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ORIGINAL ARTICLE

Prognostic model for patients with advanced cancer using a combination of routine blood test values

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Abstract

Purpose The purpose of this study was to develop a simple prognostic model based on objective indicators alone, i.e., routine blood test data, without using any subjective variables such as patient's symptoms and physician's prediction.

Methods The subjects of this retrospective study were patients at the palliative care unit of Tohoku University Hospital, Japan. Eligible patients were over 20 years old and had advanced cancer ($n = 225$). The model for predicting survival was developed based on Cox proportional hazards regression models for univariable and multivariable analyses of 20 items selected from routine blood test data. All the analyses were performed according to the TRIPOD statement (https://www.tripod-statement.org/).

Results The univariable and multivariable regression analyses identified total bilirubin, creatinine, urea/creatinine ratio, aspartate aminotransferase, albumin, total leukocyte count, differential lymphocyte count, and platelet/lymphocyte ratio as significant risk factors for mortality. Based on the hazard ratios, the area under the curve for the new risk model was 0.87 for accuracy, 0.83 for sensitivity, and 0.74 for specificity. Diagnostic accuracy was higher than provided by the Palliative Prognostic Score and the Palliative Prognostic Index. The Kaplan–Meier analysis demonstrated a survival significance of classifying patients according to their score into low-, medium-, and high-mortality risk groups having median survival times of 67 days, 34 days, and 11 days, respectively ($p < 0.001$).

Conclusions We developed a simple and accurate prognostic model for predicting the survival of patients with advanced cancer based on routine blood test values alone that may be useful for appropriate advanced care planning in a palliative care setting.

Keywords Advanced cancer · Prognostic model · Palliative care · Blood tests · Cox regression analysis

Introduction

The availability of accurate prognostic information for patients with advanced cancer is of great importance for timely and appropriate advance care planning (ACP), incorporating advanced healthcare decision-making [1–3]. Such information would be useful for discussing their condition with patients and their families and would be of help for ACP and clinical decision-making. One of the major concerns in clinical practice regarding patients with advanced cancers is the need for accurate predictions of the probability of short- and long-term survival, and such prediction is central to optimal end-of-life decisions. It is important to devise a simple and objective tool for predicting short- or long-term survival that could be used by all medical personnel to provide patient care. Validated widely used prognostic tools that have been developed thus far to predict the survival of patients with advanced cancer include the Palliative Prognostic Index (PPI) [4], Palliative Prognostic (PaP) score [5], and Prognosis in Palliative Care study (PiPS) score [6]. All of them provide acceptable sensitivity, specificity, and predictive accuracy, but have the limitation of the survival predictions being based on several subjective items, including the performance status, patient symptoms, and physician judgments, in addition to biological parameters. Most of them require the physicians to conduct a subjective assessment of the patients' status and symptoms, a

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process that is inevitably influenced by the experience and competence of the physician. The addition of clinical predictors of survival to the PaP score has been demonstrated to reduce its accuracy [7]. The modified Glasgow prognostic score (mGPS) has also been demonstrated clinically useful for patients with advanced cancers, in close association of the Karnofsky performance status with serum C-reactive protein and albumin levels [8]. Recent studies have proposed new tools for predicting the survival of advanced cancer patients based on laboratory data and vital signs, without involving clinician evaluations, and they have included a tool based on six objective predictors [9], and a tool based on a fractional polynomial model [10]. There have also been several recent reports of models [11, 12] for predicting 1-week or 2- to 3-week short-term survival of patients with advanced cancer that are based on a combination of laboratory test data. In the present study, we attempted to develop a new and simple model for survival prediction based on a combination of objective data obtained from the routine blood test data of patients with advanced cancers in a palliative care setting.

Methods

Patient population

We conducted a retrospective study in which we enrolled 225 patients with advanced cancers who were over 20 years old and had been admitted to the palliative care unit of Tohoku University Hospital, Japan, between May 2017 and October 2018. At the time of the study, none of the eligible patients was any longer receiving cancer chemotherapy or radiotherapy. Blood test data were collected from patients who had received blood tests for some clinical indication within 1-week before or after admission. All the patients were followed up until their death or until 180 days after their enrollment, and the survival time (days) was counted from the day of the blood test until death, or the case was censored if the patient was alive after 180 days. For patients with readmissions, only the first blood test values were adopted for use in the study. When a patient had been discharged from our hospital, we collected information from the discharge destination regarding the survival period. If survival information was not available after discharge, the case was treated as "censored" on the last traceable day within the 180-day period. The primary physician and nurse discussed about CPR decisions with family members when the patient was admitted, and a DNAR form was signed by each other, kept during the follow-up period in the unit. The protocol of this study conformed to the ethical guidelines of the Helsinki Declaration. The study was approved by the Ethics Committee of the Tohoku University Graduate School of Medicine.

Data collection

We collected the patient characteristic data, including age, gender, site of the primary cancer, and metastasis. To validate the predictive accuracy of our model, the PPI [4] and PaP [5] models were also applied to all the enrolled patients, in which the subjective evaluations by the primary physicians in the palliative care unit were included. Data for the following variables were collected to calculate the PPI: Palliative Performance Scale score, the oral intake ability, presence/absence of edema, the presence/absence of dyspnea at rest, and presence/absence of delirium. The PaP score was calculated on the basis of six variables: clinical prediction of survival, presence/absence of dyspnea, presence/absence of anorexia, Karnofsky Performance Status, total leukocyte count, and differential lymphocyte count. Among the routine blood test data, including the data thus far recommended as prognostic biomarkers [13, 14], we evaluated the following 16 routine blood test variables: total bilirubin (mg/dL), alkaline phosphatase (U/L), alanine aminotransferase (U/L), aspartate aminotransferase (U/L), sodium (mEq/L), calcium (mEq/L), lactate dehydrogenase (U/L), creatinine (mg/dL), blood urea nitrogen (mg/dL), albumin (g/dL), total leukocyte count (10^3/μL), C-reactive protein (mg/dL), differential lymphocyte count (%), platelet count (10^4/μL), hemoglobin (g/dL), and urea/creatinine ratio. We also assessed the following four variables that have been identified as prognostic biomarkers in previous studies: the neutrophil/lymphocyte ratio (NLR) [15], lymphocyte/monocyte ratio (LMR) [16], C-reactive protein/albumin ratio (CRP/Ab) [17], and platelet/lymphocyte ratio (PLR) [18].

Statistical analysis

Survival analyses were performed using the Cox proportional hazards model. Data for a total of 22 variables obtained in all the patients were included in the analyses: age, gender, and data for the 20 objective variables described above that were obtained from routine blood tests. First, univariable analyses were performed, and all the variables with p values less than 0.2 were entered into the multivariable model. A survival classification and regression trees (CART) analysis, which is an empirical statistical technique based on recursive partitioning of the data space to predict the response, was performed to identify the most appropriate cutoff points for the variables [19]. The split variables and split points selected as the best fit were then used in the multivariable analysis. A stepwise variable selection with backward elimination was conducted in each dataset to optimize Akaike's information criterion (AIC). The risk scores were defined based on the determined hazard ratios (HR) rounded down to integers, and they were used to calculate the scores for each patient. The patients were classified into three mortality risk groups

according to their scores. The survival curves were estimated by the Kaplan–Meier method and compared among the three score groups by using the log-rank test. A receiver operating characteristic (ROC) curve analysis was performed to validate our model in comparison with the PPI and PaP models. All the statistical analyses were performed using R version 4.0.0 software (The R Project for Statistical Computing; https//www.r-project.org/).

Results

Patient characteristics

A total of 225 patients were enrolled in this study, and the 18 cases in which the duration of survival was more than 180 days or it was impossible to follow-up after leaving the palliative unit were censored. Table 1 summarizes the patient characteristics. The mean age of the patients was 69.6 years, and the most frequent site of the primary cancer was the gastrointestinal tract, followed by the lung. The median survival time was 30 days. The results of the blood tests are summarized in Table 2. Using the PPI and PaP models, the scores of all the enrolled patients were also examined as described in the "Methods". These scores were 7.45 ± 3.03 and 10.11 ± 4.52, respectively, both of which exhibited less than 21 days of survival according to the prediction period suggested by the models.

Table 1 Patient characteristics

Characteristic	*n*=225 Mean (SD)
Age (years)	69.6 (11.8)
Male *n* (%)	88 (39.1)
Primary cancer site	
Lung	25 (11.1)
Stomach/esophagus	31 (13.8)
Colon/rectum/small intestine	29 (12.9)
Pancreas	23 (10.2)
Liver	9 (4.0)
Biliary system	11 (4.9)
Ovary/uterus	36 (16.0)
Kidney/bladder/prostate	7 (3.1)
Breast	8 (3.6)
Head and neck	11 (4.9)
Central nervous system	6 (2.7)
Others	29 (12.9)
Metastatic site[a]	
Any site	91 (40.4)
Liver	55 (24.4)
Bone	38 (16.9)
Lung	48 (21.3)
Central nervous system	24 (10.7)
Median survival (days, 95% CI)	30 (24.7–35.3)

SD, standard deviation

[a] The sum of percentages is not 100% due to cases with more than one site of metastasis

Table 2 Blood test values of the patients

Blood test items (reference value)	*n* (%)	Mean (SD)
Leucocyte count (10^3/μL) 4–8	225 (100)	10.7 (7.8)
Lymphocyte (%) 25–40	217 (96.4)	11.9 (8.9)
Platelet count (10^4/μL) 15–35	222 (98.7)	252.4 (131.1)
Hemoglobin (g/dL) 10–18	220 (97.8)	9.8 (2.4)
Total bilirubin (mg/dL) 0.2–1.2	220 (97.8)	1.51 (3.63)
Alkaline phosphatase (U/L) 104–338	216 (96.0)	591.3 (595.8)
Alanine aminotransferase (U/L) 6–43	222 (98.7)	31.7 (41.3)
Aspartate aminotransferase (U/L) 7–36	222 (98.7)	45.1 (61.4)
Lactate dehydrogenase (U/L) 120–245	204 (90.7)	401.6 (392.2)
Sodium (mEq/L) 135–145	223 (99.1)	136.3 (6.35)
Calcium (mg/dL) 8.5–10.5	209 (92.9)	8.32 (0.91)
Creatinine (mg/dL) 0.61–1.04	221 (98.2)	0.85 (0.68)
BUN (mg/dL) 9–21	220 (97.8)	22.4 (17.9)
Albumin (g/dL) 3.8–5.3	216 (96.0)	2.53 (0.81)
C-reactive protein (mg/dL) <0.3	212 (94.2)	6.16 (6.50)
BUN/creatinine >10	198 (88.0)	28.8 (14.8)
C-reactive protein/albumin (CRP/Ab) <0.156	202 (89.8)	3.31 (4.32)
Neutrophil/lymphocyte (NLR) 5<	216 (96.0)	13.1 (14.8)
Lymphocyte/monocyte (LMR) <3.68	180 (80.0)	2.27 (1.35)
Platelet/lymphocyte (PLR) <170.5	214 (95.1)	350.2 (277.9)

SD, standard deviation; *n*, number of patients with blood data; total *n*, 225

Variables associated with the overall survival

Analyses of the blood test data by univariable Cox regression analyses revealed positive associations between survival duration and the blood test parameters ($p < 0.2$), but not between survival time and gender or platelet count (Table 3a). As the initial candidates for the final risk model, the 20 variables were then entered into the multivariable Cox model and followed by stepwise variable selection by optimizing AIC. The results of this analysis identified total bilirubin, alkaline phosphatase, alanine aminotransferase, creatinine, urea/creatinine ratio, albumin, total leukocyte count, differential lymphocyte count, NLR, and PLR as the selected prognostic factors for the duration of survival.

To obtain the final risk model, the 20 variables selected by univariable Cox regression analyses were employed to determine the most appropriate cutoff points to dichotomize for clinical use. All of the variables were entered into the CART analysis model. The split variable and split point selected as the best fit were then used for the multivariable analyses and stepwise selection by AIC. The variables identified as being significant predictors of survival (Table 3b) were total bilirubin > 1.85 mg/dL ($p = 0.007$), aspartate aminotransferase > 85 U/L ($p = 0.004$), creatinine > 1.265 mg/dL ($p < 0.001$), urea/creatinine ratio > 34.15 ($p < 0.001$), albumin < 2.65 g/L ($p < 0.001$), total leukocyte count > $10.2 \times 10^3/\mu L$ ($p = 0.018$), differential lymphocyte count < 4.1% ($p = 0.070$), and PLR > 113 ($p = 0.026$), and based on the HRs, the risk scores were rounded down to the integers such as 2, 2, 3, 2, 2, 1, 1, and 2, respectively. An ROC curve was constructed using the variables identified to evaluate the predictive ability of our model in comparison with the PPI model and the PaP model (Fig. 1). The ROC curve validated our model based on the areas under the curve (AUCs) for accuracy of 0.8713, sensitivity of 0.828, and specificity of 0.738. The AUC values of the PPI and PaP for accuracy were 0.7596 and 0.8623, respectively, so the accuracy of our model was slightly higher than that of the earlier models. With the integer scores, the mortality rates in person-days with 95% CI according to the selected valuables were calculated for each score patient (Fig. 2a), and the patients were stratified into three groups: a group with scores of 0–2 whose mortality rate was 0.0097 (95% CI 0.0065–0.0138) (group I), a group with scores of 3–5 whose mortality rate was 0.0213 (0.0169–0.0265) (group II), and a group whose scores were ≥ 6 and mortality rate was 0.0628 (0.0483–0.0804) (group III) (Fig. 2b). Survival curves were then constructed by the Kaplan–Meier method and compared by the log-rank test, and the results revealed differences in the survival durations among the three groups at p values of < 0.001 (Fig. 3). The median survival times (MSTs) in group I, group II, and group III were 67 days (95% CI 45–94), 34 days (30–42), and 11 days (9–15) days, respectively. These results suggest that the model we developed may be helpful as a simple and objective tool for predicting survival outcomes in patients with advanced cancers in a palliative care setting.

Table 3 Cox proportional hazard regression analyses of blood test data

(a) Univariable Cox proportional hazard model: univariable analysis

Name	HR	Lower 0.95	Upper 0.95	*p* value
Gender	0.858	0.646	1.139	0.289
Age	0.989	0.978	1.000	0.049
Tbil	1.079	1.041	1.119	0.000
ALP	1.000	1.000	1.001	0.011
AST	1.008	1.006	1.011	0.000
ALT	1.011	1.007	1.015	0.000
Na	0.978	0.954	1.002	0.074
Ca	0.883	0.747	1.043	0.144
LDH	1.000	1.000	1.001	0.194
Cre	1.466	1.219	1.763	0.000
BUN	1.031	1.024	1.038	0.000
BUN/Cre	1.026	1.016	1.037	0.000
Alb	0.719	0.582	0.888	0.002
WBC	1.025	1.011	1.039	0.001
NLR	1.014	1.007	1.022	0.000
LMR	0.804	0.710	0.910	0.001
CRP	1.038	1.018	1.060	0.000
CRP/Alb	1.030	1.003	1.057	0.028
Lymph (%)	0.961	0.944	0.979	0.000
Hb	0.952	0.898	1.009	0.100
PLT	1.000	0.999	1.001	0.949
PLR	1.001	1.000	1.001	0.030

(b) Multivariable Cox proportional hazard model: variable selection (AIC):

Name	HR	Lower 0.95	Upper 0.95	*p* value	Score
Tbil>1.85	2.747	1.313	5.744	0.007	2
AST>85	2.664	1.369	5.184	0.004	2
Cre>1.265	3.374	1.779	6.397	0.000	3
BUN/Cre>34.15	2.529	1.647	3.884	0.000	2
Alb<2.65	2.446	1.633	3.665	0.000	2
WBC>10.2	1.645	1.088	2.487	0.018	1
Lymp<4.1	1.639	0.960	2.799	0.070	1
PLR>113	2.191	1.097	4.374	0.026	2

(a) *Tbil*, total bilirubin; *ALP*, alkaline phosphatase; *AST*, aspartate aminotransferase; *ALT*, alanine aminotransferase; Na, serum natrium; *Ca*, serum calcium; *LDH*, lactate dehydrogenase; *Cre*, creatinine; *BUN*, blood urea; *Alb*, albumin; *WBC*, leucocyte count; *NLR*, neutrophil/lymphocyte; *LMR*, lymphocyte/monocyte; *CRP*, C-reactive protein; *Lymph* (%),differential lymphocyte count; *PLT*, platelet count; *PLR*, platelet/lymphocyte

(b) To determine the appropriate cutoff points for the variables, CART analysis was performed [19]

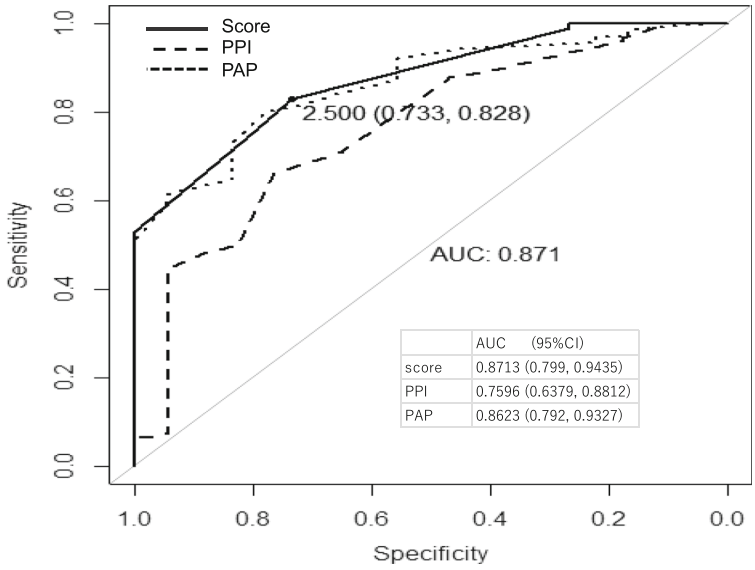

Fig. 1 Predictive value of the final model according to the receiver operating characteristic curve analysis. The analysis yielded an area under the curve (AUC) values of 0.87 for accuracy, 0.83 for sensitivity, and 0.74 for specificity, in comparison with AUC values of 0.76 and 0.86 for accuracy with PPI and PaP, respectively

Discussion

In the present study, we developed a prognostic model based on objective data from routine blood tests alone for use in patients with advanced cancer in palliative care units. Eight variables, namely, total bilirubin, aspartate aminotransferase, creatinine, urea/creatinine ratio, albumin, total leukocyte count, differential lymphocyte count, and PLR, were found to be significantly associated with patient survival. These variables were then used to construct a prognostic model, and based on the scores in the model, the patients were classified into three groups, groups I, group II, and group III, which were predictive of a low-, intermediate-, and high-mortality risk, corresponding to their MSTs of 67 days, 34 days, and 11 days, respectively. This model is unique because it is composed of only objective blood test data, and it may also predict a longer period than the models for 1-week survival [11] or for 2- to 3-week survival [12]. The survival prediction models for advanced cancer patients that have been reported thus far have been based on a variety of subjective items, including performance status, symptoms, and physicians' judgment, in addition to objective biological parameters and vital signs [17]. Thus, the model we developed appears to be a simpler and more useful model for making quick decisions about the prognosis of patients with advanced cancer that can be used by all medical personnel. Preliminary results of validation of this model revealed a higher or comparable accuracy of this model with a higher AUC value in the ROC curve, as compared to the PaP and PPI models, although the differences were not statically significant. Further investigation is needed to validate this model in comparison with the other models. This model, however, may be superior rather than the other models from the following viewpoint: no need of subjective variables and vital signs, and possible quick prediction of short- versus longer-term survival for facilitating end-of-life management by following up on the patient's status.

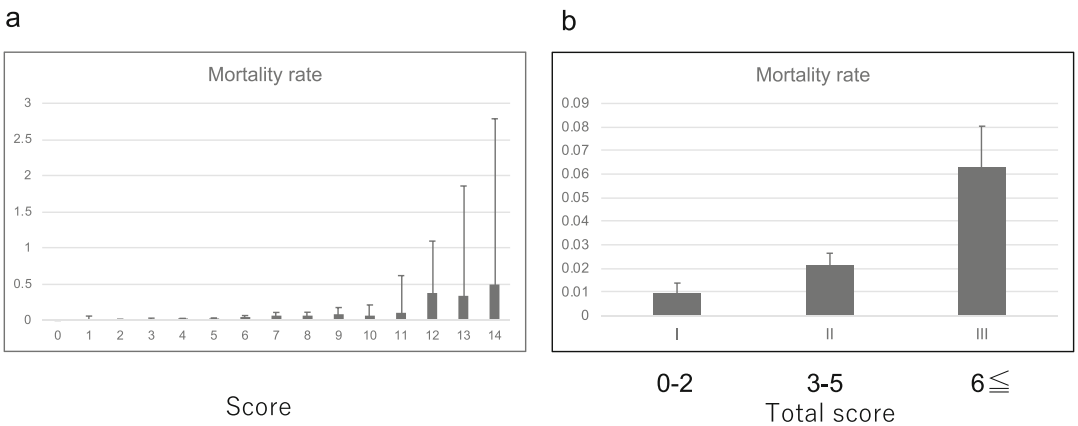

Fig. 2 Mortality rate calculations for each patient based on the hazard ratio (HR) of the final model (**a**) and classification of the patients into groups having scores of 0–2 points (I), 3–5 points (II), or ≧6 points (III) (**b**). The mortality rates of group I, group II, and group III were 0.0097 (95% CI 0.0065–0.0138), 0.0213 (0.0169–0.0265), and 0.0628 (0.0483–0.0804), respectively

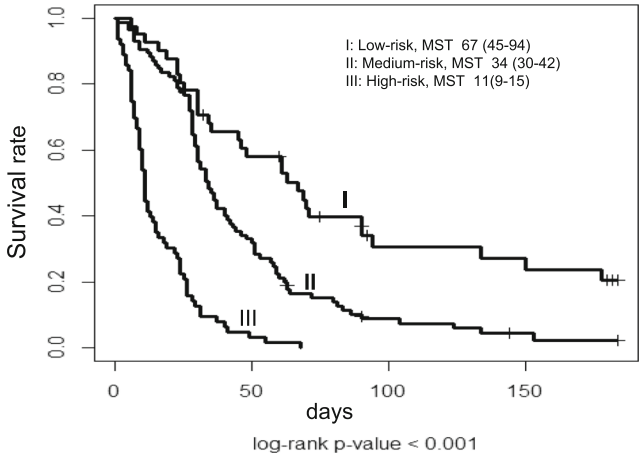

Fig. 3 Overall survival of different risk groups stratified by the final model. The Kaplan–Meier survival method and the log-rank test were used to characterize patients in different risk groups classified by the final model. There were significant differences between the overall survival rates of the low-, medium-, and high-risk groups ($p < 0.001$). The groups also exhibited distinct median survival time (MST, days, 95% CI) as shown in the insert. The cases of patients who were alive after180 days or could not be followed up were censored, and the data of patients with missing value(s) among the eight variables identified as the final model were excluded from the analysis

Accumulating evidence suggests that host inflammatory responses play a crucial role in cancer development and progression of cancer [20, 21]. In recent years, certain indicators of inflammation have been reported to be associated with the survival prognosis in cancer patients. Consistent with these reports, we identified eight variables as predictive markers of survival in our patients, particularly the total leukocyte count, differential lymphocyte count, PLR, and serum levels of acute-phase reactants, such as serum albumin. Aspartate aminotransferase and total bilirubin are also systemic inflammation factors produced by the liver, and blood urea and creatinine are biomarkers of impaired kidney function. Interestingly, Okugawa et al. [11] recently reported demonstrating significant correlation between five blood test data, i.e., elevated serum total bilirubin, creatinine, and alanine aminotransferase, and blood urea nitrogen levels and a decreased platelet count, and death within 1 week in terminally ill cancer patients, and Niki et al. [12] presented six blood test variables, i.e., total leukocyte count, platelet count, blood urea nitrogen, and C-reactive protein, aspartate aminotransferase, and lactate dehydrogenase, which were predictors of 2-week survival. These reports together with our own findings suggest that elevated levels of markers, such as the total leukocyte count, blood urea nitrogen, total bilirubin, creatinine, and aspartate aminotransferase, might be associated with shorter survival in patients with advanced cancer. Malnourished patients have low serum albumin levels, and low albumin levels are often noted in the terminal stage of various diseases [22]. Elevated PLRs have been reported to be associated with a poor prognosis in lung cancer patients [23].

Although we expected to identify the C-reactive protein level as an efficient marker, the same as in several other studies [24], after adjustment, it was no longer identified as a significant factor in our multivariable analysis. Other studies, including those by Chen et al. [9] and Hamano et al. [10], have identified vital signs such as the heart rate and respiratory rate as objective predictors of survival, in addition to blood test data. It would be interesting to determine whether vital signs and symptoms such as dyspnea, anorexia, and edema might be associated with any of the valuables identified as survival predictors in this study, since these symptoms, in particular, may be useful for predicting longer-term life expectancy of more than 2–3 weeks but less than a few months. Some of the variables associated with the activation of the systemic inflammatory response may also be valid across tumor types.

Limitations

Our study had limitations. It was conducted at only a single palliative care unit, and the number of patients enrolled was small. The indicators presented here should be validated by prospective studies in independent populations. It might be interesting to investigate whether the model we developed can improve the survival prediction in conjugation with subjective variables such as patient's symptoms and physician's predictions to help the ACP's palliative care decisions.

Conclusion

We developed a simple objective model for predicting the survival of patients with advanced cancers based on data from routine blood tests alone. Our model is expected to be clinically useful for predicting weekly to monthly survival days in patients with advanced cancer when initiating consultations for ACP in palliative care.

Data availability The authors have full control of all primary data and the journal may review the data if requested.

Compliance with ethical standards The protocol of this study was in accordance with the ethical guidelines of the Helsinki declaration and was approved by the ethics committee of the Tohoku University Graduate School of Medicine (reference no. 2019-1-281).

Conflict of interest The authors declare that they have no conflict of interest.

Consent to participate and consent for publication All authors reviewed and approved the final draft of the manuscript and approved its publication.

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