hour period, every 2 weeks. The modified FFX regimen consists of a combination of oxaliplatin at the dose of 85 mg/m² given as a 2-hour intravenous infusion, followed by l-leucovorin at the dose of 200 mg/m² given as a 2-hour intravenous infusion, with the addition, after 30 minutes, of irinotecan at the dose of 150 mg/m² given as a 90-minute intravenous infusion, followed by continuous intravenous fluorouracil infusion at 2400 mg/m² over a 46-hour period, every 2 weeks [13, 14].

Assessments

The goal of this study was to identify factors influencing the prognosis in PC patients, and then to develop and validate a prognostic nomogram in a relatively large real-world cohort derived from the NAPOLEON study. The overall survival (OS) was calculated as the interval from the date of initiation of first-line chemotherapy to the date of death from any cause or the date of the last follow-up. The 8th edition of the AJCC staging system for PC was used [15].

Statistical analysis and drawing of the nomogram

Missing data were imputed by using the method of multiple imputation with predictive mean matching [16]. The imputation model included variables for tumor size, and serum albumin, LDH, CRP and CA19-9 levels. The Cox proportional hazard model was used to identify the independent prognostic factors for OS. Factors showing differences with *P* values of <0.05 were considered as being statistically significant. Prognostic factors judged to be clinically important and those with *P* values of <0.05 were selected, and a prognostic nomogram to predict the 6-, 12-, and 18-month survival probabilities was generated on the basis of the final model and validated using the concordance index (C-index) and calibration plot by the bootstrapping method (200 resamplings). The final model was compared with the AJCC TNM staging system to assess discrimination ability for survival prediction based on the time-dependent area under the curve (*t*-AUC) in a Receiver Operating Characteristic (ROC) curve analysis. And then, we attempted to develop a method of risk stratification for survival according to the tertiles of the total nomogram points (TNP) and compared the survival times among the risk groups (Fig. 1). The statistical analyses were performed using the software program R ver. 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 318 patients were enrolled between December 2013 and March 2017. The baseline characteristics of the 318 patients are shown in Table 1. By the end of the follow-up period, 197 patients (61.9%) had died, and the median OS was 11.3 months.

Table 1
Baseline characteristics. *n*=318

Age (years), <i>n</i> (%)	
< 60	93 (29)
60–70	137 (43)
> 70	88 (28)
Sex (M/F), <i>n</i> (%)	
196/122 (62/38)	
ECOG PS, <i>n</i> (%)	
0	204 (64)
1	96 (30)
2 or more	17 (5)
Body mass index (kg/m ²), <i>n</i> (%)	
< 22	198 (62)
≥ 22	120 (38)
Tumor resection, <i>n</i> (%)	
44 (14)	
Pancreatic tumor location, <i>n</i> (%)	
Head	165 (52)
Body	94 (30)
Tail	59 (19)
Tumor size (mm), <i>n</i> (%)	
32 (1–98)	
< 20	41 (13)
20–40	181 (57)
> 40	96 (30)
Histology, <i>n</i> (%)	
Adenocarcinoma	271 (85)
Others	47 (15)
Unknown	37 (12)
Site of metastatic disease, <i>n</i> (%)	
Liver	154 (48)
Peritoneum	62 (19)

Lung	39 (12)
Number of metastatic sites, <i>n</i> (%)	
≥ 2	97 (31)
Ascites, <i>n</i> (%)	62 (19)
Albumin (g/dL), <i>n</i> (%)	
> 4	32 (10)
3–4	181 (57)
< 3	105 (33)
LDH (U/L), <i>n</i> (%)	
< 240	269 (85)
240–360	105 (33)
> 360	8 (3)
CRP (mg/dL), <i>n</i> (%)	
< 0.3	158 (50)
0.3-3.0	117 (37)
> 3.0	43 (14)
CA19-9 (U/mL), <i>n</i> (%)	
< 37	76 (24)
37–370	72 (23)
> 370	170 (53)
AJCC TNM stage, <i>n</i> (%)	
I	63 (20)
II	255 (80)
First line regimen, <i>n</i> (%)	
GnP	200 (63)
FFX	118 (37)
ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; CRP, C-reactive protein; CA19-9, carbohydrate antigen 19 – 9; AJCC, American Joint Committee on Cancer; GnP, gemcitabine plus nab-paclitaxel; FFX, FOLFIRINOX	

The results of the univariate and multivariate analysis are listed in Table 2. The univariate analyses identified higher ECOG PS scores, presence of liver metastasis, more than two sites of metastatic disease, presence of ascites, serum albumin level less than 3.0 g/dL, elevated serum LDH, elevated serum CRP, serum CA19-9 level greater than 370 U/mL, and AJCC TNM stage IV as being significantly associated with shorter OS times. Multivariate analysis identified that ECOG PS, presence/absence of liver metastasis, serum LDH, serum CRP, and serum CA19-9 as independent predictors of the OS time.

Table 2
Univariate and Multivariate Cox proportional hazards models to predict survival in patients with unresectable pancreatic cancer.

Variables	Univariate analysis			Multivariate analysis		
	HR	95%CI	P-value	HR	95%CI	P-value
Age						
< 60	reference					
60–70	0.99	0.74–1.35	0.998	1.07	0.77–1.50	0.674
> 70	0.99	0.70–1.39	0.936	1.08	0.73–1.59	0.710
Sex						
F	reference					
M	0.92	0.71–1.19	0.517	0.96	0.71–1.28	0.766
ECOG PS						
0	reference					
1	1.54	1.16–2.04	0.003	1.43	1.03–1.93	0.033
2 or more	2.22	1.30–3.79	0.003	2.52	1.34–4.71	0.004
Body mass index						
< 22	reference					
≥ 22	1.01	0.77–1.30	0.969	0.98	0.73–1.31	0.880
Tumor resection						
no	reference					
yes	0.73	0.50–1.07	0.103	0.71	0.45–1.12	0.142
Pancreatic tumor location						
Head	reference					
Body	1.04	0.78–1.39	0.800	0.89	0.63–1.25	0.496
Tail	1.14	0.81–1.61	0.461	0.72	0.47–1.10	0.133
Tumor size						
< 20	reference					
20–40	0.99	0.67–1.47	0.979	0.94	0.60–1.47	0.775
> 40	1.39	0.91–2.11	0.125	0.88	0.54–1.43	0.605

Variables	Univariate analysis			Multivariate analysis		
Histology						
Adenocarcinoma	reference					
Others	1.09	0.75–1.56	0.656	1.26	0.83–1.90	0.280
Liver metastasis						
No	reference					
Yes	2.08	1.61–2.69	< 0.001	1.85	1.26–2.73	0.002
Peritoneal metastasis						
No	reference					
Yes	0.95	0.68–1.31	0.742	0.91	0.57–1.44	0.674
Lung metastasis						
No	reference					
Yes	1.39	0.95–1.31	0.09	1.40	0.86–2.29	0.176
Number of metastasis						
0 or 1	reference					
2 or more	1.59	1.21–2.09	< 0.001	1.17	0.80–1.71	0.422
Ascites						
No	reference					
Yes	1.52	1.12–2.05	0.007	1.37	0.93–2.00	0.112
Albumin (g/dL)						
> 4	reference					
3–4	0.82	0.54–1.24	0.349	1.45	0.88–2.37	0.144
< 3	0.56	0.36–0.88	0.012	1.29	0.72–2.27	0.399
LDH (U/L)						
< 240	reference					
240–360	1.91	1.32–2.77	< 0.001	1.51	0.97–2.33	0.065
> 360	2.90	1.36–6.19	0.006	2.88	1.35–6.82	0.007
CRP (mg/dL)						
< 0.3	reference					

Variables	Univariate analysis			Multivariate analysis		
0.3-3.0	1.45	1.09–1.92	0.010	1.12	0.81–1.55	0.503
> 3.0	3.04	2.09–4.43	< 0.001	2.04	1.23–3.36	0.005
CA19-9 (U/mL)						
< 37	reference					
37–370	1.24	0.84–1.84	0.285	1.18	0.77–1.80	0.441
> 370	1.91	1.36–2.68	< 0.001	1.45	1.01–2.07	0.043
AJCC TNM stage						
I	reference					
II	1.73	1.24–2.44	0.001	1.14	0.70–1.86	0.606
First line regimen						
FFX	reference					
GnP	0.86	0.66–1.11	0.249	0.99	0.72–1.36	0.942
HR, Hazard ratio; CI, Confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; CRP, C-reactive protein; CA19-9, carbohydrate antigen 19 – 9; AJCC, American Joint Committee on Cancer; GnP, gemcitabine plus nab-paclitaxel; FFX, FOLFIRINOX						

The prognostic nomogram integrating all the significant independent predictors of the OS identified by the multivariate analysis is shown in Fig. 2. The values of the C-index (bootstrapping 95% confidence intervals [CIs]) of the prognostic nomogram for OS prediction were 0.77 (0.73–0.81), 0.72 (0.67–0.76), and 0.70 (0.65–0.75) for 6-, 12-, and 18-month survival, respectively. These values were statistically significantly higher for all the points examined, as compared to the values for the AJCC TNM staging system (all *P* values < 0.01) (Table 3, Fig. S1).

Table 3
Comparison of t-AUC between Nomogram and AJCC Staging system.

	tAUC (Nomogram)	tAUC (AJCC Stage)	P-value
6 month	0.766	0.546	< 0.001
12 month	0.715	0.554	< 0.001
18 month	0.703	0.557	< 0.001
AUC, Area under the curve; AJCC, American Joint Committee on Cancer			

The calibration plot for the probability of survival at 6, 12, and 18 months showed optimal agreement between the predictions according to the nomogram and the actual observations (Fig. S2). The mean absolute errors between the observed and predicted probabilities were < 0.01, 0.03 and 0.04 for 6-, 12-, and 18-month survival, respectively. The errors for 90% of the study population were within 0.01, 0.02 and 0.08, respectively.

Risk stratification by using the tertiles of the TNP yielded clear separations among the survival curves. The median survival times in the low- (TNP < 56), moderate- (TNP 56–115), and high- (TNP ≥ 115) risk groups were 15.8 months (reference), 12.8 months (Hazard ratio [HR], 1.44; 95% CI, 1.03–2.01; $P = 0.03$), and 7.8 months (HR, 3.34; 95% CI, 2.40–4.64; $P < 0.01$), respectively (Fig. 3).

Discussion

In this study, we developed a convenient prognostic nomogram based on five independent prognostic variables (ECOG PS, presence/absence of liver metastasis, serum LDH, serum CRP, and serum CA19-9) which could accurately predict survival in patients with unresectable PC undergoing treatment with GnP or FFX. Currently, the AJCC TNM staging system is the most widely used prognostic tool for patients with cancer, including pancreatic cancer. However, this staging system has a few limitations in regard to the analysis of survival. Importantly, it focuses only on tumor characteristics, while the importance also of patient-related factors in determining the disease outcomes in cancer patients has come to be increasingly recognized in recent years [17]. Thus, we were prompted to develop a more accurate prognostic tool, and the nomogram that we have developed is an inexpensive tool based on easily determined variables, including both patient and tumor characteristics; it is expected to be a helpful tool for clinicians engaged in the treatment of unresectable PC patients.

ECOG PS is recognized as one of the most important prognostic factors in patients with a variety of cancers [18, 19], and as in the present study, several previous studies have also reported ECOG PS as an independent prognostic factor in patients with PC [20, 21]. We demonstrated herein that the patient prognosis became poorer as the ECOG PS score increased.

Presence of liver metastasis has been reported as an important predictor of survival in patients with various cancers [4, 22], and the MPACT trial showed that the presence of liver metastasis is an important predictor of survival also in patients with PC [4]. Among the distant metastases, including those to the liver, lung and peritoneum, it is unclear why only the presence of liver metastasis was associated with a poor prognosis in our study. Liver metastasis is associated with activation of hepatic stellate cells, which are key components of the hepatic tumor microenvironment and can acquire chemoresistance [23, 24]. Another possible explanation is that patients with liver metastasis could eventually develop jaundice or hepatic coma with increase in the number of metastatic tumors, which would make it difficult to continue with effective systemic chemotherapy, and potentially result in a fatal outcome.

An elevated serum LDH level in PC patients has been recognized as an indicator of tumor aggressiveness, tumor burden, and poor outcome [25], and has also been associated with chemoresistance to several

anticancer-drugs, including paclitaxel and gemcitabine [26]. These phenomena might be explained by tumor hypoxia, which promotes the growth of immature and highly permeable blood vessels that drive the abnormal growth and metastatic behavior of PC and facilitate the passage of tumor cells into the circulation [27]. Actually, serum level of LDH significantly increases in hypoxic condition, and serves as an indirect marker of tumor hypoxia [25]. For these reasons, the results of our study, consistent with previous reports, also suggested that an elevated serum LDH level might be associated with a poor prognosis [25, 28].

An elevated serum CRP level has also been demonstrated to be an independent prognostic factor in patients with various types of cancers [29]. Proinflammatory cytokines, such as interleukin-6 (IL-6), interleukin-1, and tumor necrosis factor-alpha, are secreted by monocytes or macrophages under inflammatory conditions and cancer [30]. Serum concentrations of IL-6 and CRP are known to be positively correlated with each other, and recent evidence suggests that IL-6 also affects the rate of cancer progression [31]. Furthermore, there is also evidence to suggest that these inflammatory cytokines play important roles in the genesis of cancer-associated cachexia, which shortens the survival time in patients with advanced PC [32, 33].

Serum CA19-9 is the only biomarker that the National Comprehensive Cancer Network guidelines for PC suggest is useful as a prognostic marker in patients receiving chemotherapy [34]. One prospective study has reported the possible usefulness of serum CA19-9 as a prognostic biomarker in patients with advanced PC [35], and another prospective study showed that a decrease of the serum CA19-9 level during chemotherapy is predictive of a longer survival time in patients with advanced PC [36].

Our prognostic nomogram was created based on the above theoretical background of the above-mentioned independent prognostic factors. Then, we verified the nomogram by determining the values of the C-index and t -AUC, and constructing a calibration plot and Kaplan-Meier curves for the three risk categories. The values of the C-index of the nomogram for 6-, 12-, and 18-month survival were all more than 0.7, indicating a good match between the predicted and actual survival. Calibration and validation using the bootstrapping method also indicated satisfactory performance of the nomogram. In addition, TNP can also be useful for predicting the survival, and Kaplan-Meier curves constructed using tertiles of the TNP showed clear separations among the survival curves. Moreover, our nomogram provided better predictive performance for OS as compared to the AJCC TNM staging system using t -AUC. Notably, our nomogram was not only based on the real-world data of patients treated with GnP or FFX, but also constructed using conventional variables which can easily be obtained at any medical institution in daily practice. Compared with previous nomogram in pancreatic cancer, our nomogram was created using larger cohort of 14 institutions, which could improve the accuracy of the model. In addition, our nomogram can predict prognosis not only at 6-month but also at 12- and 18-month [37]. Thus, this nomogram can be helpful to clinicians for making appropriate clinical decisions in daily practice. Furthermore, another benefit of this prognostic nomogram includes the possibility of selecting patients who are fit for clinical trials.

This study had several limitations. Firstly, it was a non-randomized, retrospective study, which could introduce selection bias, with a smaller number of patients as compared to previous studies [38]. Thus, we were unable to include several patient data, such as weight loss, quality of life, and screening status before the diagnosis, which were not fully documented in the hospital records. The second limitation was that the study lacked cross-validation so as that it would be difficult to generalize our results to other cohorts. However, we developed the nomogram using a spatiotemporally heterogeneous population recruited from multiple centers, which could contribute to improving the validity of this model. Finally, some patients were only clinically diagnosed as having PC, without histological confirmation. These indicate that some patients in the real-world situation have no choice, but to receive systemic chemotherapy without histological evidence for various reasons, including those related to the patients themselves and/or to the facilities that they seek treatment at.

In conclusion, our prognostic nomogram is a convenient and inexpensive tool for accurate prediction of the prognosis in patients with unresectable PC undergoing treatment with GnP or FFX, and will help clinicians in selecting appropriate therapeutic strategies for individualized management.

Abbreviations

PC, pancreatic cancer; GnP, gemcitabine plus nab-paclitaxel; FFX, FOLFIRINOX; C-index, concordance index; AJCC, American Joint Committee on Cancer; TNP, total nomogram points; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; CRP, C-reactive protein; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; *t*-AUC, time-dependent area under the curve; ROC, receiver operating characteristic; OS, overall survival; CI, confidence interval; HR, hazard ratio; IL-6, interleukin-6

Declarations

Acknowledgements

We thank all of the patients and their families, and all of the investigators at the 14 institutions that participated in the NAPOLEON study. We would also like to thank the Fukuoka Medical Oncology Group - Kyushu Yamaguchi Total Oncology Group (FMOG-KYTOG) and the Saga Study Group of Liver Disease (SASLD) for their cooperation. We are indebted to Dr. Y. Okabe of the Kurume University Hospital, Dr. Y. Kawaguchi of the Saga Medical Centre Koseikan, and Dr. M. Uenomachi of the Hamanomachi Hospital for their assistance in the data collection or discussion. We also thank International Medical Information Center (Shinjuku-ku, Tokyo, Japan) for providing medical writing support.

Availability of data and materials

All data generated or analyzed in this article are stored in a secured research database. They are not publicly available, however, are available through the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was conducted with the approval of the institutional review board or ethics committee of each participating institution with a waiver for the need for informed consent, in accordance with the principles enunciated in the Declaration of Helsinki.

Funding

None declared.

Compliance with ethical standards

Conflict of interest

M.S. received a personal fee from Sysmex Corporation; S.A. received personal fees from Taiho Pharmaceutical, Novartis Pharma, Chugai, Bristol-Myers Squibb, Daiichi-Sankyo, and AstraZeneca; A.M. received fees from Eli Lilly, Chugai and Takeda; T.S. received fees from Taiho Pharmaceutical, Chugai and Takeda; T.O. received a fee from Chugai. The other authors have no competing interests or financial disclosures to declare.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018, 68(6):394-424.
2. Hori M MT, Shibata A, Katanoda K, Sobue T, Nishimoto H, et al.: Cancer incidence and incidence rates in Japan in 2009: a study of 32 population-based cancer registries for the Monitoring of Cancer Incidence in Japan (MCIJ) project. *Japanese journal of clinical oncology* 2015, 45(9):884-891.
3. Butturini G, Stocken DD, Wente MN, Jeekel H, Klinkenbijn JH, Bakkevold KE, Takada T, Amano H, Dervenis C, Bassi C *et al.*: Influence of resection margins and treatment on survival in patients with pancreatic cancer: meta-analysis of randomized controlled trials. *Arch Surg* 2008, 143(1):75-83; discussion 83.
4. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, Seay T, Tjulandin SA, Ma WW, Saleh MN *et al.*: Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med* 2013, 369(18):1691-1703.
5. Conroy T, Desseigne F, Ychou M, Bouche O, Guimbaud R, Becouarn Y, Adenis A, Raoul JL, Gourgou-Bourgade S, de la Fouchardiere C *et al.*: FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011, 364(19):1817-1825.
6. Siegel RL, Miller KD, Jemal A: Cancer statistics, 2016. *CA Cancer J Clin* 2016, 66(1):7-30.
7. Oweira H, Petrausch U, Helbling D, Schmidt J, Mannhart M, Mehrabi A, Schob O, Giryas A, Decker M, Abdel-Rahman O: Prognostic value of site-specific metastases in pancreatic adenocarcinoma: A

- Surveillance Epidemiology and End Results database analysis. *World J Gastroenterol* 2017, 23(10):1872-1880.
8. Shi S, Hua J, Liang C, Meng Q, Liang D, Xu J, Ni Q, Yu X: Proposed Modification of the 8th Edition of the AJCC Staging System for Pancreatic Ductal Adenocarcinoma. *Ann Surg* 2019, 269(5):944-950.
 9. Fu J, Wu L, Jiang M, Li D, Jiang T, Hong Z, Wang F, Li S: Clinical Nomogram for Predicting Survival Outcomes in Early Mucinous Breast Cancer. *PLoS One* 2016, 11(10):e0164921.
 10. Li Y, Ju J, Liu X, Gao T, Wang Z, Ni Q, Ma C, Zhao Z, Ren Y, Sun M: Nomograms for predicting long-term overall survival and cancer-specific survival in patients with major salivary gland cancer: a population-based study. *Oncotarget* 2017, 8(15):24469-24482.
 11. Zhang ZY, Luo QF, Yin XW, Dai ZL, Basnet S, Ge HY: Nomograms to predict survival after colorectal cancer resection without preoperative therapy. *BMC Cancer* 2016, 16(1):658.
 12. Dong F, Shen Y, Gao F, Shi X, Xu T, Wang X, Zhang X, Zhong S, Zhang M, Chen S *et al*: Nomograms to Predict Individual Prognosis of Patients with Primary Small Cell Carcinoma of the Bladder. *J Cancer* 2018, 9(7):1152-1164.
 13. Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, Adenis A, Raoul J-L, Gourgou-Bourgade S, de la Fouchardière C *et al*: FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *The New England journal of medicine* 2011, 364(19):1817-1825.
 14. Ozaka M, Ishii H, Sato T, Ueno M, Ikeda M, Uesugi K, Sata N, Miyashita K, Mizuno N, Tsuji K *et al*: A phase II study of modified FOLFIRINOX for chemotherapy-naïve patients with metastatic pancreatic cancer. *Cancer Chemother Pharmacol* 2018, 81(6):1017-1023.
 15. Chun YS, Pawlik TM, Vauthey JN: 8th Edition of the AJCC Cancer Staging Manual: Pancreas and Hepatobiliary Cancers. *Ann Surg Oncol* 2018, 25(4):845-847.
 16. Morris TP, White IR, Royston P: Tuning multiple imputation by predictive mean matching and local residual draws. *BMC Med Res Methodol* 2014, 14:75.
 17. Hanahan D, Weinberg RA: Hallmarks of cancer: the next generation. *Cell* 2011, 144(5):646-674.
 18. Suzuki Y, Kan M, Kimura G, Umemoto K, Watanabe K, Sasaki M, Takahashi H, Hashimoto Y, Imaoka H, Ohno I *et al*: Predictive factors of the treatment outcome in patients with advanced biliary tract cancer receiving gemcitabine plus cisplatin as first-line chemotherapy. *J Gastroenterol* 2019, 54(3):281-290.
 19. Lim ST, Hee SW, Quek R, Tao M: Performance status is the single most important prognostic factor in lymphoma patients aged greater than 75 overriding other prognostic factors such as histology. *Leuk Lymphoma* 2008, 49(1):149-151.
 20. Fernández A, Salgado M, García A, Buxò E, Vera R, Adeva J, Jiménez-Fonseca P, Quintero G, Llorca C, Cañabate M *et al*: Prognostic factors for survival with nab-paclitaxel plus gemcitabine in metastatic pancreatic cancer in real-life practice: the ANICE-PaC study. *BMC cancer* 2018, 18(1):1185-1185.
 21. Heinemann V, Boeck S, Hinke A, Labianca R, Louvet C: Meta-analysis of randomized trials: evaluation of benefit from gemcitabine-based combination chemotherapy applied in advanced pancreatic cancer. *BMC cancer* 2008, 8:82-82.

22. Engstrand J, Nilsson H, Strömberg C, Jonas E, Freedman J: Colorectal cancer liver metastases - a population-based study on incidence, management and survival. *BMC cancer* 2018, 18(1):78-78.
23. Ruan Q, Wang H, Burke LJ, Bridle KR, Li X, Zhao CX, Crawford DHG, Roberts MS, Liang X: Therapeutic modulators of hepatic stellate cells for hepatocellular carcinoma. *Int J Cancer* 2020.
24. Nielsen SR, Quaranta V, Linford A, Emeagi P, Rainer C, Santos A, Ireland L, Sakai T, Sakai K, Kim YS *et al*: Macrophage-secreted granulins supports pancreatic cancer metastasis by inducing liver fibrosis. *Nat Cell Biol* 2016, 18(5):549-560.
25. Yu SL, Xu LT, Qi Q, Geng YW, Chen H, Meng ZQ, Wang P, Chen Z: Serum lactate dehydrogenase predicts prognosis and correlates with systemic inflammatory response in patients with advanced pancreatic cancer after gemcitabine-based chemotherapy. *Sci Rep* 2017, 7:45194.
26. Zhou M, Zhao Y, Ding Y, Liu H, Liu Z, Fodstad O, Riker AI, Kamarajugadda S, Lu J, Owen LB *et al*: Warburg effect in chemosensitivity: targeting lactate dehydrogenase-A re-sensitizes taxol-resistant cancer cells to taxol. *Mol Cancer* 2010, 9:33.
27. Maftouh M, Avan A, Sciarrillo R, Granchi C, Leon LG, Rani R, Funel N, Smid K, Honeywell R, Boggi U *et al*: Synergistic interaction of novel lactate dehydrogenase inhibitors with gemcitabine against pancreatic cancer cells in hypoxia. *Br J Cancer* 2014, 110(1):172-182.
28. Gan J, Wang W, Yang Z, Pan J, Zheng L, Yin L: Prognostic value of pretreatment serum lactate dehydrogenase level in pancreatic cancer patients: A meta-analysis of 18 observational studies. *Medicine (Baltimore)* 2018, 97(46):e13151.
29. Allin KH, Nordestgaard BG: Elevated C-reactive protein in the diagnosis, prognosis, and cause of cancer. *Crit Rev Clin Lab Sci* 2011, 48(4):155-170.
30. Whiteside TL: The tumor microenvironment and its role in promoting tumor growth. *Oncogene* 2008, 27(45):5904-5912.
31. Scheller J, Chalaris A, Schmidt-Arras D, Rose-John S: The pro- and anti-inflammatory properties of the cytokine interleukin-6. *Biochim Biophys Acta* 2011, 1813(5):878-888.
32. Strassmann G, Fong M, Kenney JS, Jacob CO: Evidence for the involvement of interleukin 6 in experimental cancer cachexia. *J Clin Invest* 1992, 89(5):1681-1684.
33. Vainer N, Dehlendorff C, Johansen JS: Systematic literature review of IL-6 as a biomarker or treatment target in patients with gastric, bile duct, pancreatic and colorectal cancer. *Oncotarget* 2018, 9(51):29820-29841.
34. Tempero MA: NCCN Guidelines Updates: Pancreatic Cancer. *J Natl Compr Canc Netw* 2019, 17(5.5):603-605.
35. Hess V, Glimelius B, Grawe P, Dietrich D, Bodoky G, Ruhstaller T, Bajetta E, Saletti P, Figer A, Scheithauer W *et al*: CA 19-9 tumour-marker response to chemotherapy in patients with advanced pancreatic cancer enrolled in a randomised controlled trial. *Lancet Oncol* 2008, 9(2):132-138.
36. Halm U, Schumann T, Schiefke I, Witzigmann H, Mössner J, Keim V: Decrease of CA 19-9 during chemotherapy with gemcitabine predicts survival time in patients with advanced pancreatic cancer. *Br J Cancer* 2000, 82(5):1013-1016.

37. Fornaro L, Leone F, Vienot A, Casadei-Gardini A, Vivaldi C, Lièvre A, Lombardi P, De Luca E, Vernerey D, Sperti E *et al*: Validated Nomogram Predicting 6-Month Survival in Pancreatic Cancer Patients Receiving First-Line 5-Fluorouracil, Oxaliplatin, and Irinotecan. *Clin Colorectal Cancer* 2019, 18(4):e394-e401.

38. Song W, Miao DL, Chen L: Nomogram for predicting survival in patients with pancreatic cancer. *Onco Targets Ther* 2018, 11:539-545.

Figures

Figure 1

Flow diagram showing the development of the prognostic nomogram.

Figure 2

The prognostic nomogram for predicting the 6-, 12-, and 18-month survivals.

Figure 3

The median survival times in the low-, moderate-, and high-risk groups were 15.8 months (reference), 12.8 months (HR, 1.44; 95% CI, 1.03–2.01; $P=0.03$), and 7.8 months (HR, 3.34; 95% CI, 2.40–4.64; $P<0.01$), respectively.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Fig.S1.eps](#)
- [Fig.S2.eps](#)