A combination of routine laboratory findings and vital signs can predict survival of advanced cancer patients without physician evaluation: a fractional polynomial model

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Running head: Objective survival prediction for advanced cancer patients

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Abstract

Introduction: There have been no reports about predicting survival of patients with advanced cancer constructed entirely with objective variables. We aimed to develop a prognostic model based on laboratory findings and vital signs using a fractional polynomials (FP) model.

Methods: A multicenter prospective cohort study was conducted at 58 specialist palliative care services in Japan from September 2012 to April 2014. Eligible patients were > 20 years old and had advanced cancer. We developed models for predicting 7-day, 14-day, 30-day, 56-day, and 90-day survival by using the FP modelling method.

Results: Data from 1039 patients were analyzed to develop each prognostic model (Objective Prognostic Index for advanced cancer: OPI-AC). All models included the heart rate, urea, and albumin, while some models included the respiratory rate, creatinine, C-reactive protein, lymphocyte count, neutrophil count, total bilirubin, lactate dehydrogenase, and platelet / lymphocyte ratio. The area under the curve was 0.77, 0.81, 0.90, 0.90, and 0.92 for the 7-day, 14-day, 30-day, 56-day, and 90-day model, respectively. The accuracy of the OPI-AC predicting 30-day, 56-day, and 90-day survival was significantly higher than that of the Palliative Prognostic Score or the Prognosis in Palliative Care Study model, which are based on a combination of symptoms and physician estimation.

Conclusion: We developed highly accurate prognostic indexes for predicting the survival of patients with advanced cancer from objective variables alone, which may be useful for end-of-life management. The FP modelling method could be promising for developing other prognostic models in future research.

Keywords: prognostic index, laboratory findings, vital signs, fractional polynomials model

Introduction

For patients with life-threatening illnesses such as advanced cancer, accurate prognostic information is essential to provide the opportunity for patients, family members, and clinicians to engage in open discussion about advance care planning[1–3].

Several validated prognostic tools have been developed to predict the survival of patients with advanced cancer[4], including the Palliative Prognostic Index (PPI)[5], Palliative Prognostic Score (PaP score)[6], and Prognosis in Palliative Care Study (PiPS)[7]. These have acceptable predictive accuracy with area under the curve (AUC) values of 0.62-0.86[7,8], but a major limitation is use of subjective variables, such as the patient's symptoms and condition (e.g., performance status) and the physician's prediction of survival[9–11]. Recent studies have revealed that such subjective variables are influenced by the evaluator's experience and competence[11,12]. Therefore, more extensive use of objective variables, such as laboratory findings and vital signs, has been strongly recommended when developing prognostic models[13–17].

Furthermore, the existing prediction tools are based on routine statistical methods such as regression analysis, but the guidelines for transparent reporting of a multivariable model for individual prognosis or diagnosis (TRIPOD statement) recommend the fractional polynomials (FP) modelling method as one of the ideal approaches for

developing a multivariable prediction model[18].

To our best knowledge, there are currently only 2 prognostic models that are entirely composed of objective variables, which are the Objective Palliative Prognostic Score (OPPS) and the set of six adaptable prognosis prediction (SAP) models[19,20]. The OPPS predicts 7-day survival by using 6 variables (heart rate, white blood cell count, platelet count, creatinine, potassium, and history of chemotherapy) and has an AUC of 0.82[19]. The SAP models predict survival for 1–6 months by using 3 variables (neutrophil count, lactate dehydrogenase, and albumin), with AUC values ranging from 0.71 to 0.85[20]. Although these models suggest that exclusive use of objective parameters may allow successful prediction of survival, several major limitations should be noted: development from a small patient sample, no validation study, limited or varied target time span, and lack of advanced statistical methods.

Therefore, we decided to explore the accuracy of a prognostic index that only incorporated objective parameters (laboratory findings and vital signs) and was based on the FP modelling method. We wanted to obtain insights into the predictability of patient survival using only objective parameters and the variables that would be effective for prediction of short-term to long-term survival. Accordingly, this study was performed to develop prognostic models for prediction of short-term to long-term survival

using only objective parameters and the FP modelling method.

Material and Methods

This study was a secondary analysis of the Japan-prognostic assessment tools validation (J-ProVal) study, which was a multicentre prospective cohort study performed to investigate the feasibility and accuracy of existing prognostic tools[21]. It was conducted at 58 palliative care services in Japan from September 2012 through April 2014. The participating services included 19 hospital palliative care teams, 16 palliative care units, and 23 home-based palliative care services. The primary physician of each patient performed evaluation and recorded demographic and clinical characteristics of the participants. Data from laboratory tests were only obtained if the patient underwent blood tests as a clinical necessity within 1 week after enrolment.

This study was conducted in accordance with the ethical standards of the Helsinki Declaration and the ethical guidelines for epidemiological research presented by the Ministry of Health, Labour and Welfare of Japan. The Institutional Review Boards of all participating services approved this study.

Patients

Eligible patients were enrolled consecutively as they were referred to the participating

services during the study period. All services were asked to evaluate and collect data on a specific number of patients, ranging from 20 to 100, based on the size of the service. Patients were eligible for the study if they were adults (aged 20 years or older) with locally advanced or metastatic cancer (including hematopoietic neoplasms) who had been admitted to a palliative care unit, referred to a hospital palliative care team, or were receiving home-based palliative care.

Outcome

We used the FP method to develop prognostic models based on laboratory findings and vital signs for predicting the 7-day, 14-day, 30-day, 56-day, and 90-day survival of patients with advanced cancer (Objective Prognostic Index for advanced cancer: OPI-AC).

Measurements and Variables

The physician assessed variables on the day of admission, including the patient's age, gender, site of the primary tumor and metastases, anticancer treatment during the 1-month period before assessment (i.e., chemotherapy, hormone therapy, or radiotherapy), symptoms and general condition, vital signs (heart rate and respiratory rate), and the results of blood tests performed during the 1-week period before assessment. The

following laboratory tests were assessed: leukocyte count (10^9/L), neutrophil count (10^9/L), lymphocyte count (10^9/L), platelet count (10^9/L), urea (mg/dL), creatinine (mg/dL), alanine transaminase (U/L), alkaline phosphatase (U/L), total bilirubin (mg/dL), lactate dehydrogenase (U/L), albumin (g/dL), and C reactive protein (mg/dL). Physicians followed the patients until death or 6 months after enrolment.

We used the heart rate and respiratory rate on the day of admission and the laboratory data obtained during the 1-week period before assessment as objective variables. We also added 3 composite variables, which were the neutrophil / lymphocyte ratio (NLR)[22], Prognostic Nutritional Index (PNI)[23], and platelet / lymphocyte ratio (PLR)[24]. Thus, a total of 17 variables were considered for the prognostic models.

Modified PiPS-B14/56

The modified PiPS-B14/56 can identify patients with an expected survival of days (0-13 days) or weeks (14-55 days), respectively. Scores were calculated from the following variables: symptoms (presence or absence of anorexia, dyspnoea, dysphagia, fatigue, and weight loss during the last month); Eastern Cooperative Oncology Group performance status; global health status (1 = extremely poor health, 7 = normal health); cognitive status assessed according to the Abbreviated Mental Test score; pulse rate; and

laboratory data (leukocyte count, neutrophil count, lymphocyte count, platelet count, urea, creatinine, alanine aminotransferase, alkaline phosphatase, total bilirubin, lactate dehydrogenase, albumin, and C-reactive protein). Cognitive status was evaluated according to the Abbreviated Mental Test score by physician proxy, and was rated as zero if the score was ≤ 3 points[7,21].

PaP score

PaP scores were used to classify patients into three groups according to the probability of 30-day survival: group A >70%, group B 30–70%, and group C <30%[6]. PaP scores were calculated from the following variables: symptoms (presence or absent of dyspnoea and anorexia); Karnofsky Performance Status; clinical prediction of survival (>12, 11–12, 7–10, 5–6, 3–4, and 1–2 weeks); and laboratory findings (leucocyte count and lymphocyte percentage)[6].

SAP models

SAP models are used to predict death within 1–6 months for cancer patients on chemotherapy[20]. Scores were calculated from data on the neutrophil count, lactate dehydrogenase, and albumin. The regression equation corresponding to each prediction

period was $p=1/(1+\exp(-C_{Alb}\times_{Alb}- C_{Alb} -C_{LDH}\times_{LDH}-C_{Neutrophil}\times_{Neutrophil}-\text{const.}))$

Statistical analysis

Comparison of patient background factors was performed by using the Student t-test, chi-square test, or log-rank test, as appropriate. We used the FP modelling method to predict the survival time (in days) from enrolment to death. FP modelling is an alternative to standard polynomial regression models and provides more flexible parameterization based on fractional polynomial functions[25]. All 17 variables were entered into the initial FP model: heart rate, respiratory rate, leukocyte count, neutrophil count, lymphocyte count, platelet count, urea, creatinine, alanine aminotransferase, alkaline phosphatase, total bilirubin, lactate dehydrogenase, albumin, C-reactive protein, NLR, PNI, and PLR. Then, we conducted 10-fold cross validation to correct for over-optimism in development of the models and identified the model with the best predictive accuracy for each target survival period.

FP modelling differs from regular polynomials in that logarithms and noninteger powers can be employed, and powers can also be repeated. We used the degree-2 fractional polynomial of x for regression. The FP modelling technique employed the equation $Y=\beta_0+\beta_1X^{(p1)}+\beta_2X^{(p2)}$, where p1, and p2 are exponent powers selected from among {-2, -1,

-0.5, 0, 0.5, 1, 2, and 3}, with the model showing the best fit being chosen. The convention is that X_0 equals LN(X)[26,27].

We also estimated the probability of survival using various prognostic models, i.e., the FP, PiPS-B 14/56, PaP, and SAP models, by calculating the AUC values. Using three patients extracted from the database, the survival times targeted by each model at the time of development were compared, i.e., 14-day survival for the PiPS-B 14 model, 30-day survival for the PaP model, 30/56/90-day survival for the SAP models, and 56-day survival for the PiPS-B 56 model. All analyses were carried out using SAS software (ver. 9.4) and R software (ver. 3.4.4), and $p < 0.05$ was considered significant.

Results

Participants

A total of 2426 subjects were recruited in the original study. Among them, 1387 patients were excluded because of missing data (date of death, laboratory findings, or vital signs), and we analyzed the remaining 1039 patients for this study. Patient characteristics are summarized in Table 1. The mean age of the patients was 67.7 years, and lung cancer was the most frequent primary cancer, followed by cancer of the stomach/esophagus. The median survival time was 33 days. Among the patients analyzed, 24.9% and 5.6% were

receiving chemotherapy and/or radiotherapy, respectively. Patient background factors including survival periods were largely consistent between the analyzed and non-analyzed patients (Appendix 1), except that the analyzed patients were significantly younger, showed male predominance, had more metastatic tumors, and more chemotherapy. Laboratory findings are summarized in Table 2.

FP models and performance

Table 3 summarizes the best FP models for predicting 7-day, 14-day, 30-day, 56-day, and 90-day survival. We designated each of these models as an OPI-AC. All indexes included heart rate, urea, and albumin. In addition, the respiratory rate, creatinine, C-reactive protein, lymphocyte count, neutrophil count, total bilirubin, lactate dehydrogenase, and PLR were included in some indexes. The AUC values of these OPI-AC models exceeded 0.89 for prediction of 30-day to 90-day survival, while the AUC was 0.77 for 7-day survival and 0.81 for 14-day survival (Table 3). Accuracy of the OPI-AC was better than the PiPS-B 56 model (0.89 vs. 0.83), the PaP model (0.89 vs. 0.87), and all three SAP models (0.89-0.92 vs. 0.74-0.82).

Examples of using OPI-AC (Figure 1,2,3)

We calculated the estimated probability of survival for three patients using all of the OPI-AC models. Patient A died 10 days after enrolment, and the largest change in the estimated probability of survival was noted between 7 and 14 days (Figure 1). Similarly, the largest change was seen between 14 and 30 days for patient B who died 27 days after enrolment (Figure 2). Patient C died 53 days after enrolment, and the second largest change in the estimated probability of survival was noted between 30 and 56 days for this patient (Figure 3).

Discussion

Prediction of patient survival with minimum bias is challenging. In this study, we demonstrated that the prognostic prediction model using only objective data (i.e., routine laboratory findings and vital signs) showed high accuracy than existing predication tools requiring direct patient assessment by physicians and health care professionals.

The most important finding of this study was that the OPI-AC models for relatively longer survival (30-90 days) were more accurate than existing predictive models that include subjective patient factors and physician evaluation. That is, the AUC for the 30-day OPI-AC was 0.89, while the AUC for the PaP score was 0.87 in this dataset and 0.72 in the original study[8]. Similarly, the AUC for the 56-day OPI-AC was 0.90, while the AUC for the PiPS-B 56 model was 0.83 in this dataset and 0.81 in the original study[7]. These findings indicate that prediction of survival by FP modelling is sufficiently accurate, even when based entirely on objective variables (i.e., laboratory findings and vital signs) without data from direct examination of the patient by a physician or other healthcare professional.

Furthermore, the AUC for the 90-day OPI-AC was larger than that for the SAP model, a linear model incorporating 3 laboratory parameters that was developed from a large

prospective cohort database accumulated at a single centre[20]. AUC values for the 30-day, 56-day, and 90-day OPI-AC were 0.89, 0.90, and 0.92, respectively. In contrast, the AUC values for the 1-month, 2-month, and 3-month SAP models were respectively 0.74, 0.77, and 0.82 in the present study, or 0.74, 0.70, and 0.71 in the original reports[20]. These results indicate that addition of more variables and use of converted variables can contribute to improvement of predictive accuracy.

However, the OPI-AC showed relatively lower accuracy for predicting short-term survival, with the AUC values of the 7-day and 14-day OPI-AC being were 0.77 and 0.81 respectively. Among the other models, the AUC for prediction of 7-day survival using the OPPS was 0.82 (0.75-0.89) in a Korean study[19], while the AUC for prediction of 14-day survival using the PiPS-B14 was 0.86 (0.84-0.89)[7]. One possible reason is that the 7-day and 14-day OPI-AC did not include sodium, which might be sensitive marker of impending death,[13] so addition of sodium could contribute to improving the predictive power[13]. Another possible reason is that relatively small number of patients who died in period of 7-days, 14-days might lead to instability of constructed prediction models. A more likely interpretation is that prediction of impending death is improved by assessing changes of vital signs and physical findings, such as drooping of the nasolabial fold, respiration with mandibular movement, or the death rattle[15–17]. These findings

suggest that further investigation of indexes containing more variables or daily changes of variables is required to determine whether relatively short-term survival can be predicted from objective data alone.

Regarding clinical practice, the OPI-AC makes it possible to predict the survival of patients without direct involvement of physicians or other healthcare professionals. As previous studies have shown that physicians tend to markedly overestimate the survival of patients,[9,28] our models could be useful to improve the conversation among patients, families, and physicians regarding preparation for end-of-life care [29,30].

In terms of research implications, FP modelling seems to be a strong method for developing prognostic models. We stress the importance of the methodology itself rather than the details of the formula, as the formula may change when using more data or a different study population, but the basic methodology is widely applicable[26,27]. In addition, our prognostic model could be used to identify patients who are eligible for participation in clinical trials to minimize attrition rates.

This study has some limitations. First, the subjects analyzed in this study were limited to patients who received blood test due to clinical necessity. There may be a selective bias, but the patient backgrounds were similar between analyzed and non-analyzed patients and we believe this bias would not have large influence on the results. Second, although

we conducted 10-fold cross validation in this study, no external validation was performed. Independent validation might add some insights for final model.

Conclusions

We used FP modelling to develop highly accurate prognostic models for patients with advanced cancer that exclusively employed objective variables (OPI-AC). Accurate objective prediction may facilitate conversations about end-of-life care, and FP modelling seems to be a promising method for development of other prognostic indexes in future research.

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Conflict of interest statement

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Table 1 Patients Characteristics

	All patients (n=2426)		Analyzed patients (n=1039)	
	Mean	S.D.	Mean	S.D.
Age (yrs)	69.1	12.8	67.7	13.1
Heart rate (beat/minute)	85.8	16.5	85.3	16.5
Respiratory rate (breath/minute)	16.0	4.5	15.8	4.4
	N	%	N	%
Male sex	1387	57.2	627	60.3
Site of primary cancer				
Lung	519	21.4	259	24.9
Stomach/oesophagus	326	13.4	144	13.9
Colon/rectum/small intestine	293	12.1	125	12.0
Pancreas	250	10.3	111	10.7
Liver/Biliary system	221	9.1	90	8.7
Ovary/uterus	139	5.7	57	5.5
Kidney/renal pelvis/ureter/bladder/prostate	162	6.7	53	5.1
Breast	122	5.0	51	4.9
Head and neck	78	3.2	37	3.6
Others	258	10.6	112	10.8
Metastatic site				
Anywhere	1927	79.4	855	82.3
Liver	855	35.2	403	38.8
Bone	723	29.8	308	29.6
Lung	807	33.3	349	33.6
Central nervous system	278	11.5	127	12.2
Dyspnoea	700	28.9	281	27.0
Anorexia	1813	74.7	784	75.5
Fatigue	1712	70.6	745	71.7
Weight loss in the previous month	1589	65.5	681	65.5
Karnofsky Performance Scale				
≧50	1143	47.1	490	47.2
30-40	822	33.9	346	33.3
10-20	455	18.8	200	19.2
ECOG-PS*[1]				
0-1	255	10.5	122	11.7
2	440	18.1	204	19.6
3	882	36.4	357	34.4
4	846	34.9	353	34.0
Global Health				
1: extremely poor	248	10.2	106	10.2
2	567	23.4	257	24.7
3	814	33.6	316	30.4

4	443	18.3	202	19.4
5-7: normal health	348	14.3	155	14.9
Abbreviated Mental Test by physician-proxy ratings				
≦3	623	25.7	267	25.7
Clinical prediction of survival (wks)				
>12	472	19.5	228	21.9
11-12	144	5.9	66	6.4
7-10	437	18.0	196	18.9
5-6	300	12.4	113	10.9
3-4	611	25.2	238	22.9
1-2	455	18.8	196	18.9
Anticancer treatment				
Chemotherapy	539	22.2	259	24.9
Hormone therapy	36	1.5	14	1.3
Radiotherapy	128	5.3	58	5.6
Survival period				
≦7-day	334	14.1	141	14.1
≦14-day	642	27.2	270	26.9
≦30-day	1117	47.3	478	47.7
≦56-day	1559	66.0	654	65.2
≦90-day	1812	76.7	764	76.2
Median survival (days; 25%, 75% tile)	33 (13, 84)		33 (13, 85)	

***1 ECOG-PS: Eastern Co-operative Oncology Group Performance Status**

Table 2 Laboratory data of the analyzed patients

	Mean	S.D.
Leukocyte count (10^9/L)	9.35	6.20
Neutrophil count (10^9/L)	7.61	5.71
lymphocyte count (10^9/L)	0.97	0.68
Platelet count (10^9/L)	234.1	123.0
Urea (mg/dL)	22.9	20.0
Creatinine (mg/dL)	0.90	0.8
Alanine aminotransferase (U/L)	42.0	79.6
Alkaline phosphatase (U/L)	691.4	828.6
Total bilirubin (mg/dL)	1.65	3.91
Lactate dehydrogenase (U/L)	461.4	638.2
Albumin (g/dL)	28.4	7.3
C-reactive protein (mg/dL)	6.3	6.6

Table 3 Variables used in each model

Estimated survival time	OPI-AC formula*6	AUC*1 (95% CI)			
		OPI-AC	PiPS*2-B model	PaPs*3 model	SAP*4 model
7 days	Y=heart rate + urea + albumin	0.765 (0.658 - 0.872)			
14 days	Y=heart rate + urea + albumin + respiratory rate + creatinine + (C-reactive protein)$^{-1}$	0.806 (0.720 - 0.892)	0.862 (0.837 - 0.888)		
30 days	Y=heart rate + (urea)$^{-1}$+ (urea)$^{-2}$ + albumin + (percentage of lymphocytes)$^{-0.5}$ + (total bilirubin)$^{-0.5}$ + (PLR*5)$^{-2}$	0.894 (0.836 - 0.953)		0.870 (0.848 - 0.892)	0.742 (0.653 - 0.832)
56 days	Y=heart rate + ($\log_{urea}{}^{-2}$)+ (urea)$^{-2}$ + albumin + percentage of lymphocytes + (total bilirubin)$^{-1}$ + (PLR*5)^{3} + lactate dehydrogenase	0.897 (0.834 - 0.960)	0.827 (0.800 - 0.853)		0.769 (0.680 - 0.859)
90 days	Y=heart rate + ($\log_{urea}{}^{-2}$)+ (urea)$^{-2}$ + albumin + neutrophil count + (total bilirubin)$^{-0.5}$ + (PLR*5)$^{-2}$ + lactate dehydrogenase	0.923 (0.860 - 0.986)			0.819 (0.734 - 0.904)

***1 AUC: Area under the curve**

***2 PiPS: Prognosis in Palliative Care Study**

***3 PaPs: Palliative Prognostic Score**

***4 SAP: Set of six adaptable prognostic models**

***5 PLR: Platelet / lymphocyte ratio (platelet count divided by the lymphocyte count).**

***6 OPI-AC: Objective Prognostic Index**

Appendix 1 Characteristics of analyzed vs. non-analyzed patients

	Analyzed patients (n=1039)		Non-analyzed patients (n=1387)		
	Mean	S.D.	Mean	S.D.	p value
Age (yrs)	67.7	13.1	70.1	12.6	<0.001
Heart rate (beats/minute)	85.3	16.5	86.1	16.6	0.232
Respiratory rate (breaths/minute)	15.8	4.4	16.3	4.5	0.014
	N	%	N	%	
Male sex	627	60.3	760	54.8	0.007
Site of primary tumor					0.129
Lung	259	24.9	260	18.7	
Stomach/esophagus	144	13.9	182	13.1	
Colon/rectum/small intestine	125	12.0	168	12.1	
Pancreas	111	10.7	139	10.0	
Liver/Biliary tract	90	8.7	131	9.4	
Ovary/uterus	57	5.5	82	5.9	
Kidney/renal pelvis/ureter/bladder/prostate	53	5.1	109	7.9	
Breast	51	4.9	71	5.1	
Head and neck	37	3.6	41	3.0	
Others	112	10.8	146	10.5	
Metastatic sites					
Multiple	855	82.3	1072	77.3	0.004
Liver	403	38.8	452	32.6	0.003
Bone	308	29.6	415	29.9	0.784
Lung	349	33.6	458	33.0	0.875
Central nervous system	127	12.2	151	10.9	0.344
Dyspnea	281	27.0	419	30.2	0.092
Anorexia	784	75.5	1029	74.2	0.496
Fatigue	745	71.7	967	69.7	0.301

Weight loss in the previous month	681	65.5	908	65.5	0.877
Karnofsky Performance Scale					0.811
≥50	490	47.2	653	47.1	
30-40	346	33.3	476	34.3	
10-20	200	19.2	255	18.4	
ECOG-PS*[1]					0.064
0-1	122	11.7	133	9.6	
2	204	19.6	236	17.0	
3	357	34.4	525	37.9	
4	353	34.0	493	35.5	
Global Health					0.072
1: extremely poor	106	10.2	142	10.2	
2	257	24.7	310	22.4	
3	316	30.4	498	35.9	
4	202	19.4	241	17.4	
5-7: normal health	155	14.9	193	13.9	
Abbreviated Mental Test by physician-proxy ratings					
≤3	267	25.7	356	25.7	0.992
Clinical prediction of survival (wks)					0.015
>12	228	21.9	244	17.6	
11-12	66	6.4	78	5.6	
7-10	196	18.9	241	17.4	
5-6	113	10.9	187	13.5	
3-4	238	22.9	373	26.9	
1-2	196	18.9	259	18.7	
Anticancer therapy					
Chemotherapy	259	24.9	280	20.2	0.022
Hormone therapy	14	1.3	22	1.6	0.563
Radiotherapy	58	5.6	70	5.1	0.208

Survival period						
	≦7-day	141	14.1	193	14.2	0.927
	≦14-day	270	26.9	372	27.4	0.815
	≦30-day	478	47.7	639	47.0	0.749
	≦56-day	654	65.2	905	66.5	0.497
	≦90-day	764	76.2	1048	77.1	0.614
Median survival (days; 25%, 75%)		33 (13, 85)		34 (13, 83)		

***1 ECOG-PS: Eastern Cooperative Oncology Group Performance Status**

Figure 1 Examples of using Objective Prognostic Index for advanced cancer for patient A

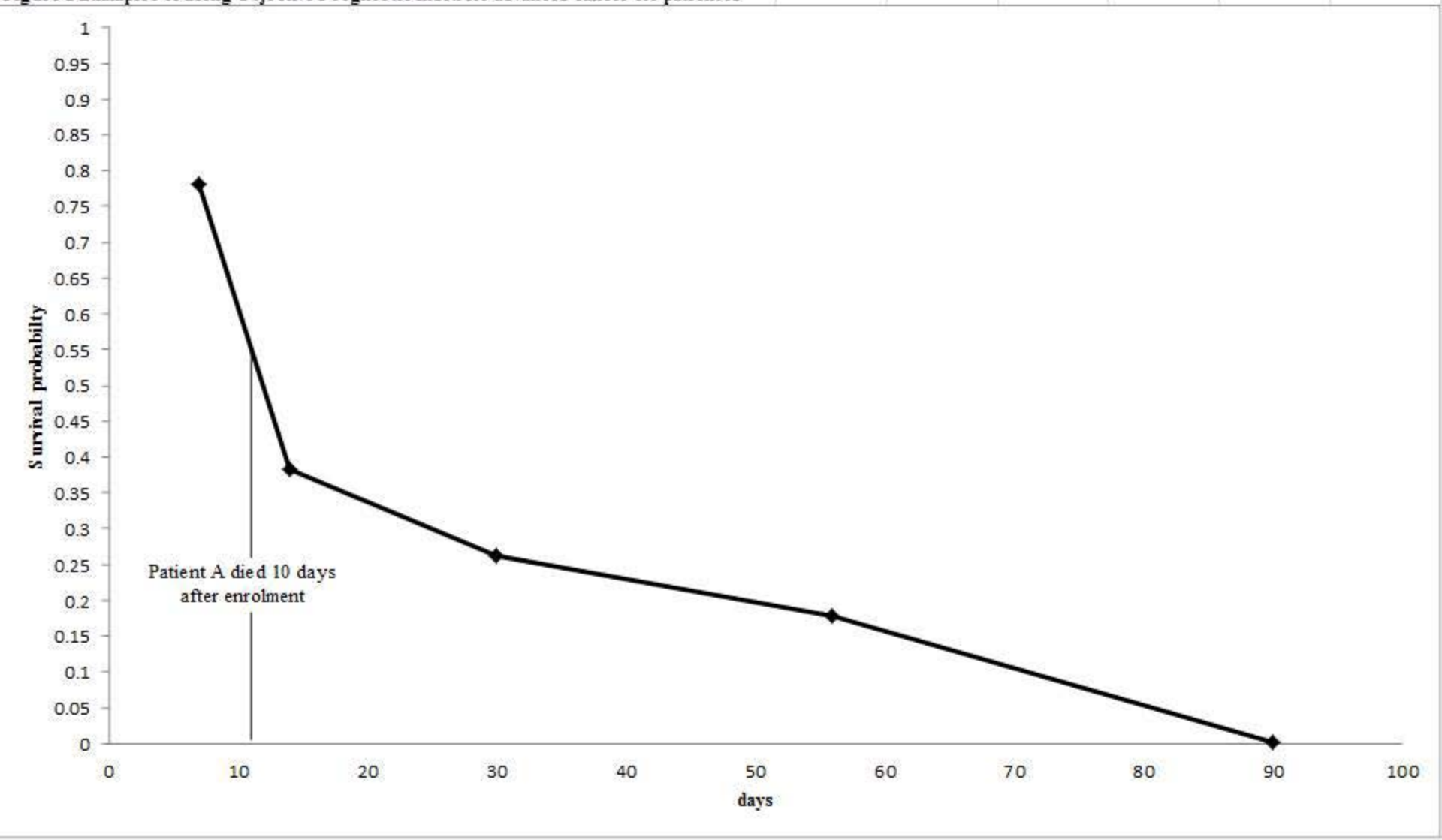

Figure 2 Examples of using Objective Prognostic Index for advanced cancer for patient B

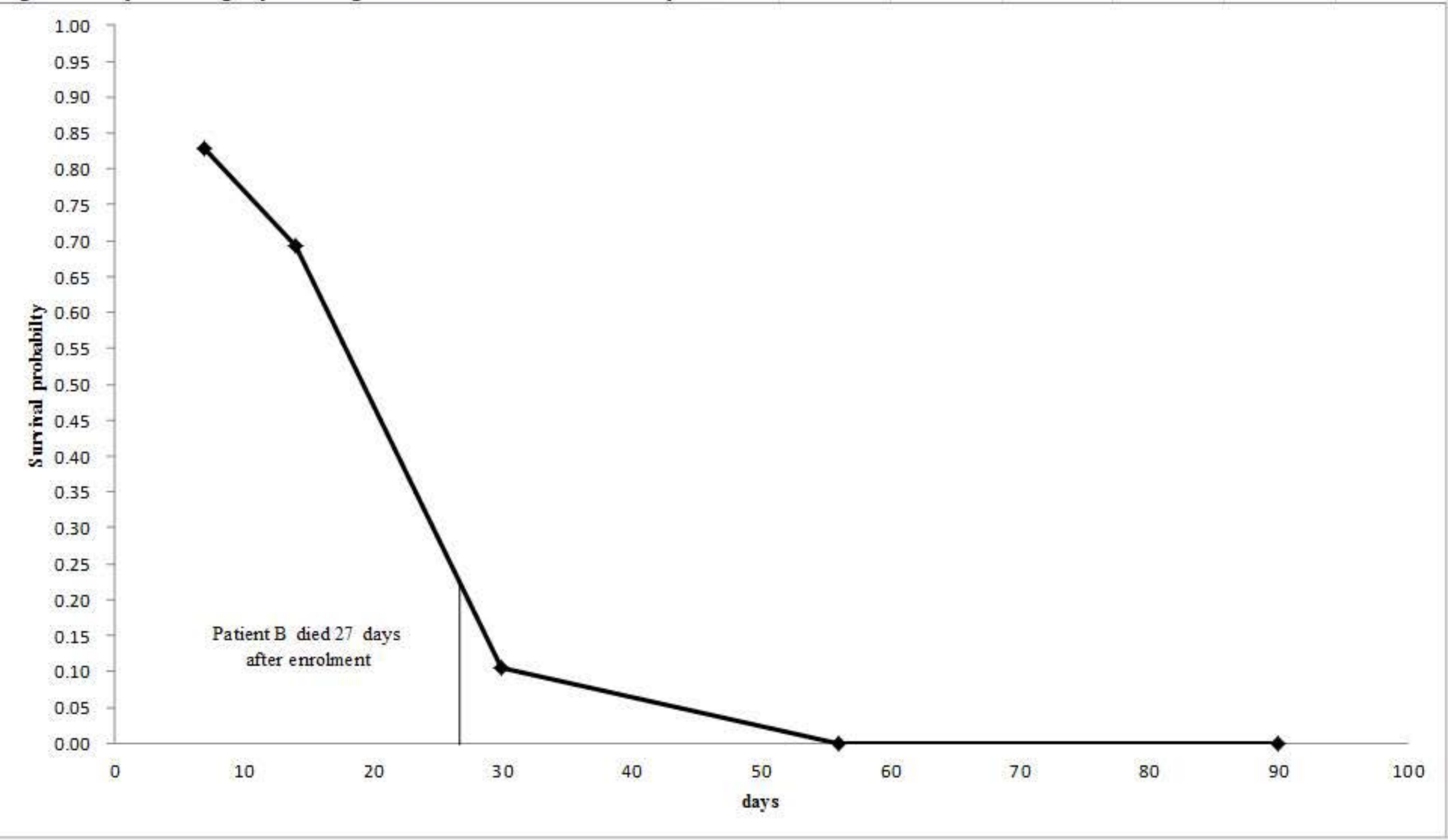

Figure 3 Examples of using Objective Prognostic Index for advanced cancer for patient C

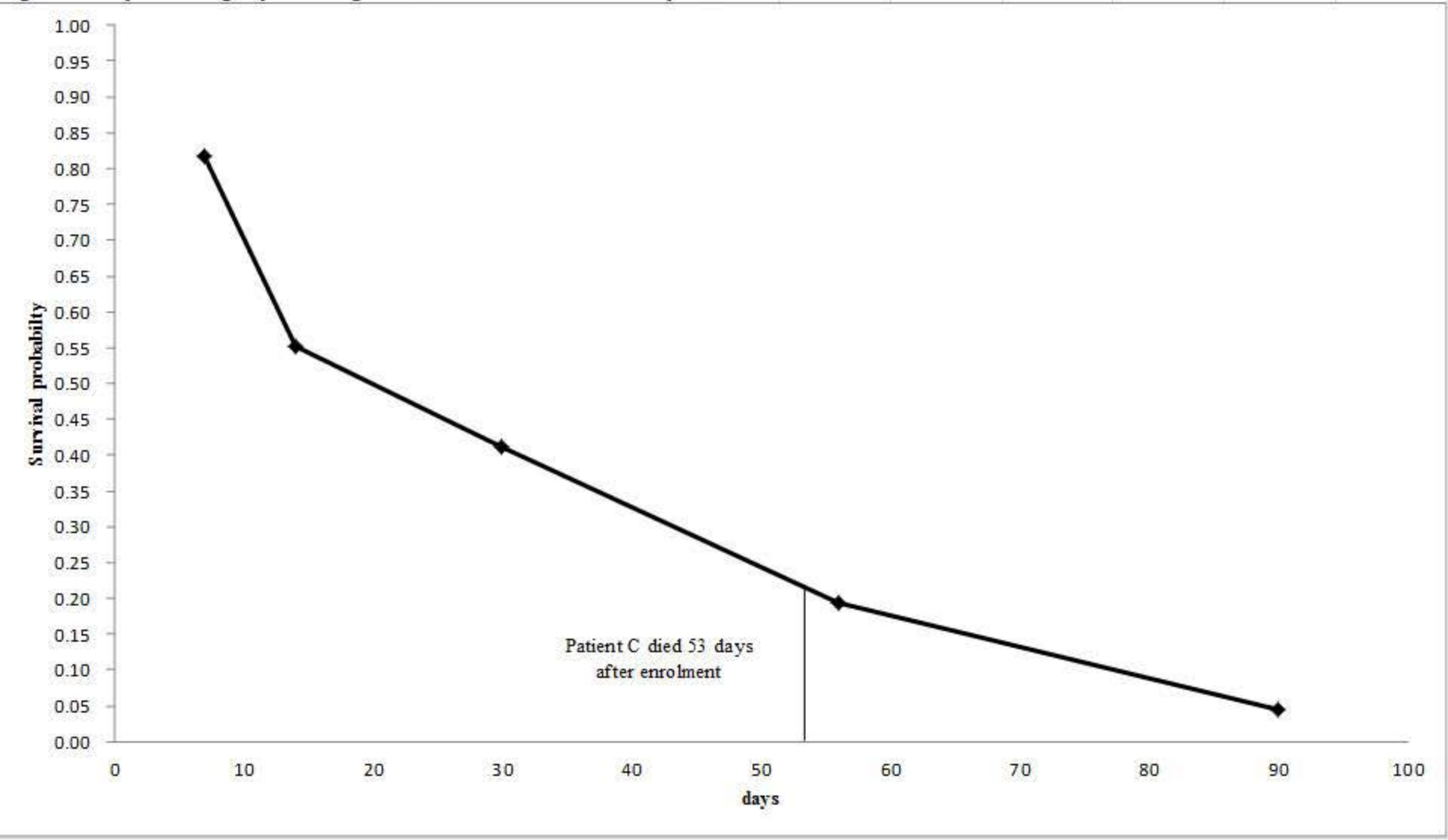

Figure Legends

Figure 1

The variables for patient A were as follows: heart rate (78 beats/minute), respiratory rate (16 breaths/minute), neutrophil count (25.37×10^9/L), lymphocyte count (1.49×10^9/L), platelet count (317.0×10^9/L), urea (90.1 mg/dL), creatinine (1.89 mg/dL), total bilirubin (1.2 mg/dL), lactate dehydrogenase (343 U/L), albumin (2.4 g/dL), and C-reactive protein (18.3 mg/dL).

Figure 2

The variables for patient B were as follows: heart rate (86 beats/minute), respiratory rate (16 breaths/minute), neutrophil count (6.27×10^9/L), lymphocyte count (0.90×10^9/L), platelet count (106.0×10^9/L), urea (9.0 mg/dL), creatinine (0.54 mg/dL), total bilirubin (2.6 mg/dL), lactate dehydrogenase (1594 U/L), albumin (2.6 g/dL), and C-reactive protein (5.2 mg/dL).

Figure 3

The variables for patient C were as follows: heart rate (90 beats/minute), respiratory rate (15 breaths/minute), neutrophil count (8.67×10^9/L), lymphocyte count (0.88×10^9/L), platelet count (509.0×10^9/L), urea (13.0 mg/dL), creatinine (0.61 mg/dL), total bilirubin (1.0 mg/dL), lactate dehydrogenase (171 U/L), albumin (2.7 g/dL), and C-reactive protein (16.2 mg/dL).