

Laboratory prognostic score for predicting 30-day mortality in terminally ill cancer patients

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ABSTRACT

Conventional prognostic scores for terminally ill cancer patients may have less objectivity because they include subjective or categorical variables that do not consider intensity or severity. The aim of this study was to identify prognostic factors for 30-day mortality from routine blood examination of terminally ill cancer patients. A total of 1308 study patients in a hospice setting were divided into investigation (n=761) and validation (n=547) groups. Twenty laboratory blood parameters were analyzed. Multivariate analysis revealed that ten variables (C-reactive protein ≥ 5.4 mg/dL, serum albumin < 2.8 g/dL, blood urea nitrogen ≥ 21 mg/dL, white blood cell count $\geq 8.600 \times 10^3/\mu\text{L}$, eosinophil percentage $< 0.8\%$, neutrophil-to-lymphocyte ratio ≥ 11.1 , hemoglobin level ≥ 13.2 g/dL, mean corpuscular volume ≥ 93.7 fl, red cell distribution width ≥ 16 , and platelet count $< 159 \times 10^3/\mu\text{L}$) were significant independent prognostic factors for 30-day survival. The laboratory prognostic score (LPS) was calculated by the sum of blood indices among the ten variables. The LPS showed acceptable accuracy for 30-day mortality in the investigation and validation groups. LPS 5 (including any five factors) predicted death within 30 days, with a sensitivity of 85%, a specificity of 55%, a positive predictive value of 72%, and a negative predictive value of 74%. The predictive value of LPS was comparable to those of conventional prognostic scores, which include signs and symptoms. The LPS can provide additional information to conventional prognostic scores.

Keywords: end-of-life care, palliative care, prognostic factors, prognosis, blood data

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INTRODUCTION

Accurate prognostic information in palliative settings is necessary for patients to make decisions and set goals and priorities. Palliative care physicians should carefully provide patients and their families with the most accurate prognostic information in order to improve end-of-life care. A number of prognostic factors in terminal cancer patients, such as performance status, cancer anorexia, cachexia, dyspnea, and delirium have been identified, and several prognostic scores have been developed. These scores include the Palliative Prognostic (PaP) Score, Palliative Prognostic Index (PPI), Objective Prognostic Score (OPS), Japan Palliative Oncology Study Prognostic Index (JPOS-PI) and Prognosis Palliative Care Study (PiPS) predictor models.¹⁻⁷⁾

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Because these conventional prognostic scores include subjective or categorical variables (e.g., clinical judgement, anorexia, or edema) for which the intensity or severity is less quantifiable, there can be limitations for more objective evaluation. The aim of this study was to identify, from routine laboratory blood examination, prognostic factors for 30-day mortality and to develop an objective additional prognostic model in terminally ill cancer patients.

PATIENTS AND METHODS

Study design and patient population

This retrospective study attempted to identify prognostic factors for 30-day mortality based on routine blood examination results for terminally ill cancer patients and to examine the internal validity of a laboratory test-based prognostic model. Between April 2006 and March 2014, a total of 1,766 terminally ill cancer patients with disseminated malignancy, who were no longer subject to specific anticancer therapy, were admitted to our hospice. Of these, 458 patients were excluded from this study due to a lack of comprehensive blood data. A total of 1308 patients were included in this study. Patients were divided into an investigation group (n=761), admitted to our hospice between April 2006 and March 2011, and a validation group (n=547), admitted to our hospice between April 2011 and March 2014. Data were obtained from the final blood test before hospice discharge in each patient and included C-reactive protein (CRP), serum albumin (Alb), total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), creatinine, estimated glomerular filtration rate (eGFR), white blood cell (WBC) count, basophil percentage, eosinophil percentage (Eosino), neutrophil percentage, lymphocyte count, neutrophil-to-lymphocyte ratio (N/L), red blood cell (RBC) counts, hemoglobin (Hb) level, hematocrit (Ht), mean corpuscular volume (MCV), red cell distribution width (RDW), and platelet (Plt) count. The eGFR was calculated based on the serum creatinine level according to the equation recommended by the Japanese Society of Nephrology.⁸⁾

Our hospice care involves medical care, pain management, drug administration and infusion to reduce patients' physical and psychological discomfort. In April 2013, the number of hospice beds was reduced from 25 to 20; however, there was no change in general care management or hospitalization criteria that included withdrawing life-sustaining treatment and cytoreductive therapy. There is no hospice standard for performing blood tests. Our hospice physicians usually perform blood test, if the blood test results can change the management of patient's symptom.

The study protocol was approved by the Institutional Review Board of our hospital (approval reference number: 2016.082), which waived the requirement for informed consent owing to the retrospective nature of the study.

Statistical Analysis

Continuous variables, expressed as the median (interquartile range (IQR)), were compared using the Mann-Whitney U test. Differences in categorical data were compared using the chi-squared test. The Kaplan-Meier method was used to estimate survival curves, and the log-rank test was used to evaluate survival differences between groups. Follow-up information to hospice discharge was compiled for all patients, and survival was calculated from the day the final blood test was performed before hospice discharge until the date of hospice discharge. When the survival was calculated, patients who left the hospice alive were censored.

For univariate analyses in the investigation group, receiver operating characteristic (ROC) analysis was performed, and the area under each ROC curve (AUC) was calculated to assess the prognostic value for 30-day survival. In ROC analysis, the optimal cutoff values were determined

to be the point where the vertical distance between the ROC curve and the diagonal line was maximal.

Multiple logistic regression analysis was performed using 30-day survival (yes/no) as the dependent variable.⁹⁾ Variables with $p < 0.05$ by univariate analysis were entered into the equation to identify significant independent prognostic factors of 30-day mortality, while AST and ALT were integrated to ALT, because they had a close relationship, and the AUC of ALT was larger than that of AST. Similarly, red blood cell count, hemoglobin, and hematocrit were integrated to hemoglobin. In the validation group, the predictive factors identified from the investigation group were examined for validity. Statistical analyses were performed using JMP software (version 10.0 for Windows; SAS Institute Inc., Cary, NC, USA). Significance was set at a level of $p < 0.05$.

RESULTS

Patient demographics

Patient demographics are presented in Table 1. The most common sites of primary malignancy were the respiratory, gastrointestinal, and hepatobiliary systems. Although there were statistically significant differences in albumin, ALT, WBC, lymphocyte count, MCV and Plt between the investigation and validation groups, there were no significant differences in age and sex. The mean duration between blood examination and hospice discharge in the investigation group was significantly longer than that in the validation group (24 days vs. 23 days, respectively); the 30-day survival of the investigation and validation group was 42.3% and 39.0%, respectively.

Identification of significant independent prognostic factors for predicting 30-day survival

The AUC and optimal cutoff value for the 20 blood test data used to estimate 30-day survival are presented in Table 2. Univariate analyses of survival revealed that cutoff values of the 19 variables were statistically discriminative. Multivariate analysis showed that the following ten indices were significant independent prognostic factors for 30-day survival (Table 2): CRP ≥ 5.4 mg/dL, Alb < 2.8 g/dL, BUN ≥ 21 mg/dL, WBC $\geq 8.600 \times 10^3/\mu\text{L}$, Eosino $< 0.8\%$, N/L ≥ 11.1 , Hb ≥ 13.2 g/dL, MCV ≥ 93.7 fL, RDW ≥ 16 , and Plt $< 159 \times 10^3/\mu\text{L}$ had odds ratios for 30-day mortality between 1.47 and 2.54.

Prognostication by laboratory prognostic score (LPS)

To develop a scoring system for 30-day mortality, laboratory prognostic score (LPS) was calculated by the sum of indices among the ten variables. In the investigation group, the median survival was decreased according to the LPS (Figure 1(A)). Figure 2(A) shows the number of patients with each LPS and 30-day survival, which was decreased from 100% to 0% according to the LPS between 0 and 10. The LPS ROC curve is shown in Figure 3(A); the AUC was 0.7901 at the optimal cutoff value of LPS 5. LPS 5 predicted death within 30 days, with a sensitivity of 85%, a specificity of 55%, a positive predictive value (PPV) of 72%, and a negative predictive value (NPV) of 74% (Table 3).

Table 1 Patient demographics

	Investigation group (n=761)	Validation group (n=547)	p-value
Age	73 (65–80)	73 (65–79)	0.5575
Sex (Male : Female)	479 : 282	342 : 205	0.8766
Site of primary malignancy			0.0484
Respiratory (including lung, pleura)	298 (39.2%)	208 (38.0%)	
Gastrointestinal	225 (29.6%)	142 (26.0%)	
Hepatobiliary	105 (13.8%)	64 (11.7%)	
Breast	22 (2.9%)	19 (3.5%)	
Bladder, kidney, urinary tracts	21 (2.8%)	22 (4.0%)	
Hematological	20 (2.6%)	20 (3.7%)	
Oral cavity	16 (2.1%)	8 (1.5%)	
Pharyngolarynx	9 (1.2%)	11 (2.0%)	
Female genital organs (including ovary, uterus)	9 (1.2%)	21 (3.8%)	
Head and neck (including thyroid, parotid gland)	9 (1.2%)	6 (1.1%)	
Male genital organs (including prostate)	8 (1.1%)	11 (2.0%)	
Skin	6 (0.8%)	2 (0.4%)	
Brain	3 (0.4%)	1 (0.2%)	
Others	10 (1.3%)	12 (2.2%)	
Blood examination data			
C-reactive protein (mg/dL)	5.5 (1.9–10.6)	5.2 (2.1–10.9)	0.9725
Albumin (g/dL)	2.6 (2.2–3.1)	2.8 (2.4–3.2)	0.0019
Total bilirubin (mg/dL)	0.6 (0.4–1.1)	0.6 (0.5–1.0)	0.7574
Aspartate aminotransferase (AST) (IU/L)	30 (20–53)	27 (19–51)	0.2076
Alanine aminotransferase (ALT) (IU/L)	19 (13–37)	17 (11–33)	0.0095
Blood urea nitrogen (BUN) (mg/dL)	20 (14–30)	20 (15–32)	0.1522
Creatinine	0.74 (0.57–1.03)	0.75 (0.55–1.12)	0.6237
Estimated glomerular filtration rate (eGFR) (ml/min/1.73 m ²)	71 (48–96)	70 (46–96)	0.5508
White blood cell count ($\times 10^3/\mu\text{L}$)	9.0 (6.4–13.1)	8.4 (6.2–11.6)	0.0251
Basophil (%)	0.3 (0.1–0.5)	0.3 (0.1–0.6)	0.0567
Eosinophil (%)	0.6 (0.2–1.6)	0.4 (0.1–1.5)	0.0333
Neutrophil (%)	80.7 (72.2–87.2)	81.7 (73.5–88.3)	0.1251
Lymphocyte count ($\times 10^3/\mu\text{L}$)	0.924 (0.591–1.344)	0.804 (0.531–1.165)	0.0003
Neutrophil-to-lymphocyte ratio (N/L)	7.6 (4.5–13.8)	8.3 (4.8–15.2)	0.0644
Red blood cell count ($\times 10^6/\mu\text{L}$)	3.33 (2.82–3.84)	3.32 (2.71–3.81)	0.4353
Hemoglobin (g/dL)	10.2 (8.8–11.7)	10.2 (8.5–11.6)	0.3058
Hematocrit (%)	30.3 (26.0–34.6)	30.7 (25.8–34.9)	0.8400
Mean corpuscular volume (MCV) (fl)	91.8 (87.2–96.8)	92.8 (88.4–97.9)	0.0102
Red cell distribution width (RDW)	16.6 (15.2–18.8)	16.7 (15.0–18.8)	0.9475
Platelet count ($\times 10^3/\mu\text{L}$)	257 (183–352)	229 (158–308)	<0.0001
Hospice discharge (Dead : Alive)	740 : 21	515 : 32	0.0052
Length of hospice stay (days)	17 (7–38)	19 (8–39)	0.4105
Duration between the last blood examination and hospice discharge (days)	24 (11–48)	23 (9–42)	0.0242
Median survival (days) after the last blood examination	24	23	0.3792
30-day survival after the last blood examination	42.3%	39.0%	0.3792

Continuous variables are expressed as the median (interquartile range), and categorical variables are described as numbers (percentages). Bold values indicate statistical significance ($p < 0.05$).

Laboratory prognostic score for terminal care

Table 2 Predictive value for 30-day survival of blood test data

Blood test data	AUC	Optimal cut-off value	Univariate analysis			Multivariate analysis			
			Number of patients	30-day survival (%)	p	Odds ratio for 30-day mortality	95%CI	p	
C-reactive protein	0.6752	5.4 mg/dL	≥5.4	385	29.4%	<0.0001	1.86	1.30 – 2.67	0.0007
			<5.4	376	55.5%		1		
Albumin	0.6275	2.8 g/dL	≥2.8	294	56.0%	<0.0001	1	1.31 – 2.76	0.0006
			<2.8	467	33.7%		1.9		
Total bilirubin	0.5909	1.3 mg/dL	≥1.3	151	23.8%	<0.0001	1.55	0.93 – 2.62	0.0953
			<1.3	610	46.8%		1		
Aspartate aminotransferase (AST)	0.5783	47 IU/L	≥47	218	47.3%	<0.0001			
			<47	243	31.2%				
Alanine aminotransferase (ALT)	0.6141	19 IU/L	≥19	401	33.5%	<0.0001	1.44	0.99 – 2.29	0.0511
			<19	360	54.0%		1		
Blood urea nitrogen (BUN)	0.6782	21 mg/dL	≥21	354	27.8%	<0.0001	1.98	1.33 – 2.95	0.0007
			<21	407	54.8%		1		
Creatinine	0.5481	1.09 mg/dL	≥1.09	168	25.8%	<0.0001	1.80	0.86 – 3.79	0.1172
			<1.09	593	46.9%		1		
Estimated glomerular filtration rate (eGFR)	0.5577	45 ml/min/ 1.73 m ²	≥45	596	46.6%	<0.0001	1	0.60 – 2.64	0.5568
			<45	165	27.3%		1.25		
White blood cell count	0.6589	8.600 × 10 ³ /μL	≥8.600	417	30.2%	<0.0001	1.47	1.00 – 2.15	0.0495
			<8.600	344	57.0%		1		
Basophil	0.5940	0.1 %	≥0.1	605	46.6%	<0.0001	1	0.75 – 2.00	0.4266
			<0.1	156	25.4%		1.22		
Eosinophil	0.6524	0.8 %	≥0.8	304	59.0%	<0.0001	1	1.03 – 2.18	0.0349
			<0.8	457	32.7%		1.50		
Neutrophil	0.6551	83.7 %	≥83.7	300	25.9%	<0.0001	1.02	0.59 – 1.78	0.9329
			<83.7	461	53.0%		1		
Lymphocyte count	0.4352	2.218 × 10 ³ /μL	≥2.218 × 10 ³	60	26.7%	0.0019	1.84	0.92 – 3.81	0.0847
			<2.218 × 10 ³	701	43.6%		1		
Neutrophil-to-lymphocyte ratio (N/L)	0.6684	11.1	≥11.1	257	22.5%	<0.0001	2.23	1.29 – 3.91	0.0043
			<11.1	504	54.3%		1		
Red blood cell count	0.5163	4.17 × 10 ⁶ /μL	≥4.17 × 10 ⁶	96	32.9%	0.0309			
			<4.17 × 10 ⁶	665	43.6%				
Hemoglobin	0.5016	13.2 g/dL	≥13.2	51	30.4%	0.0101	2.54	1.34 – 4.96	0.0041
			< 13.2	687	43.5%				
Hematocrit	0.5011	34.70%	≥34.7	186	37.4%	0.0749			
			<34.7	575	43.8%				
Mean corpuscular volume (MCV)	0.5433	93.7 fL	≥93.7	295	49.9%	<0.0001	1	1.43 – 3.02	0.0001
			<93.7	466	37.5%		2.07		
Red cell distribution width (RDW)	0.5871	16	≥16	474	35.4%	0.0027	1.71	1.19 – 2.46	0.0034
			<16	287	53.4%		1		
Platelet count	0.5473	159 × 10 ³ /μL	≥159 × 10 ³	605	45.9%	<0.0001	1	1.39 – 3.50	0.0007
			<159 × 10 ³	156	28.2%		2.19		

Bold values indicate statistical significance (p<0.05).

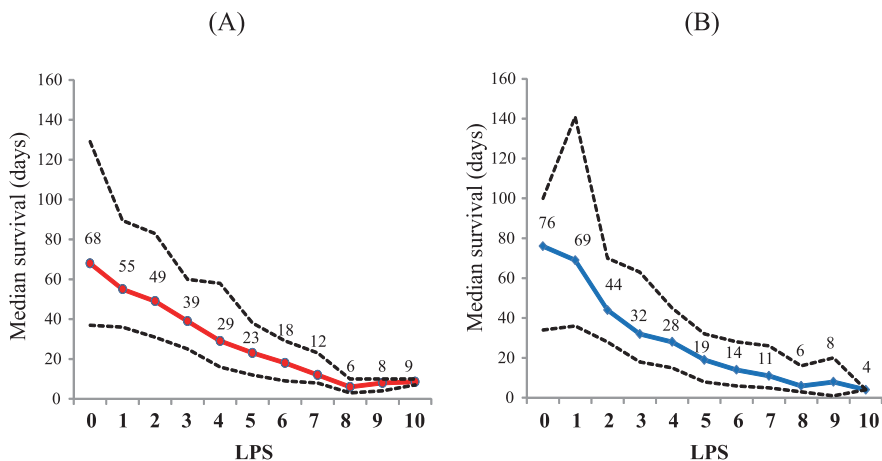


Fig. 1 Median survival (solid line) and 25% and 75% percentiles (dotted lines) of patients with each laboratory prognostic score (LPS).

(A) Investigation group (n=761), (B) Validation group (n=547).

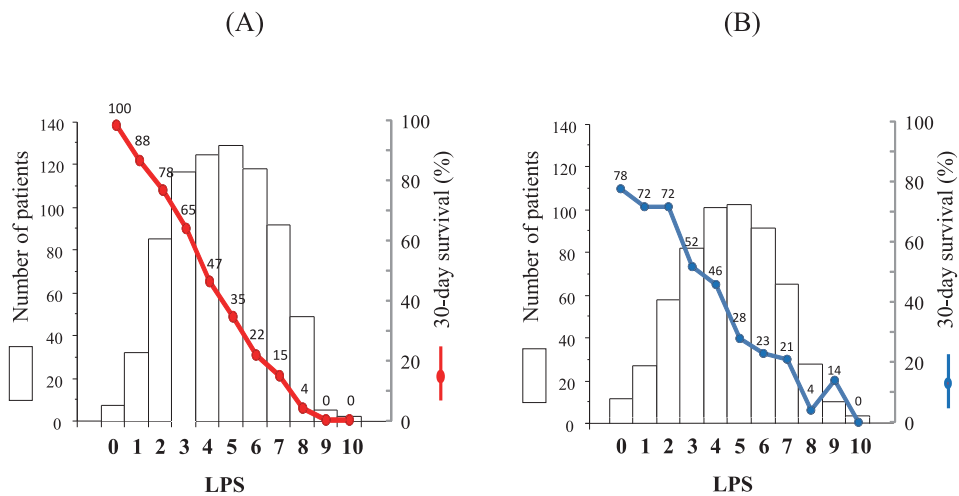


Fig. 2 Number of patients with each laboratory prognostic score (LPS) (primary graph, presented as bars) and 30-day survival (secondary graph, presented as a line)

(A) Investigation group (n=761), (B) Validation group (n=547).

Laboratory prognostic score for terminal care

Table 3 Thirty-day survival and predictive value for 30-day mortality classified by laboratory prognostic score (LPS) comprised of 10 blood indices (CRP ≥ 5.4 mg/dL, Alb < 2.8 g/dL, BUN ≥ 21 mg/dL, WBC $\geq 8,600 \times 10^3/\mu\text{L}$, Eosino $< 0.8\%$, N/L ≥ 11.1 , Hb ≥ 13.2 g/dL, MCV ≥ 93.7 fL, RDW ≥ 16 , and Plt $< 159 \times 10^3/\mu\text{L}$).

LPS	Investigation group										
	0	1	2	3	4	5	6	7	8	9	10
Number of patients	7	32	85	117	125	129	118	92	49	5	2
30-day survival (%)	100%	88%	78%	65%	47%	35%	22%	15%	4%	0%	0%
Sensitivity (%)	100%	100%	100%	99%	94%	85%	70%	51%	30%	12%	1%
Specificity (%)	0%	2%	2%	11%	31%	55%	73%	87%	95%	99%	100%
Positive predictive value (%)	57%	58%	58%	60%	65%	72%	78%	84%	89%	96%	100%
Negative predictive value (%)	–	100%	78%	85%	81%	74%	65%	57%	50%	46%	43%

LPS	Validation group										
	0	1	2	3	4	5	6	7	8	9	10
Number of patients	9	24	55	79	98	99	88	62	25	7	1
30-day survival (%)	78%	72%	72%	52%	46%	28%	23%	21%	4%	14%	0%
Sensitivity (%)	100%	99%	99%	98%	93%	82%	66%	44%	24%	9%	2%
Specificity (%)	0%	3%	3%	12%	30%	50%	71%	83%	93%	99%	100%
Positive predictive value (%)	60%	61%	61%	63%	67%	71%	77%	80%	84%	94%	86%
Negative predictive value (%)	–	78%	70%	76%	74%	64%	58%	50%	45%	42%	40%

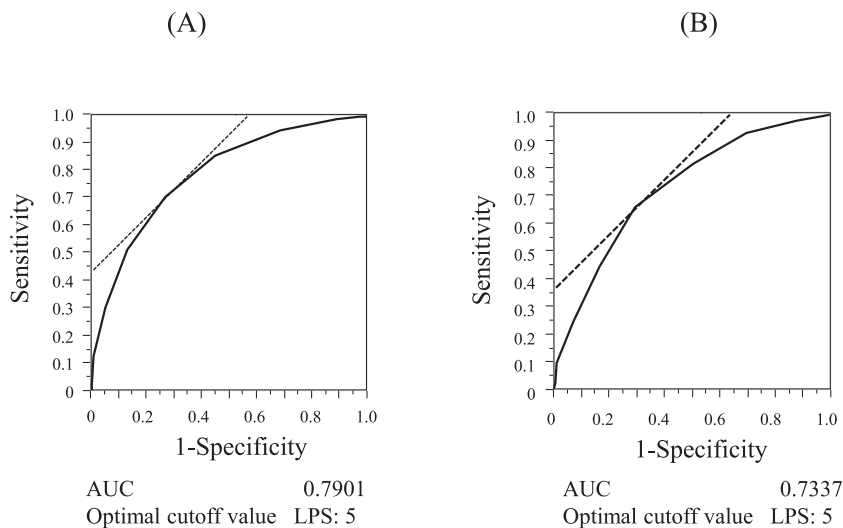


Fig. 3 Receiver operating characteristic curve of laboratory prognostic score (LPS)

(A) Investigation group (n=761), (B) Validation group (n=547).

Validation of LPS for predicting 30-day mortality

In the validation group, the median survival was decreased according to the LPS (Figure 1(B)). Figure 2(B) shows the number of patients with each LPS and 30-day survival, which was decreased from 78% to 0% according to the LPS between 0 and 10. The LPS ROC curve is shown in Figure 3(B); the AUC was 0.7337 at the optimal cutoff value of LPS 5. LPS 5 predicted death within 30 days, with a sensitivity of 82%, a specificity of 50%, a PPV of 71%, and a NPV of 64% (Table 3).

DISCUSSION

The present study revealed that ten blood indices were independent prognostic factors for 30-day mortality of terminally ill cancer patients. The LPS comprising these ten indices showed acceptable accuracy, which was comparable to those of the validation group.

Conventional prognostic scores previously reported in the literature are based on physical signs, symptoms, and psychological factors with/without data from laboratory blood tests.^{1-7,10-11} Those prognostic scores are universally available and useful for terminal care of cancer patients; however, their potential limitation is the inclusion of subjective or categorical variables such as physician's judgment (i.e., clinical prediction of survival), dyspnea, anorexia, edema, pleural effusion, or consciousness, for which the intensity or severity is less quantifiable; and consequently, there can be limitations for more objective evaluation.¹² Table 4 shows reported predictive values of several prognostic scores for terminally ill cancer patients.^{4-5,13-14} The predictive value of the LPS was comparable to those of conventional prognostic scores, although the median survivals were different among the studies (22–27 days).

Many studies have found several biomarkers to have prognostic value for terminally ill cancer patients: lymphocyte count, WBC, lactate dehydrogenase, BUN, Hb, CRP, Alb, and creatinine.^{2,5-6,15-18} The current study implies that the sum of blood indices of the ten indices (CRP ≥ 5.4 mg/dL, Alb < 2.8 g/dL, BUN ≥ 21 mg/dL, WBC $\geq 8.600 \times 10^3/\mu\text{L}$, Eosino $< 0.8\%$, N/L

Table 4 Comparison of the predictive values among conventional prognostic scores and laboratory prognostic score

No.	1	2	3	4	5	6
Predicting Model	Objective Prognostic Score (OPS)	Palliative Prognostic Score (PaP Score)	Palliative Prognostic Index (PPI)			Laboratory Prognostic Score (LPS)
Year	2010	2012	1999	2012	2017	
Author	Suh SY	Maltoni M	Morita T	Maltoni M	Yamada T	Kawai N
Country	South Korea	Italy	Japan	Italy	Japan	Japan
Number of patients	185	549	150	549	892	761
Setting	inpatient	in hospice	in hospice	in hospice	in palliative care unit	in hospice care unit
Median survival	26 days	22 days	27 days	22 days	25 days	24 days
30-day survival	nd	nd	nd	nd	nd	42%
3-week survival	nd	nd	63%	nd	nd	57%
Score range	0–8	0–17.5	0–15.0	0–15.0	0–15.0	0–10
Mortality prediction	3 weeks	30 days	3 weeks	30 days	3 weeks	30 days
Cutoff value	OPS: 3	PaP Score: 5	PPI: 6.0	PPI: 4.0	PPI: 6.0	LPS: 5
Sensitivity	75 %	92 %	75 %	85 %	71 %	85 %
Specificity	77 %	58 %	84 %	54 %	67 %	55 %
Positive Predictive Value	42 %	76 %	73 %	73 %	63 %	72 %
Negative Predictive Value	79 %	82 %	85 %	70 %	75 %	74 %

nd: not described

≥ 11.1 , Hb ≥ 13.2 g/dL, MCV ≥ 93.7 fL, RDW ≥ 16 , and Plt $< 159 \times 10^3/\mu\text{L}$) has an acceptable prognostic value. An elevated CRP, WBC and N/L suggest inflammation or overproduction of cytokine produced by malignant tumor, while a decreased Alb implies malnutrition. An increased BUN suggests dehydration, gastrointestinal bleeding, or impaired renal function. Decreased immune status is suggested by an elevated N/L. A decreased platelet count implies bone marrow suppression or bleeding tendency. An elevated Hb suggests dehydration.

To the best of our knowledge, this is the first study showing a significant prognostic value of eosinophil percentage, MCV, and RDW in terminally ill cancer patients. Eosinophils are a component of the innate immune system and have a variety of functions.¹⁹⁾ Several studies have reported a lower eosinophil count as a worse prognostic marker in patients with acute heart failure, chronic obstructive pulmonary disease, critical medical illness, and bacteremia.²⁰⁻²³⁾ The

MCV indicates the volume of RBC and is frequently used for the diagnosis of megaloblastic or iron-deficiency anemia. A high MCV was associated with worse outcomes in patients with coronary artery disease and renal failure.²⁴⁻²⁵⁾ The RDW is a measure of the range of variation of RBC volume and has traditionally been used to differentiate various types of anemia.²⁶⁾ The evidence associating RDW with a higher risk of mortality has been reported in patients with coronary disease, heart failure, acute cerebral infarction, and septic shock.²⁷⁻³⁰⁾

To improve the discriminative ability of LPS, we developed a scoring system in which each one of ten categories was assigned various points based on the logarithm of odds ratio. The AUC of this model was 0.7528, which was lower than the AUC of the original LPS model developed from the sum of indices. We, therefore, adopted the original LPS model.

We acknowledge that our study has several limitations. First, this study was retrospective and was conducted at a single hospice; thus, the results could not be extrapolated to other palliative care settings (e.g., hospital palliative care, home palliative care, and patients undergoing antineoplastic therapy). Second, venipuncture is necessary for LPS determination. It may not be easy for physicians to perform invasive procedures on frail patients. Third, the timing of blood examination was not specifically planned for prognostication but mostly for symptom management, and the last day at which blood samples were collected was chosen among several days for analyzing 30-day mortality. Scheduled blood sampling should have been performed for accurate prognostic estimation; however, this could not be done because of the retrospective nature of the study. Fourth, this study included patients with hematological malignancy. Such patients often have blood disorder even in the early phase of disease; therefore, LPS may be less prognostic for patients with hematological malignancy. Fifth, this study did not compare the prognostic values between conventional prognostic scores and LPS in each patient. The comparison may reveal the significance of LPS; however, it was not performed due to the limited number of patients who were evaluated by conventional prognostic scores. Sixth, although this study revealed ten indices (CRP ≥ 5.4 mg/dL, Alb < 2.8 g/dL, BUN ≥ 21 mg/dL, WBC $\geq 8.600 \times 10^3/\mu\text{L}$, Eosino $< 0.8\%$, N/L ≥ 11.1 , Hb ≥ 13.2 g/dL, MCV ≥ 93.7 fL, RDW ≥ 16 , and Plt $< 159 \times 10^3/\mu\text{L}$) that have an acceptable prognostic value in terminally ill cancer patients, we could not provide sufficient meaning in some indices.

The strength of this study was the large number of patients and comprehensive analysis of routine blood tests. The predictive value of LPS was comparable to that of conventional prognostic scores. Although the estimation of 30-day mortality by LPS requires venipuncture, it was objective and easily understandable. The LPS can be used in combination with physical signs and symptoms to improve prognostication. Future studies should focus on validating our results and estimating more accurately the short-term mortality of terminally ill cancer patients.

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CONFLICTS OF INTEREST

Natsuko Kawai and Norihiro Yuasa do not have any conflict of interest to disclose.

REFERENCES

- 1) Pirovano M, Maltoni M, Nanni O, Marinari M, Indelli M, Zaninetta G, *et al.* A new palliative prognostic score: a first step for the staging of terminally ill cancer patients. Italian Multicenter and Study Group on Palliative Care. *J Pain Symptom Manage*, 1999; 17: 231–239.
- 2) Maltoni M, Nanni O, Pirovano M, Scarpi E, Indelli M, Martini C, *et al.* Successful validation of the palliative prognostic score in terminally ill cancer patients. Italian Multicenter study Group on palliative care. *J Pain Symptom Manage*, 1999; 17: 240–247.
- 3) Scarpi E, Maltoni M, Miceli R, Mariani L, Caraceni A, Amadori D, *et al.* Survival prediction for terminally ill cancer patients: revision of the palliative prognostic score with incorporation of delirium. *Oncologist*, 2011; 16: 1793–1799.
- 4) Morita T, Tsunoda J, Inoue S, Chihara S. The Palliative Prognostic Index: a scoring system for survival prediction of terminally ill cancer patients. *Support Care Cancer*, 1999; 7: 128–133.
- 5) Suh SY, Choi YS, Shim JY, Kim YS, Yeom CH, Kim D, *et al.* Construction of a new, objective prognostic score for terminally ill cancer patients: a multicenter study. *Support Care Cancer*, 2010; 18: 151–157.
- 6) Hyodo I, Morita T, Adachi I, Shima Y, Yoshizawa A, Hiraga K. Development of a predicting tool for survival of terminally ill cancer patients. *Jpn J Clin Oncol*, 2010; 40: 442–448.
- 7) Gwilliam B, Keeley V, Todd C, Gittins M, Roberts C, Kelly L, *et al.* Development of prognosis in palliative care study (PiPS) predictor models to improve prognostication in advanced cancer: prospective cohort study. *BMJ*, 2011 25; 343: d4920.
- 8) Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, *et al.* Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis*. 2009; 53: 982–992.
- 9) Katz MH. Multivariate analysis: a practical guide for clinicians. 2008, Cambridge University Press, Cambridge.
- 10) Reuben DB, Mor V, Hiris J. Clinical symptoms and length of survival in patients with terminal cancer. *Arch Intern Med*, 1988; 148: 1586–1591.
- 11) Bruera E, Miller MJ, Kuehn N, MacEachern T, Hanson J. Estimate of survival of patients admitted to a palliative care unit: a prospective study. *J Pain Symptom Manage*, 1992; 7: 82–86.
- 12) Glare P, Virik K, Jones M, Hudson M, Eychmuller S, Simes J. A systematic review of physicians' survival predictions in terminally ill cancer patients. *BMJ*, 2003; 327: 195–198.
- 13) Maltoni M, Scarpi E, Pittureri C, Martini F, Montanari L, Amaducci E. Prospective comparison of prognostic scores in palliative care cancer populations. *Oncologist*, 2012; 17: 446–454.
- 14) Yamada T, Morita T, Maeda I, Inoue S, Ikenaga M, Matsumoto Y, *et al.* A prospective, multicenter cohort study to validate a simple performance status-based survival prediction system for oncologists. *Cancer*, 2017; 123: 1442–1452.
- 15) Kikuchi N, Ohmori K, Kuriyama S, Shimada A, Nakaho T, Yamamuro M, *et al.* Survival prediction of patients with advanced cancer: the predictive accuracy of the model based on biological markers. *J Pain Symptom Manage*, 2007; 34: 600–606.
- 16) Kao YH, Chen CN, Chiang JK, Chen SS, Huang WW. Predicting factors in the last week of survival in elderly patients with terminal cancer: a prospective study in southern Taiwan. *J Formos Med Assoc*, 2009; 108: 231–239.
- 17) Chiang JK, Lai NS, Wang MH, Chen SC, Kao YH. A proposed prognostic 7-day survival formula for patients with terminal cancer. *BMC Public Health*, 2009; 29: 365.
- 18) Miura T, Matsumoto Y, Hama T, Amano K, Tei Y, Kikuchi A, *et al.* Glasgow prognostic score predicts prognosis for cancer patients in palliative settings: a subanalysis of the Japan-prognostic assessment tools validation (J-ProVal) study. *Support Care Cancer*, 2015; 23: 3149–3156.
- 19) Valent P, Gleich GJ, Reiter A, Roufosse F, Weller PF, Hellmann A, *et al.* Pathogenesis and classification of eosinophil disorders: a review of recent developments in the field. *Expert Rev Hematol*, 2012; 5: 157–176.
- 20) Cikrikioglu MA, Soysal P, Dikerdem D, Cakirca M, Kazancioglu R, Yolbas S, *et al.* Absolute blood eosinophil count and 1-year mortality risk following hospitalization with acute heart failure. *Eur J Emerg Med*, 2012; 19: 257–263.
- 21) Holland M, Alkhalil M, Chandromouli S, Janjua A, Babores M. Eosinopenia as a marker of mortality and length of stay in patients admitted with exacerbations of chronic obstructive pulmonary disease. *Respirology*, 2010; 15: 165–167.
- 22) Abidi K, Belayachi J, Derras Y, Khayari ME, Dendane T, Madani N, *et al.* Eosinopenia, an early marker of increased mortality in critically ill medical patients. *Intensive Care Med*, 2011; 37: 1136–1142.
- 23) Terradas R, Grau S, Blanch J, Riu M, Saballs P, Castells X, *et al.* Eosinophil count and neutrophil-

- lymphocyte count ratio as prognostic markers in patients with bacteremia: a retrospective cohort study. *PLoS One*, 2012; 7: e42860. Available at: <https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0042860> Accessed on July 29, 2018.
- 24) Myojo M, Iwata H, Kohro T, Sato H, Kiyosue A, Ando J, *et al.* Prognostic implication of macrocytosis on adverse outcomes after coronary intervention. *Atherosclerosis*, 2012; 221: 148–153.
 - 25) Tennankore KK, Soroka SD, West KA, Kiberd BA. Macrocytosis may be associated with mortality in chronic hemodialysis patients: a prospective study. *BMC Nephrol*, 2011; 12: 19.
 - 26) Tefferi A, Hanson CA, Inwards DJ. How to interpret and pursue an abnormal complete blood cell count in adults. *Mayo Clin Proc*, 2005; 80: 923–936.
 - 27) Lappé JM, Horne BD, Shah SH, May HT, Muhlestein JB, Lappé DL, *et al.* Red cell distribution width, C-reactive protein, the complete blood count, and mortality in patients with coronary disease and a normal comparison population. *Clin Chim Acta*, 2011; 412: 2094–2099.
 - 28) Kim J, Kim YD, Song TJ, Park JH, Lee HS, Nam CM, *et al.* Red blood cell distribution width is associated with poor clinical outcome in acute cerebral infarction. *Thromb Haemost*, 2012; 108: 349–356.
 - 29) Sadaka F, O'Brien J, Prakash S. Red cell distribution width and outcome in patients with septic shock. *J Intensive Care Med*, 2013; 28: 307–313.
 - 30) Forhecz Z, Gombos T, Borgulya G, Pozsonyi Z, Prohászka Z, Jánoskúti L. Red cell distribution width in heart failure: prediction of clinical events and relationship with markers of ineffective erythropoiesis, inflammation, renal function, and nutritional state. *Am Heart J*, 2009; 158: 659–666.