Doctor of Phliosophy

Development and validation of a new prognostic model for active cancer patients with suspected infection

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Bora Chae

Development and validation of a new prognostic model for active cancer patients with suspected infection

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Bora Chae

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This certifies that the dissertation of Bora Chae is approved.

Shin Ahn
Committee Chair Dr.

Yoon-Seon Lee
Committee Member Dr.

Jae-Ho Lee
Committee Member Dr.

Hwa-Jung Kim
Committee Member Dr.

Jae-Chul Yoon
Committee Member Dr.

Department of Medicine

University of Ulsan, Korea

February 2021

Abstract

Bora Chae

Department of Emergency Medicine, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea

Background and Aims

Cancer has been a major medical condition globally with a substantial socioeconomic impact. Although the incidence and mortality have been decreasing, the prevalence and the complications of cancer patients are still significant. Patients with cancer are more susceptible to infection and have poorer outcomes from infection than the general population. Therefore, it is essential to recognize early before the beginning or the worsening of organ failures and promptly provide proper treatment in cancer patients with suspected infection. This study aimed to develop a new prognostic model for predicting mortality in cancer patients with suspected infection.

Methods

This study is a retrospective cohort study and was conducted from August 2019 to December 2019 at Asan Medical Center, Seoul, Korea. Adult active cancer patients with suspected infection were enrolled among visitors to the Emergency Room (ER). Data were collected by reviewing a medical record. The initial values of vital signs and laboratory findings at ER were used for analysis. Cox proportional-hazards regression analysis was used to identify potential predictors for a new model. The predictive performance was analyzed using receiver operating characteristic (ROC) curves and area under the ROC curve (AUC) values.

Results

A total of 998 patients were included; 500 in the derivation cohort and 498 in the validation cohort. The total patients were followed during a median time of 130 days (range 1-334). A new prognostic

model for survival consisted of seven components: Eastern Cooperative Oncology Group (ECOG) performance status (PS), distant metastasis, white blood cell (WBC), prothrombin time (PT), creatinine, albumin, and lactate. Each component was assigned a score as follows: ECOG PS 2 (2 points), ECOGS PS 3-4 (3 points), distant metastasis (2 points), WBC ≧ 10,000/mm^3 (1 point), PT ≧ 1.2 international normalized ratio (INR) (1 point), creatinine ≧ 1.2 mg/dL (1 point), lactate ≧ 4.0 mmol/L (1 point), albumin 2.5-3.5 g/dL (2 points), albumin < 2.5 g/dL (4 points). The concordance index of the new model was 0.729 in the internal validation and 0.759 in the temporal validation. In comparison for 30-day and 180-day mortality, the new model was superior to SIRS, qSOFA, and SOFA [AUC for 30-day mortality: 0.828 (95% CI, 0.790-0.867) vs. 0.612 (95% CI, 0.556-0.669) vs. 0.681 (95% CI, 0.624-0.738) vs. 0.752 (95% CI, 0.703-0.801), respectively; AUC for 180-day mortality: 0.810 (95% CI, 0.770-0.849) vs. 0.531 (95% CI, 0 .478-0.583) vs. 0.637 (95% CI, 0.587-0.686) vs. 0.678 (95% CI, 0.630-0.725), respectively]. The total patients were grouped into three according to the new model's total scores: low-risk, intermediate-risk, and high-risk. The low-risk group (scores 0-4) has 3.0-9.8% of 30-day mortality and 12.3-35.7% of 180-day mortality, the intermediate-risk group (scores 5-8) has 13.0-29.3% of 30-day mortality and 45.0-77.4% and 180-day mortality, and the high-risk group (scores 9-13) has 37.5-79.5% of 30-day mortality and 86.77-99.9% of 180-day mortality. The three groups showed markedly significant differences in 30-day and 180-day mortalities ($p < 0.001$).

Conclusions

The new prognostic model for predicting mortality in cancer with suspected infection consisted of two cancer-specific components, ECOG PS and distant metastasis, and five laboratory variables, WBC, PT, albumin, creatinine, and lactate. The new model was superior to the current severity scoring systems, SIRS, qSOFA, and SOFA.

Keywords

Suspected infection; Cancer; Mortality; ECOG PS; Distant metastasis; WBC; PT; Creatinine; Albumin; Lactate

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Introduction

Cancer is a common medical condition and a significant health issue globally. Although the incidence rates and mortality of cancer have decreased, the absolute number of cancer patients is still numerous such as 18.1 million newly diagnosed and 9.6 million deaths from cancer.[1-4] With advances in cancer treatment, patients living with cancer have been increasing, and its socioeconomic burden also has been expanding.[5-7]

Patients with cancer are susceptible to infection, so they tend to have poorer outcomes than the general population.[8, 9] Many previous studies have shown that cancer patients have higher incidences of sepsis and sepsis-related mortality than non-cancer patients in practice.[10-14] Cancer patients' vulnerability to infection results from many reasons, such as their immunosuppressed status caused by anticancer treatments, frequent use of broad-spectrum antibiotics, and indwelling catheters.[15-17] Malnutrition caused by disruption of mucosal integrity and insufficient oral intake can also aggravate cancer patients' immunosuppressive condition.[18] Therefore, it is critical to early recognize patients' severity and provide proper treatment promptly before the worsening of organ failures in cancer patients with suspected infection.

The clinical presentation of cancer patients with infection can differ from typical symptoms and signs of infected patients. Non-febrile due to myelosuppression or immunomodulation can be presented even in severe cases with infection. Inflammatory markers can be elevated in non-infectious insults as well as in infectious conditions.[19-22] Also, severe signs of severe infection, including organ dysfunction indicators such as elevated levels of creatinine or bilirubin, confused mentality, or respiratory distress, are often chronically held in cancer patients regardless of infection. Such altered and inconstant clinical features may lead physicians to wrong clinical judgment. As a result, serious consequences can occur, and medical expenses can be wasted significantly.

Existing severity scoring systems such as Systemic Inflammatory Response Syndrome (SIRS), Sequential Organ Failure Assessment (SOFA), and quick SOFA (qSOFA) in patients with a suspected infection have been used generally to predict the outcomes for critically ill patients.[23-25] However, they have not shown sufficient predictability in cancer patients than the general population

in a similar clinical setting.[26, 27] To accurately risk-stratify cancer patients with suspected infection, the optimal prognostic scoring system specialized for them is needed. This study aimed to develop a new prognostic model for predicting mortality in cancer patients with suspected infection.

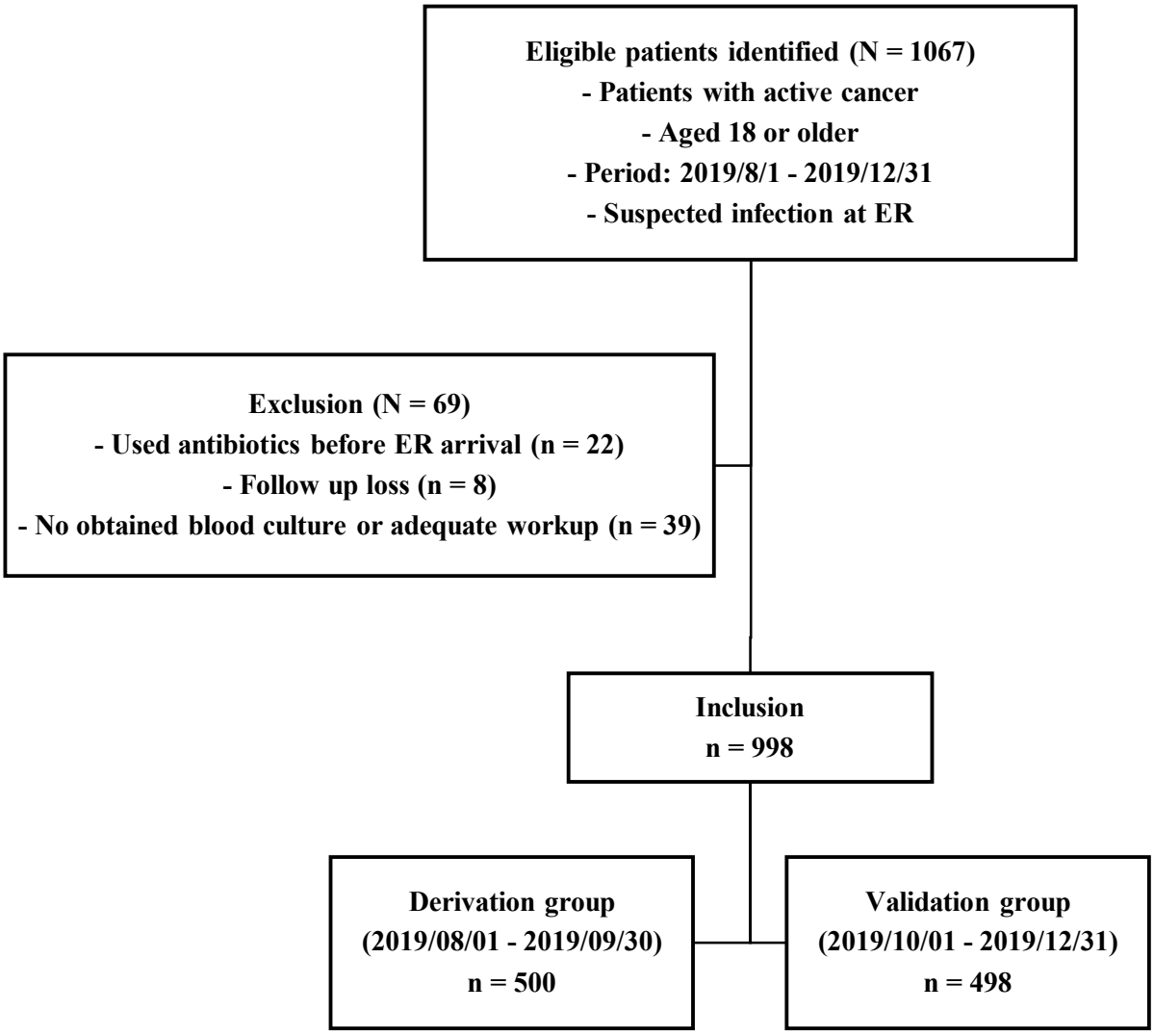
Methods

Study design and patients

This study was designed as a retrospective cohort study. It was conducted at Asan Medical Center, Seoul, Korea, from August 2019 to December 2019. Study subjects who met all the criteria as follows were consecutively enrolled among visitors at the emergency room (ER); 1) who were 18 years age or older, 2) had active cancer, and 3) were suspected of having an infection by the physician. Active cancer was defined as one of the following; 1) cancer newly diagnosed within the past six months; 2) receiving anticancer treatment (chemotherapy, radiotherapy, immunotherapy, stem cell transplantation, surgery, or intervention for resolving a specific condition due to cancer); and 3) cancer has progressed within the past six months.[28] All the cancer patients with suspected infection were performed with body-fluid cultures, imaging studies for detecting infection foci, and were administered antibiotics for therapeutic purposes.[26, 29, 30] Patients who had used antibiotics before the ER arrival; who lost follow-up; who did not have blood cultures or adequate workup at ER; or who refused even minimal life-sustaining treatment were excluded. Patients with no suspected infection or low probability of infection were also excluded.

According to the time of visit, all the included patients were divided into two groups: a derivation cohort from August 1st, 2019 to September 30th, 2019 and a validation cohort from October 1st, 2019 to December 18st, 2019, as shown in Figure 1. In multiple visits during the study period, only information on the first visit was collected. Our hospital's institutional review board approved this study, and informed consent was waived due to its retrospective design. The information which could identify the patient was not involved.

Figure 1. Flow chart for study subjects



ER, emergency room

Data collection and evaluation

Demographic, clinical, and laboratory data were collected retrospectively from the hospital's electronic medical records to drive a new prognostic model. Clinical variables included demographics, comorbidities, type of cancer, cancer stages, Eastern Cooperative Oncology Group (ECOG) performance status (PS)[31], and initial vital signs, including mental status. Comorbidities including hypertension, diabetes mellitus, chronic renal disease, chronic liver disease, chronic lung disease, cardiovascular disease were analyzed based on medical records at the ER presentation. Patients with solid tumors were classified according to metastasis for cancer stages, and those with hematologic malignancies were classified as hematologic. According to the Alert/responsive to Voice/responsive to Pain/Unresponsive (AVPU) scale, mental status was assessed. The AVPU values could be substituted to Glasgow coma scale (GCS) scores of 15, 13, 8, and 6, respectively.[32] The GCS scores less than 15 were considered 'altered mental status'. Three sets of blood cultures were obtained before the administration of antibiotics during the ER stay. If patients had a catheter, one set of the three was conducted from the catheter.

Laboratory data, which were performed once during the ER stay, included complete blood count, chemistry, electrolytes, coagulation battery, inflammatory markers such as c-reactive protein (CRP) and procalcitonin, and serum lactate were retrieved. The first obtained value was used in cases with several matters. For lactate, the values higher than 15.0 mmol/L were not reported as measured values but as '> 15.0 mmol/L'.

The SIRS, qSOFA, and SOFA scores were calculated based on the ER's physiological and laboratory data. The $PaCO_2$ and immature band as SIRS criteria were not used due to their unavailability in the study. Mental status at the presentation was regarded as acute changes from the baseline while calculating the scores. Patients with known chronically altered mentation due to brain metastasis or underlying neurological disease were given points for "change of mental status" when SOFA and qSOFA scores were calculated.

Follow up and outcomes

All the subjects were followed regularly for cancer checkups. The follow-up periods were calculated from the ER presentation to the last hospital visit or the day of death. Death was investigated by checking the insurance expiration. The primary outcome was long-term mortality in study subjects.

Statistical analysis

Data were reported as the mean ± standard deviation (SD) or median and inter-quartile range (IQR) for continuous variables due to their normal distribution. They were compared between groups using a Student's *t*-test. Categorical variables were presented as the number and percentage and were compared using a chi-squared test to assess the statistical association's significance.

To develop a new prognostic model, univariate and multivariate Cox proportional hazards regression analyses were performed with an entering procedure in the derivation set. Results were summarized as hazard ratios and respective 95% confidence intervals (CIs). Missing data were handled with single imputation using the Markov chain Monte Carlo method. Variables yielding *P* value was below 0.1 by univariate analysis, and those considered 'clinically relevant' according to the outcomes were entered into the multivariate analysis. Some variables considered 'clinically irrelevant' were eliminated even though their *P* value was below 0.1.

Candidate predictors were selected by using a multivariable Cox proportional hazard analysis with 1000-fold bootstrap resampling. A simple risk score was devised using the penalized maximum likelihood estimates of the predictors in the multivariable model. The score was the weighted sum of those predictors. The weights were defined as the rounded integer value of the regression coefficients' quotient value divided by the regression coefficient of the reference predictor. The risk score's discrimination capability was assessed using Harrell's C-index and area under the time-dependent receiver operating curve (AUC) at 30 days, 90 days, and 180 days. Internal validation was performed by using bootstrapping with 1000 iterations and calculated optimism-corrected C-index and AUC. The calibration capability of the risk score was assessed using a calibration plot, comparing the predicted versus observed Kaplan-Meier estimates of overall survival (OS) at each time. The model for predicting overall survival was built using the predictors selected in more than 50% of bootstrap

models with backward elimination. The Cox regression equation estimated the probabilities of OS according to the risk score. The risk score was then categorized into low, intermediate, and high-risk groups based on the likelihood of 30-day OS. Kaplan-Meier survival curves for OS were then plotted according to the risk groups and compared using the log-rank test. $P < 0.05$ was considered a statistically significant difference.[33, 34]

Sensitivity, specificity, negative predictive value, and positive predictive values were calculated according to standard formulas.[35] The predictive performances of the SOFA, qSOFA, SIRS scores, and the new prognostic model were analyzed with using receiver operating characteristic (ROC) curves and AUC values. An AUC of 1.0 denotes perfect, whereas a value close to 0.50 indicates no apparent accuracy. All statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC), R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org), and IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, USA).

Results

Baseline characteristics of the study subjects

Table 1 shows the baseline characteristics of the total study subjects. The mean age was 62.8 ± 12.0 years, and the male was 55.4%. Hypertension (HTN) and diabetes mellitus (DM) were common comorbidities shown in 30.7% and 23.0%, respectively. Chronic liver disease and cardiovascular disease were also presented in 12.7% and 10.0%, respectively. Most of the patients had solid tumors in 94.4%, and only 5.6% of the patients had hematologic malignancy. The most common cancer type was lung cancer in 17.3%, followed by biliary cancer in 14.6%, and pancreatic cancer in 12.5%. For ECOG PS, 30.0% had PS 0 to 1, 47.8% had PS 2, and 23.5% had PS 3 to 4. Approximately half of the total patients (50.1%) had distant metastasis, and 16.5% had bacteremia. In comparison between derivation and validation sets, there was no significant difference in clinical characteristics. However, fewer patients in the derivation set were undergoing anticancer treatments than in the validation set

(64.6% vs. 73.3%, p = 0.003). There was no significant difference between derivation and validation sets in vital signs, including metal status and laboratory data.

Figure 2 depicts the origin of infection in all patients. Lung was the most common origin of infection in derivation and validation sets (26.4% and 22.9%, respectively). The hepatobiliary system was also commonly found as the infection origin in more than 20% for both groups. There was no significant difference between the two sets ($p = 0.317$).

Table 2 demonstrates SIRS, qSOFA, and SOFA scores in the derivation and validation sets. For SIRS, most of the patients scored 2 points, 1 point, and 3 points in order of frequency. For qSOFA, more than 60% of patients scored '0' in both sets. For SOFA, more than 50% had SOFA scores 0 to 2. There was also no difference between the two groups ($p > 0.05$)

Table 3 shows the outcomes and dispositions of total patients. A total of 998 patients were followed during a median time of 130.0 days (range 1-334): 145.0 days (range 1-334) in the derivation set and 120.6 days (range 1-275) in the validation set.

Among the total 998 patients, 14 (1.4%) died at the ER, and 52 (5.2%) were admitted to the intensive care unit (ICU). The 30-day and 180-day mortality rates were 22.5% and 54.0%, respectively. In comparison between derivation and validation sets, the 180-day mortality was higher in the validation set (58.6%) than in the derivation set (51.2%) ($p = 0.018$). However, there was no difference in the number of deaths at ER, 30-day mortality, and ICU admission.

Table 1. Baseline characteristics of the total subjects

	Total	Derivation set (*n* = 500)	Validation set (*n* = 498)	*P* value
Age (years)	62.8 ±12.0	63.2 ± 12.0	62.5 ± 11.9	0.320
Male	553 (55.4)	290 (58.0)	263 (52.8)	0.099
Comorbidities				
Hypertension	306 (30.7)	157 (31.4)	149 (29.9)	0.612
Diabetes Mellitus	230 (23.0)	122 (24.4)	108 (21.7)	0.309
Chronic kidney disease	35 (3.5)	23 (4.6)	12 (2.4)	0.060
Chronic liver disease	127 (12.7)	64 (12.8)	63 (12.7)	0.944
Cardiovascular disease	100 (10.0)	52 (10.4)	48 (9.6)	0.689
Type of cancer				
Lung	173 (17.3)	99 (19.8)	74 (14.9)	0.202
Biliary system	146 (14.6)	71 (14.2)	75 (15.1)	
Pancreas	125 (12.5)	65 (13.0)	60 (12.0)	
Breast	86 (8.6)	41 (8.2)	45 (9.0)	
HCC	74 (7.4)	40 (8.0)	34 (6.8)	
Upper GI tract	74 (7.4)	38 (7.6)	36 (7.2)	
Gynecologic	69 (6.9)	28 (5.6)	41 (8.2)	
Urogenital	54 (5.4)	22 (4.4)	32 (6.4)	
Lower GI tract	51 (5.1)	28 (5.6)	23 (4.6)	
Head and neck	24 (2.4)	7 (1.4)	17 (3.4)	
Other solid tumors	26 (2.6)	11 (2.2)	15 (3.0)	
Hematologic	96 (5.6)	50 (10.0)	46 (9.2)	
Cancer stages				
No metastasis	402 (40.3)	202 (40.4)	200 (40.2)	0.903
Distant metastasis	500 (50.1)	248 (49.6)	252 (50.6)	
Hematologic	96 (9.6)	50 (10.0)	46 (9.2)	
ECOG PS				
0 - 1	299 (30.0)	151 (30.2)	148 (29.7)	0.629
2	233 (47.8)	244 (48.8)	233 (46.8)	
3 - 4	117 (23.5)	105 (21.0)	117 (23.5)	
Anti-cancer treatment	688 (68.9)	323 (64.6)	365 (73.3)	0.003
Bacteremia	165 (16.5)	80 (16.0)	85 (17.1)	0.650

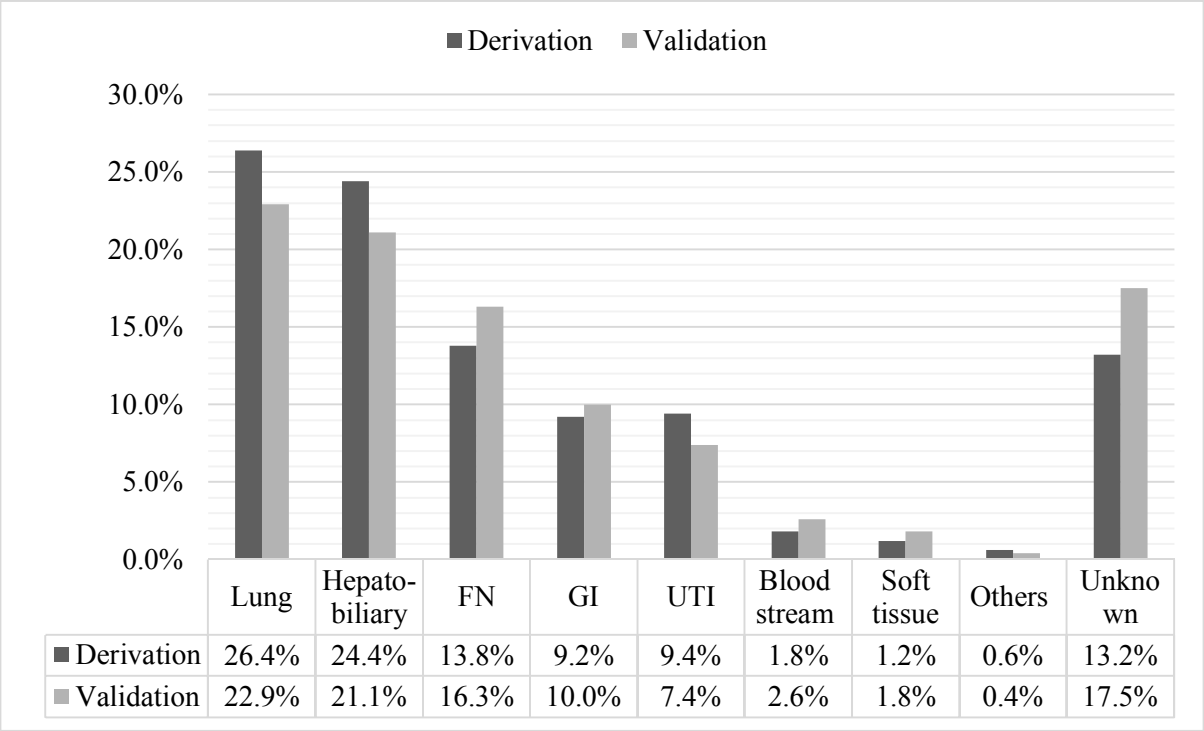
(continued)

Vital sign				
Systolic blood pressure (mmHg)	117.23 ± 24.43	117.01 ± 23.62	117.45 ± 25.24	0.777
Diastolic blood pressure (mmHg)	73.33 ± 16.92	72.94 ± 14.60	73.72 ± 18.98	0.469
Heart rate (bpm)	104.81 ± 20.47	104.07 ± 20.71	105.56 ± 20.23	0.252
Respiratory rate (bpm)	19.97 ± 3.54	19.87 ± 3.60	20.07 ± 3.49	0.387
Body temperature (℃)	37.52 ± 1.06	37.56 ± 1.04	37.47 ± 1.08	0.187
Change of mental status	41 (4.1)	17 (3.4)	24 (4.8)	0.259
Laboratory data				
WBC ($x10^3/\mu L$)	10.44 ± 15.39	10.15 ± 12.95	10.74 ± 17.51	0.546
Hemoglobin (g/dL)	10.30 ± 2.09	10.35 ± 2.09	10.24 ± 2.10	0.377
Platelet ($x10^3/\mu L$)	199.14 ± 132.39	197.88 ± 133.85	200.40 ± 131.03	0.764
PT (INR)	1.22 ± 0.29	1.21 ± 0.25	1.23 ± 0.33	0.332
BUN (mg/dL)	21.21 ± 17.27	21.13 ± 17.81	21.29 ± 16.72	0.887
Creatinine (mg/dL)	1.10 ± 0.98	1.12 ± 1.02	1.09 ± 0.94	0.562
Total Bilirubin (mg/dL)	1.93 ± 3.78	1.89 ± 3.26	1.97 ± 4.25	0.745
AST (IU/L)	75.06 ± 147.19	81.47 ± 175.41	68.62 ± 111.72	0.168
ALT (IU/L)	48.32 ± 84.29	50.61 ± 87.99	46.06 ± 80.41	0.394
Albumin (g/dL)	2.83 ± 0.64	2.85 ± 0.64	2.81 ± 0.64	0.348
CRP (mg/dL)	10.91 ± 10.00	10.51 ± 10.77	11.31 ± 9.15	0.205
Procalcitonin (ng/dL)	5.94 ± 29.43	6.70 ± 37.05	5.22 ± 19.68	0.488
Lactate (mmol/L)	2.17 ± 1.93	2.06 ± 1.90	2.29 ± 1.94	0.058
Lactate ≥ 4.0 mmol/L	91 (9.1)	37 (7.4)	54 (10.8)	0.059

Values are expressed as the mean ± standard deviation and the number (%).

HCC, hepatocellular carcinoma; GI, gastrointestinal; ECOG, Eastern Cooperative Oncology Group; PS, performance status; WBC, white blood cell; PT, prothrombin time; INR, international normalized ratio; BUN, blood urea nitrogen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CRP, C-reactive protein

Figure 2. Comparison of the infection origin between derivation and validation sets.



	Lung	Hepato-biliary	FN	GI	UTI	Blood stream	Soft tissue	Others	Unknown
Derivation	26.4%	24.4%	13.8%	9.2%	9.4%	1.8%	1.2%	0.6%	13.2%
Validation	22.9%	21.1%	16.3%	10.0%	7.4%	2.6%	1.8%	0.4%	17.5%

Values are expressed as number (%). The lung is the most common infection origin, and the hepatobiliary system is the second common infection origin in both sets.

FN, febrile neutropenial; GI, gastrointestinal; UTI, urinary tract infection

Table 2. Distribution of SIRS, qSOFA, and SOFA scores in derivation and validation sets

Score		Derivation set	Validation set	*P* value
SIRS				
	0	51 (10.2)	44 (8.8)	
	1	147 (29.4)	122 (24.5)	
	2	170 (34.0)	202 (40.6)	0.092
	3	109 (21.8)	116 (23.3)	
	4	23 (4.6)	14 (2.8)	
qSOFA				
	0	341 (68.2)	309 (62.0)	
	1	141 (28.2)	161 (32.3)	0.167
	2	16 (3.2)	25 (5.0)	
	3	2 (0.4)	3 (0.6)	
SOFA				
	0	91 (18.2)	95 (19.1)	
	1	100 (20.0)	93 (18.7)	
	2	91 (18.2)	98 (19.7)	
	3	77 (15.4)	71 (14.3)	
	4	61 (12.2)	57 (11.4)	
	5	27 (5.4)	33 (6.6)	
	6	20 (4.0)	22 (4.4)	0.813
	7	18 (3.6)	11 (2.2)	
	8	8 (1.6)	5 (1.0)	
	9	3 (0.6)	3 (0.6)	
	10	2 (0.4)	3 (0.6)	
	11	2 (0.4)	3 (0.6)	
	12	0 (0.0)	3 (0.6)	
	13	0 (0.0)	1 (0.2)	

Values are expressed as number (%).

SIRS, systemic inflammatory response syndrome; qSOFA score, quick sequential organ failure assessment score; SOFA, sequential organ failure assessment

Table 3. Outcomes and dispositions of total subjects

	Total	Derivation (*n* = 500)	Validation (*n* = 498)	*P* value
30-day mortality	225 (22.5)	101 (20.2)	124 (24.9)	0.076
180-day mortality	548 (54.9)	256 (51.2)	292 (58.6)	0.018
Death at ER	14 (1.4)	6 (1.2)	8 (1.6)	0.585
ICU admission	52 (5.2)	23 (4.6)	29 (5.8)	0.385

Values are expressed as the number (%).

ER, emergency room; ICU, intensive care unit;

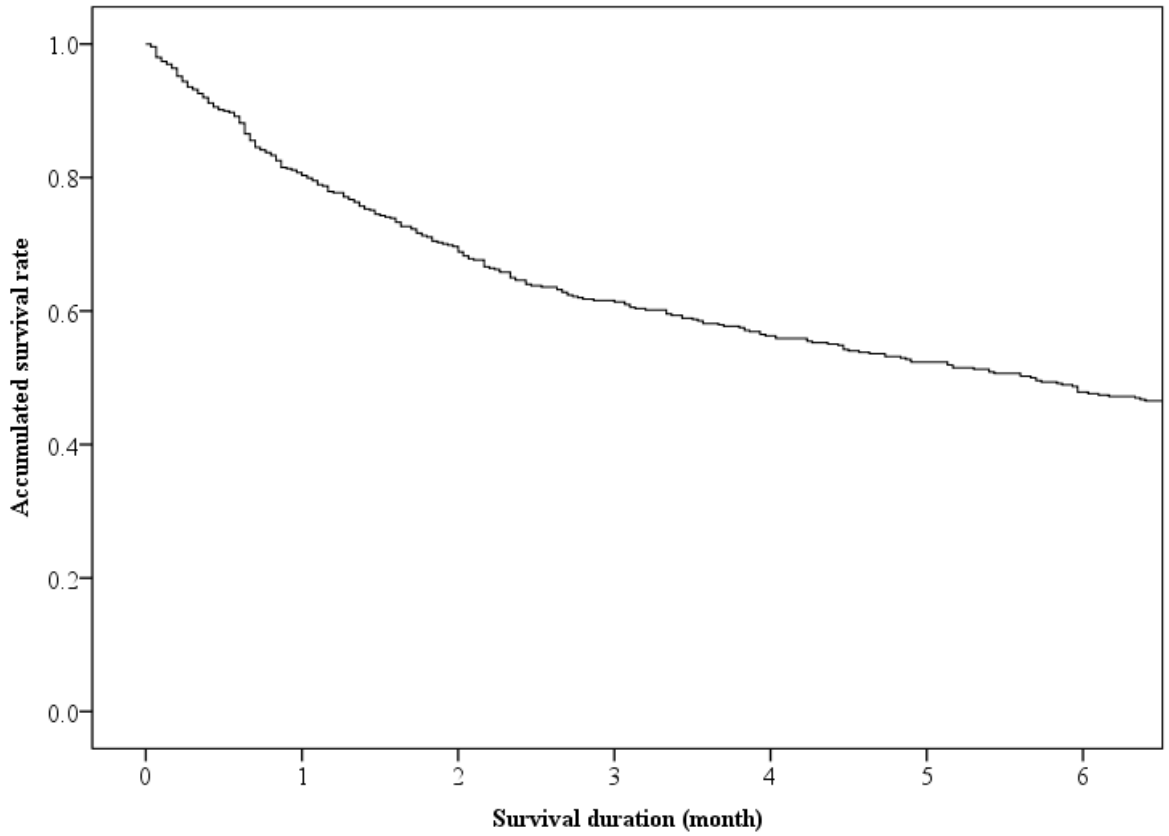
Cox proportional hazards regression analysis for survival in the derivation set

The accumulated survival rates were shown in Figure 3. The 30-day, 60-day, 90-day, and 180-day survival rates were 80.3%, 68.9%, 61.4% and 47.7%, respectively.

Table 4 shows the univariate Cox proportional hazards regression analysis for survival. Age (HR, 1.012; 95% CI, 1.002-1.022), ECOG PS 2 (HR, 2.505; 95% CI, 1.840-3.409), ECOG PS 3-4 (HR, 4.826; 95% CI, 3.435-6.780), distant metastasis (HR, 2.013; 95% CI, 1.571-2.581), respiratory rate (RR) (HR, 1.041; 95% CI, 1.010-1.073), body temperature (BT) (HR, 0.738; 95% CI, 0.660-0.824), mental change (HR, 2.302; 95% CI, 1.346-3.937), bacteremia (HR, 1.616 95% CI, 1.222-2.137), white blood cell (WBC) (HR, 1.022; 95% CI, 1.016-1.028), hemoglobin (Hb) (HR, 0.876; 95% CI, 0.830-0.924), prothrombin time (PT) (HR, 4.928; 95% CI, 3.518- 6.903), blood urea nitrogen (BUN) (HR, 1.018; 95% CI, 1.013-1.023), creatinine (HR, 1.188; 95% CI, 1.079-1.308), total bilirubin (HR, 1.068; 95% CI, 1.039-1.097), albumin (HR, 0.345; 95% CI, 0.288-0.414), and lactate (HR, 1.129; 95% CI, 1.075-1.187) were significantly associated with survival ($p < 0.05$ for all). However, male, co-morbidities, systolic blood pressure, diastolic blood pressure, heart rate, and platelet were not associated with survival in the univariate Cox model ($p > 0.05$).

For the multivariate Cox proportional hazards regression analysis, the variables with p value below 0.1 in the univariate Cox proportional hazards model were included except variables with no or weak clinical relevance. Table 5 shows the multivariate Cox proportional hazards regression analysis. ECOG PS 2 (HR, 1.888; 95% CI, 1.370-2.602), ECOG PS 3-4 (HR, 3.320; 95% CI, 2.322-4.746), distant metastasis (HR, 1.577; 95% CI, 1.221-2.038), WBC $\geq$ 10,000/mm^3 (HR, 1.263; 95% CI, 1.002-1.593), PT $\geq$ 1.2 (HR, 2.051; 95% CI, 1.076-3.909), creatinine $\geq$ 1.2 mg/dL (HR, 1.432; 95% CI, 0.999-2.051), albumin < 3.5 g/dL (HR, 0.420; 95% CI, 0.283-0.623), and lactate $\geq$ 4.0 mmol/L (HR, 1.626; 95% CI, 1.100-2.402) were independently associated with survival.

Figure 3. Accumulated survival rates over time in the derivation set.



Duration	30-day	60-day	90-day	180-day
Survival rate (%)	80.3	68.9	61.4	47.7

Table 4. Univariate analysis of the Cox proportional hazards model

	Univariate				
Parameters	Coefficient	HR	95% CI		*P* value
Age	0.012	1.012	1.002	1.022	0.015
Male	0.080	1.083	0.862	1.358	0.491
Comorbidities					
Hypertension	0.013	1.013	0.796	1.288	0.918
Diabetes Mellitus	0.179	1.196	0.927	1.543	0.168
Chronic kidney disease	0.338	1.402	0.834	2.356	0.202
Chronic liver disease	-0.045	0.956	0.681	1.343	0.796
Cardiovascular disease	0.014	1.014	0.707	1.455	0.940
Cancer stages					
No metastasis		1.000			
Distant metastasis	0.700	2.013	1.571	2.581	0.000
Hematologic	0.311	1.365	0.906	2.058	0.137
ECOG PS					
0 - 1		1.000			
2	0.918	2.505	1.840	3.409	0.000
3 - 4	1.574	4.826	3.435	6.780	0.000
Vital sign					
Systolic blood pressure	-0.003	0.997	0.992	1.002	0.206
Diastolic blood pressure	-0.002	0.998	0.990	1.006	0.602
Heart rate	0.004	1.004	0.999	1.010	0.151
Respiratory rate	0.040	1.041	1.010	1.073	0.009
Body temperature	-0.304	0.738	0.660	0.824	0.000
Mental change	0.834	2.302	1.346	3.937	0.002
Laboratory data					
WBC	0.022	1.022	1.016	1.028	0.000
Hemoglobin	-0.133	0.876	0.830	0.924	0.000

(continued)

Platelet	0.000	1.000	0.999	1.000	0.834
PT	1.595	4.928	3.518	6.903	0.000
BUN	0.018	1.018	1.013	1.023	0.000
Creatinine	0.172	1.188	1.079	1.308	0.000
Total Bilirubin	0.065	1.068	1.039	1.097	0.000
Albumin	-1.064	0.345	0.288	0.414	0. 000
Procalcitonin	0.008	1.008	1.005	1.010	0.000
Lactate ≥ 4.0 mmol/L	0.753	2.123	1.456	3.096	0.000

HR, hazard ratio; CI, confidence interval; HCC, hepatocellular carcinoma; GI, gastrointestinal; ECOG, Eastern Cooperative Oncology Group; PS, performance status; WBC, white blood cells; PT, prothrombin time; BUN, blood urea nitrogen

Table 5. Multivariate analysis of the Cox proportional hazards model

		Multivariate			
Parameters	Coefficient	HR	95% CI		*P* value
ECOG PS 2	0.636	1.888	1.370	2.602	0.000
ECOG PS 3-4	1.200	3.320	2.322	4.746	0.000
Distant metastasis	0.456	1.577	1.221	2.038	0.000
Hematologic	0.223	1.250	0.891	1.910	0.301
WBC ≥ 10,000/mm^3	0.234	1.263	1.002	1.593	0.048
PT (INR) ≥ 1.2	0.718	2.051	1.076	3.909	0.029
Creatinine ≥ 1.2 mg/dL	0.359	1.432	0.999	2.051	0.050
Albumin < 3.5 g/dL	-0.868	0.420	0.283	0.623	0.000
Lactate ≥ 4.0 mmol/L	0.486	1.626	1.100	2.402	0.015

HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; PS, performance status; WBC, white blood cells; PT, prothrombin time; INR, international normalized ratio

Development of a new prognostic model

ECOG PS, distant metastasis, WBC, PT, albumin, creatinine, and lactate were selected for a new prediction model through multivariate analysis. The calculation of the allocated point is described in Table 6. For calculating points of each variable, continuous values were used for more accurate predictive power. The reference value is an actual average value. Betai represented an effect size with each increase of 1 in reference values. Bi was calculated by multiplying the difference of reference values and the Betai value. In the case of the Betai and the Bi are the same, the Betai value was omitted. Point allocation was performed based on the value with the Bi divided by the B.

The new prognostic model for predicting mortality in active cancer patients with suspected infection was shown in Table 7. Final allocated points for each variable is as follows; 1 point for each creatinine ≧ 1.2 mg/dL, PT (INR) ≧ 1.2, WBC ≧ 10,000/mm^3, lactate ≧ 4.0 mmol/L, 2 points for each distant metastasis, ECOG PS 2, albumin 2.5 to 3.5 g/dL, 3 points for ECOG PS 3-4, 4 points for albumin < 2.5 g/dL. Selected variables were seven, as mentioned above, and the total score ranges from 0 to 13. Table 8 shows the estimated risk to each point, along with the total summation of allocated points for 30-day and 180-day mortalities. The 30-day mortality risk was 3.01%, and the 180-day mortality risk was 12.3% when the total score was 0 in the new prognostic model. The 30-day and 180-day mortality risks were 79.5% and 99.9%, respectively, when the total summation was the maximum score of 13 in the new prognostic model.

As presented in Table 9, the overall concordance index (C index) was 0.729 for internal validation and 0.759 for temporal validation. The C indices for 30-day, 90-day, and 180-day mortalities were 0.824, 0.852, and 0.834, respectively, in temporal validation. It indicated that the new prognostic model is good to strong for predicting mortality in cancer patients with suspected infection than existing models. The diagonal line for each mortality at 30-day, 90-day, 180-day was within the ranges of confidential intervals presented vertical lines in a calibration graph, which means that the new prognostic model's overall prediction accuracy for mortality is good, as illustrated in Figure 4.

To stratify the mortality risk, the total calculated scores were grouped into three: 0 to 4 into low risk, 5 to 8 into intermediate risk, 9 to 13 into high risk. The predicted 30-day mortality risk for the low-risk group was below 10%, whereas the high-risk group was 37.5% to 79.5%%. For the 180-

day mortality, the predicted risk for the low-risk group is 12.3% to 35.7%, but the high-risk group is 86.7% to 99.9%, as shown in Table 10.

Table 6. Point allocation for each factor in a new prognostic model

		Reference value	Betai	Bi	B	Bi/B	Points
Baseline survival	30-day	0.923					
	90-day	0.813					
	180-day	0.710					
Cancer stages					0.304		
No metastasis		0		0		0	0
Distant metastasis		1		0.470		1.547	2
Hematologic		1		0.095		0.312	0
ECOG PS							
0-1		0		0		0	0
2		1		0.476		1.566	2
3-4		1		0.911		3.000	3
Creatinine							
(mg/dL)	<1.2	0		0		0	0
	≥1.2	1		0.231		0.762	1
Albumin			-0.770				
(g/dL)	<2.5	2.06		1.301		4.276	4
	2.5-3.5	2.97		0.606		1.961	2
	≥3.5	3.75		0		0	0
PT (INR)			1.003				
	<1.2	1.08		0		0	0
	≥1.2	1.42		0.341		1.125	1
WBC			0.014				
(/mm^3)	<4	1.93		0		0	0
	4-10	6.98		0.071		0.237	0
	≥10	18.41		0.231		0.775	1
Lactate			0.053				
(mmol/L)	<4.0	1.63		0		0	0
	≥4.0	7.42		0.307		1.002	1

Betai, raw coefficient value; Bi, estimated coefficient value; B, regression coefficient of the reference predictor; ECOG, eastern cooperative oncology group; PS, performance status; PT, prothrombin time; INR, international normalized ratio; WBC, white blood cells

Table 7. The new prognostic model for the mortality risk in cancer patients with suspected infection

Variables	**score**
Distant metastasis	2
ECOG PS 2	2
ECOG PS 3-4	3
Creatinine ≧ 1.2 mg/dL	1
Albumin 2.5-3.5 g/dL	2
Albumin < 2.5 g/dL	4
PT (INR) ≧ 1.2	1
WBC ≧ 10,000/mm^3	1
Lactate ≧ 4.0 mmol/L	1
Total score	13

ECOG, Eastern Cooperative Oncology Group; PS, performance status;

PT, prothrombin time; INR, international normalized ratio; WBC, white blood cells

Table 8. Estimation of risk to each point for the 30-day and the 180-day mortalities

Total points	30-day mortality risk	180-day mortality risk	Number of patients
0	0.0301	0.1228	23
1	0.0406	0.1627	11
2	0.0546	0.2138	44
3	0.0732	0.2782	33
4	0.0979	0.3570	55
5	0.1303	0.4503	37
6	0.1723	0.5555	72
7	0.2260	0.6666	74
8	0.2933	0.7742	54
9	0.3752	0.8669	37
10	0.4712	0.9349	35
11	0.5782	0.9753	13
12	0.6895	0.9934	10
13	0.7950	0.9989	2

Table 9. Internal and temporal validation of the new prognostic model

	Internal validation		Temporal validation		
Mortality	C index	95% CI	C index	SE	95% CI
Overall	0.729	0.700-0.759	0.759	0.013	0.734-0.784
30-day	0.796	0.750-0.842	0.824	0.019	0.786-0.862
90-day	0.796	0.758-0.834	0.852	0.017	0.819-0.885
180-day	0.769	0.728-0.810	0.834	0.019	0.795-0.872

C index, Concordance index; SE, standard error; CI, confidence intervals

Figure 4. Calibration graph between actual and predicted survival probabilities in the derivation set.

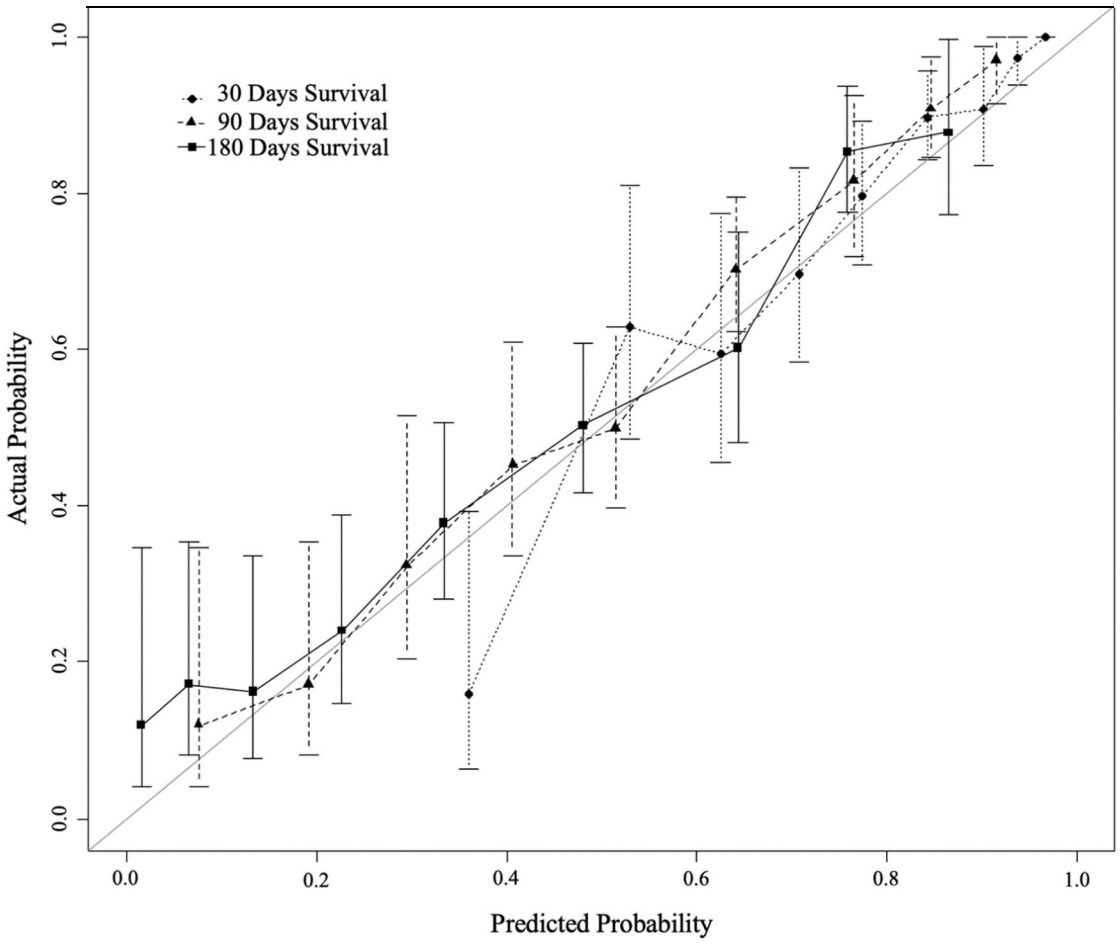


Table 10. Risk group classification of the new prognostic model

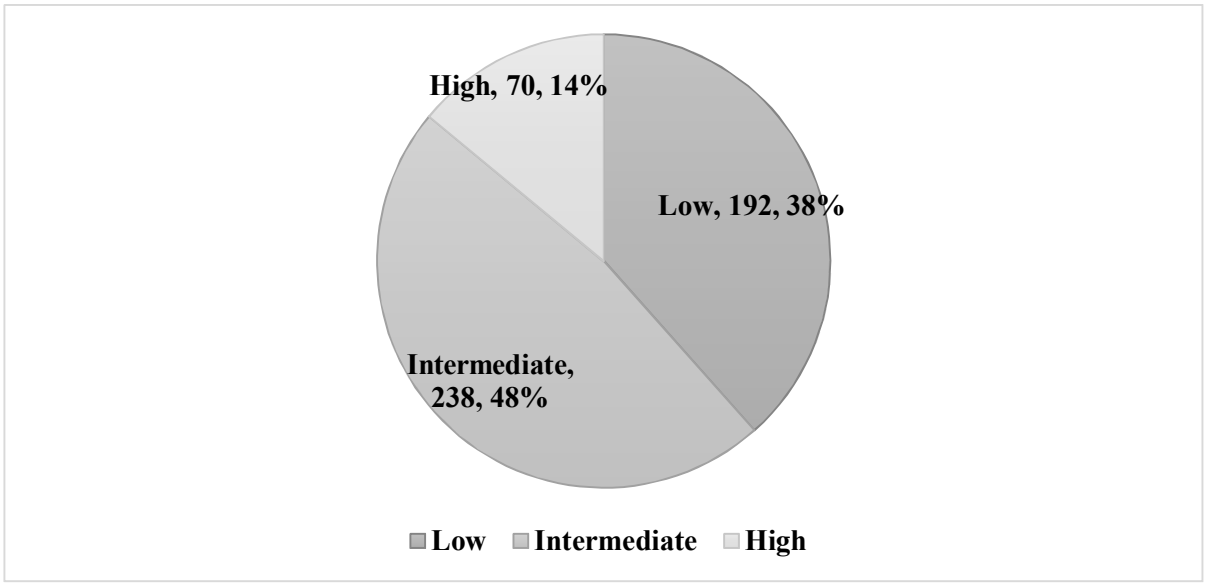
Score	Class	Predictive 30-day mortality risk	Predictive 180-day mortality risk
0 - 4	Low	3.0 - 9.8 %	12.3 – 35.7 %
5 - 8	Intermediate	13.0 – 29.3 %	45.0 - 77.4 %
9 - 13	High	37.5 – 79.5 %	86.7 – 99.9 %

Distribution and performance of the new prognostic model

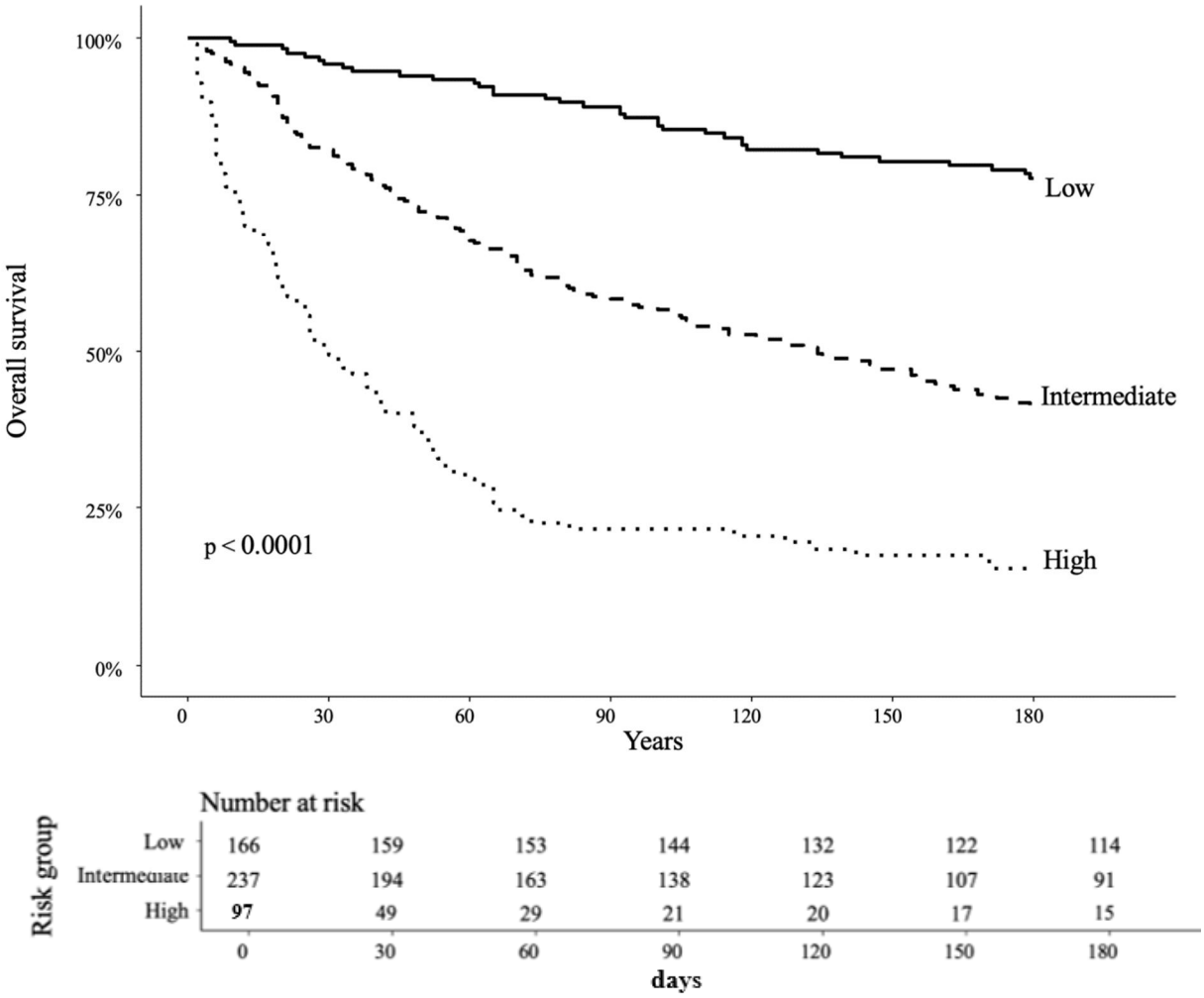
In the derivation set, there were 192 (38.0%) patients in the low-risk group, 238 (48%) in the intermediate-risk group, and 70 (14%) in the high-risk group (Figure 5-a). The overall survival in three risk-stratified groups was shown in Figure 5-b. There was a significant difference in survival among the three groups. Especially, the survivals in the high-risk group decreased steeply during the first 60 days.

Table 11 shows the new prognostic model's performance for 30-day and 180 mortalities in the high-risk group. For the 30-day mortality, the new prognostic model's sensitivity and specificity were 58.6% and 86.0%, respectively, and the positive and negative predictive values were 40.6% and 92.7%, respectively. For the 180-day mortality, the sensitivity and specificity were 82.9% and 48.1%, respectively, and the positive and negative predictive values were 20.7% and 94.1%, respectively. The AUC value of the new prognostic model was 0.792 (95% CI, 0.733-0.840; $p = 0.000$) for the 30-day mortality and 0.744 (95% CI, 0.701-0.787; $p = 0.000$) for the 180-day mortality in Figure 6.

Figure 5. Distribution (a) and survival rates (b) in three risk-stratified groups in the derivation set.



(a)



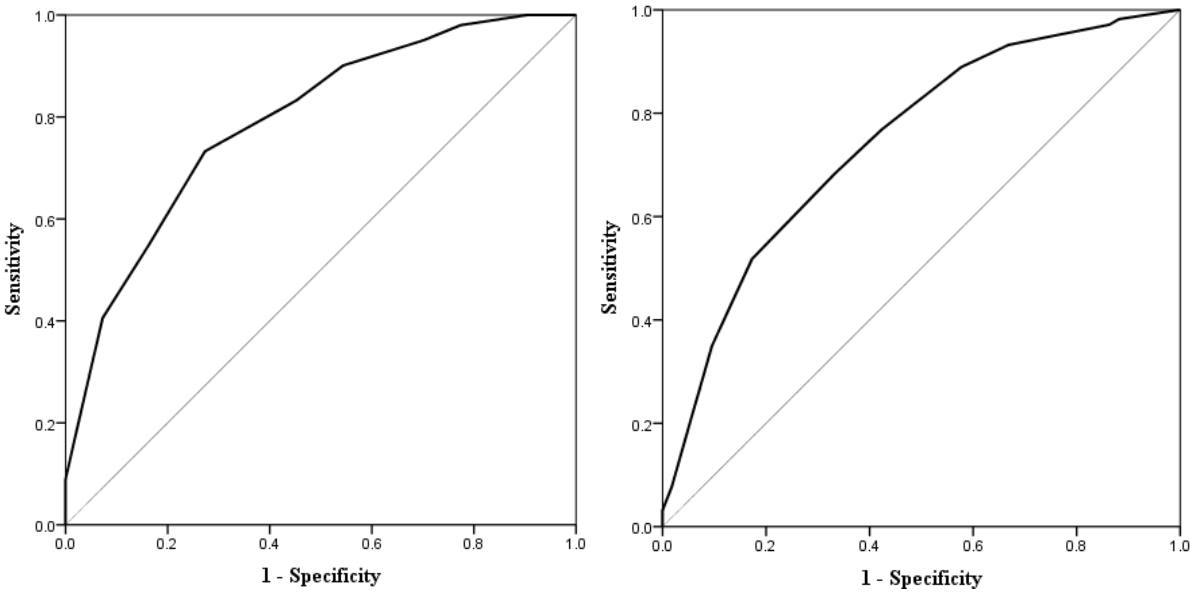
(b)

Table 11. Performance of the new prognostic model for 30-day and 180-day mortalities in the high-risk group

	30-day mortality	180-day mortality
Sensitivity (%)	58.6	82.9
Specificity (%)	86.0	48.1
PPV (%)	40.6	20.7
NPV (%)	92.7	94.1

NPV, negative predictive value; PPV, positive predictive value

Figure 6. AUCs of 30-day (a) and 180-day mortalities (b) for the new prognostic model in the derivation set.



	AUC	SE	95% CI		*P* value
30-day mortality	0.792	0.025	0.744	0.840	0.000
180-day mortality	0.744	0.022	0.701	0.787	0.000

AUC, area under the receiver operating curve; SE, standard error; CI, confidence intervals

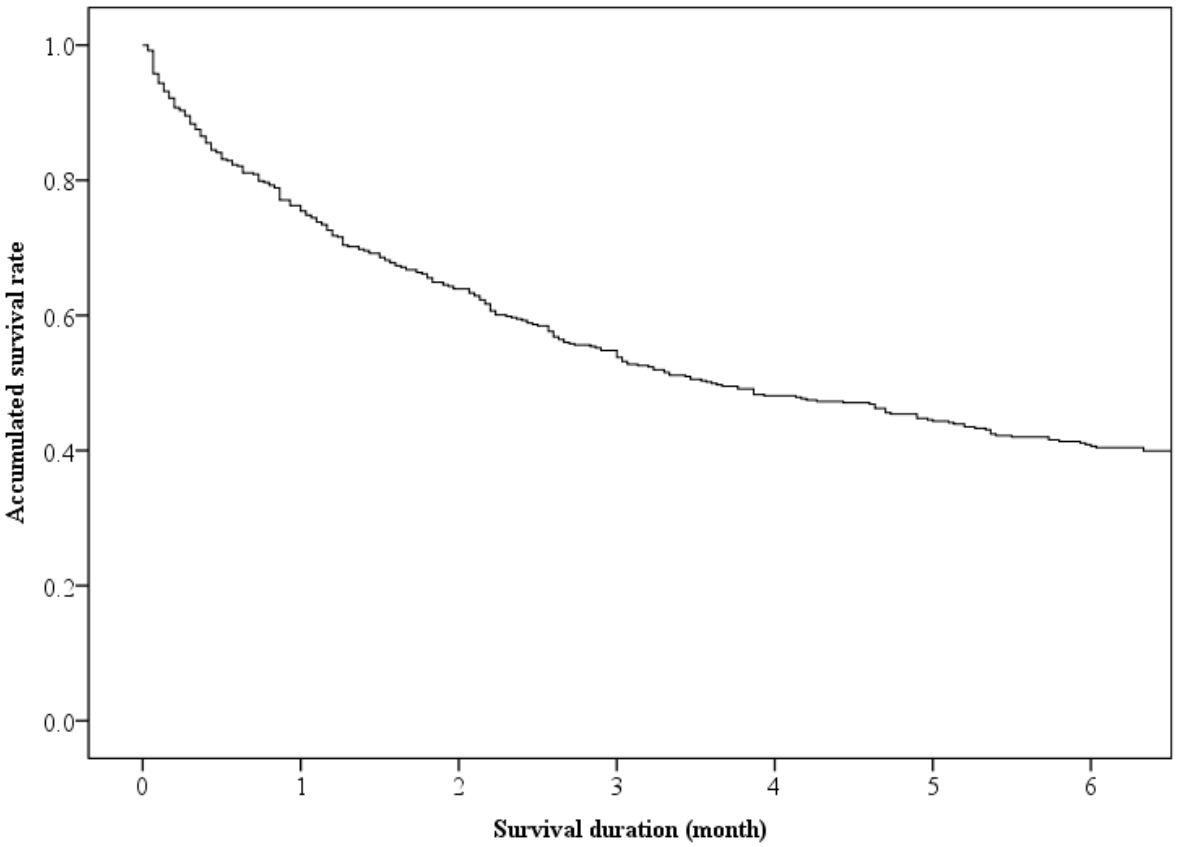
Validation of a new prognostic model

Figure 7 depicted the survival rates in the validation set. The 30-day, 60-day, 90-day, and 180-day survival rates were 75.4%, 63.7%, 53.8%, and 40.7%, respectively.

As shown in the derivation set, the diagonal lines for each mortality at 30 days, 60 days, 90days, and 180 days were within the ranges of confidential intervals in a validation set calibration graph. Although the graph of 90-day survival was slightly downward between the predicted probability of 0.4-0.6, the new prognostic model's overall accuracy in predicting mortality was good. (Figure 8)

There were 160 (32%), 216 (43%), and 122 (25%) in the low-risk, intermediate-risk, and high-risk groups, respectively, in the validation set, as shown in Figure 9-a. As in the derivation set, the three groups showed a significant difference in the overall survival shown in Figure 9-b ($p < 0.0001$). The survival rates within 60 days decreased abruptly in the high-risk group, as observed in the derivation set.

Figure 7. Accumulated survival rates over time in the validation set.



Duration	30-day	60-day	90-day	180-day
Survival rate (%)	75.4	63.7	53.8	40.7

Figure 8. Calibration graph between actual and predicted survival probabilities in the validation set.

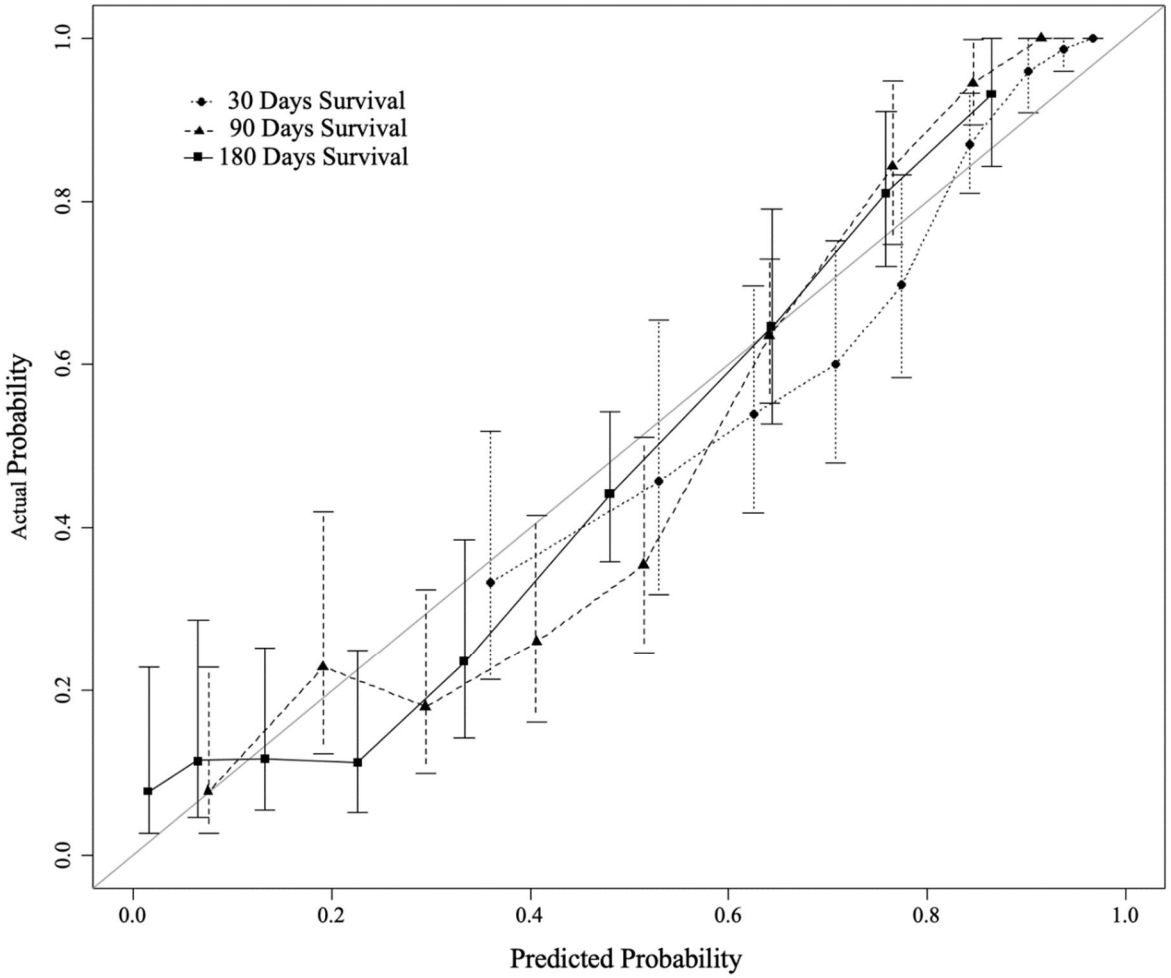
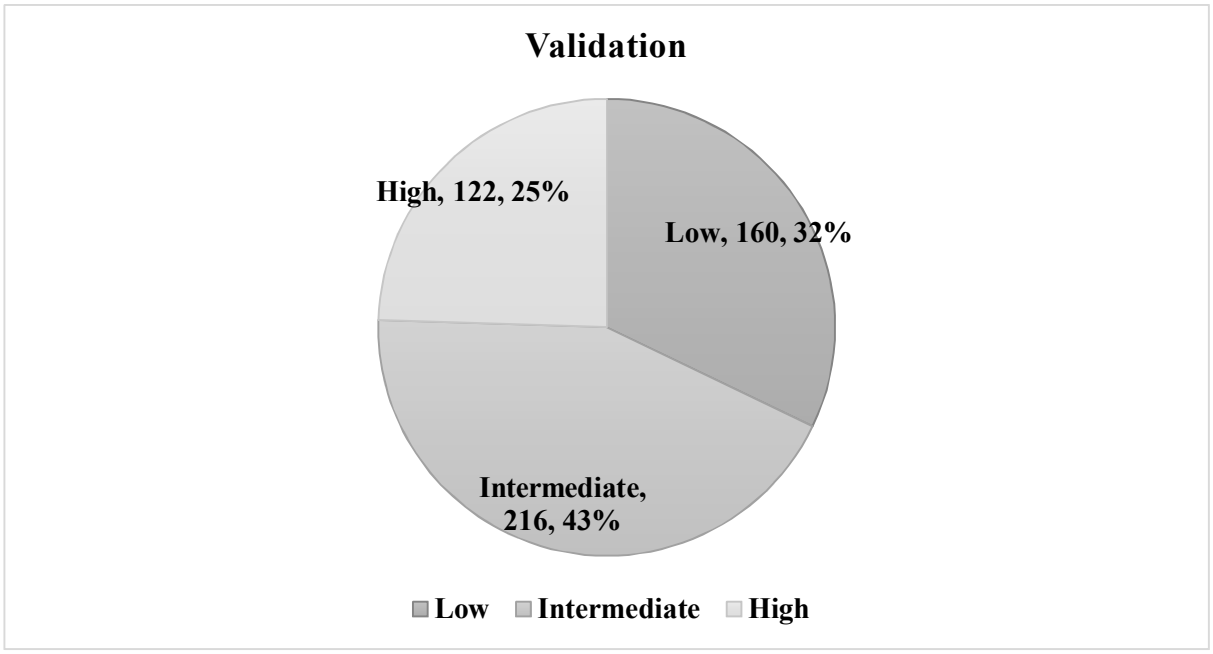
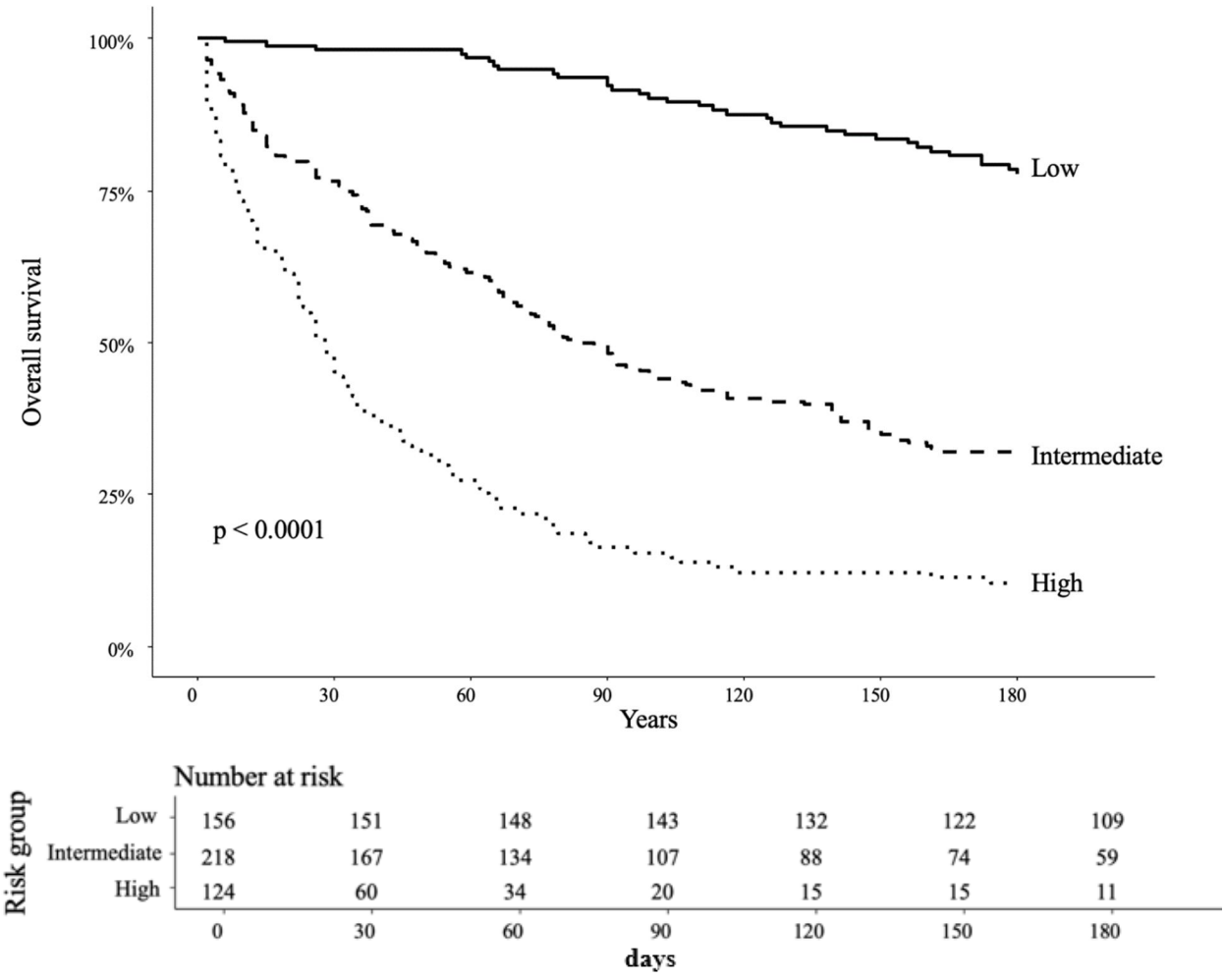


Figure 9. Distribution (a) and survival rates (b) in three risk-stratified groups in the validation set.



(a)

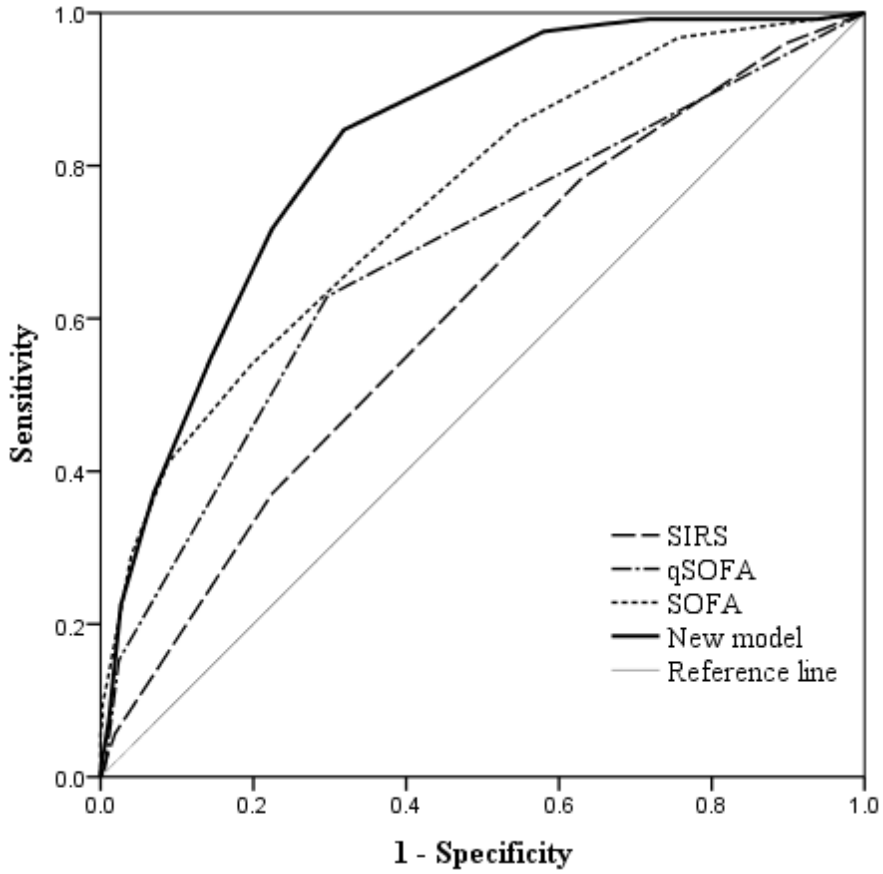


(b)

Comparison of the new prognostic model with SIRS, qSOFA, and SOFA

The AUC of the new prognostic model for the 30-day mortality was 0.828 (95% CI, 0.790-0.867) in the validation set. The AUC for the 30-day mortality was 0.612 (95% CI, 0.556-0.669) for SIRS, 0.681 (95% CI, 0.624-0.738) for qSOFA, and 0.752 (95% CI, 0.703-0.801) for SOFA in Figure 10. For the 180-day mortality prediction, the new prognostic model (AUC, 0.810; 95% CI, 0.770-0.849) was also stronger than SIRS (AUC, 0.531; 95% CI, 0 .478-0.583), qSOFA (AUC, 0.637; 95% CI, 0.587-0.686), and SOFA (AUC, 0.678; 95% CI, 0.630-0.725) in Figure 11. Compared with the existing models, the new prognostic model was more powerful for predicting the mortality in cancer patients with suspected infection ($p = 0.000$).

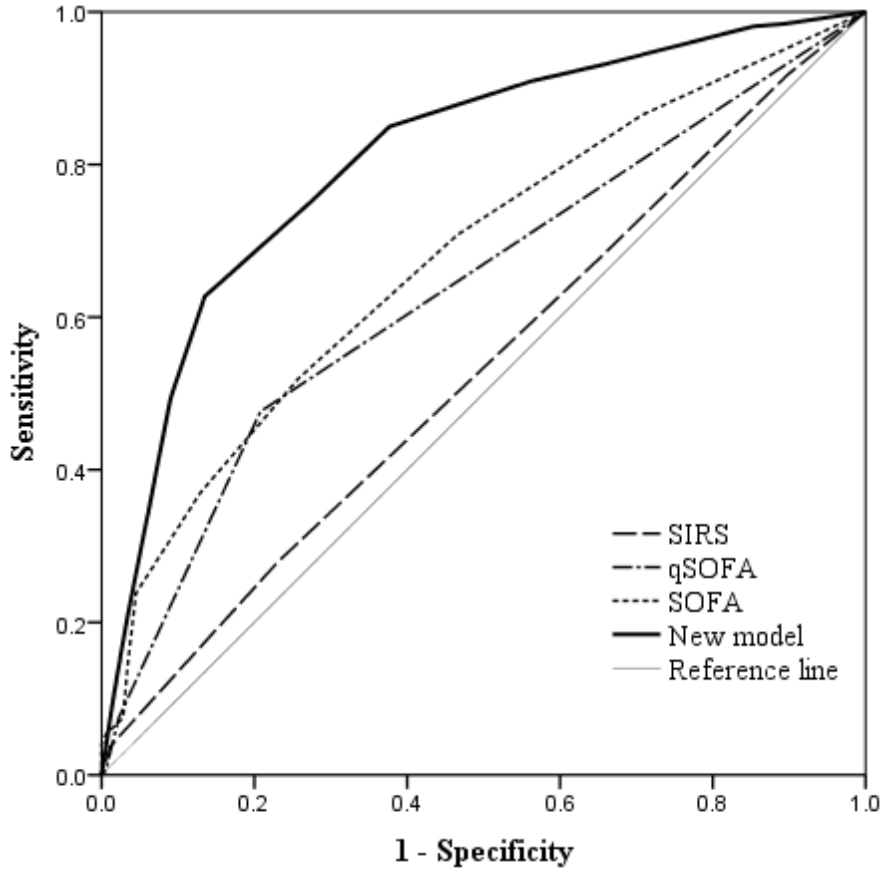
Figure 10. Comparison of the new prognostic model with SIRS, qSOFA, and SOFA scores for 30-day mortality in the validation set.



	AUC	SE	95% CI		*P* value
SIRS	0.612	0.029	0.556	0.669	0.000
qSOFA	0.681	0.029	0.624	0.738	0.000
SOFA	0.752	0.025	0.703	0.801	0.000
New model	0.828	0.020	0.790	0.867	0.000

AUC, area under the receiver operating curve; SE, standard error; CI, confidence intervals; SIRS, systemic inflammatory response syndrome; qSOFA, quick sequential organ failure assessment; SOFA score, sequential organ failure assessment

Figure 11. Comparison of the new prognostic model with SIRS, qSOFA, and SOFA scores for 180-day mortality in the validation set.



	AUC	SE	95% CI		*P* value
SIRS	0.531	0.027	0.478	0.583	0.259
qSOFA	0.637	0.025	0.587	0.686	0.000
SOFA	0.678	0.024	0.630	0.725	0.000
New model	0.810	0.020	0.770	0.849	0.000

AUC, area under the receiver operating curve; SE, standard error; CI, confidence intervals; SIRS, systemic inflammatory response syndrome; qSOFA, quick sequential organ failure assessment; SOFA score, sequential organ failure assessment

Discussion

In this study, we have developed a new prognostic model for active cancer patients with suspected infection. It used seven components, two clinical and five laboratory factors. The two clinical factors, distant metastasis and ECOG PS, were cancer-specific, and the remaining five laboratory components were creatinine, albumin, PT, WBC, and lactate. Each component was assigned different scores, and the sum of all scores (ranged 0 to 13) was a measure of predicting mortality. The total scores were not deviated to one side and distributed evenly throughout in the study patients. As the total score increased, the risk of death rose. A new clinical prognostic model's applicability relies on patients in the derivation group and fits well with patients from the validation group. The new prognostic model predicted the mortality risk more accurately with c statistics from 0.729 to 0.769. For the 30-day mortality, the new model had the most potent discrimination power with an AUC of 0.828 compared to SIRS (AUC 0.612), qSOFA (AUC 0.681), and SOFA (AUC 0.752). The new model was more accurate with an AUC 0.810 compared to SIRS (AUC 0.531), qSOFA (AUC 0.637), and SOFA (AUC 0.678) in predicting the 180-day mortality.

As described above, there were two cancer-specific components in the new model. One of the two, distant metastasis was an independent predictor of mortality in this study (HR, 1.610; 95% CI, 1.242-2.088). Distant metastasis was allocated 2 points in the new prognostic model. Metastasis is one of the major causes of cancer-related death. It is also well known that patients with distant metastasis have poorer outcomes than patients without metastasis.[36-39] A malignant cell is unstable genetically and not able to be fully differentiated.[40] Alterations of gene expression and products can result in the susceptibility of tumor cells in the micro-pathological aspect.[41] Moreover, most metastatic states have a tolerance to anticancer treatment, and anatomical disruption or immunomodulation due to progressed cancer contributes to poor prognosis.

In addition to distant metastasis, the PS of cancer patients has been considered as an essential prognostic factor through many previous studies.[12, 42-45] PS is affected by many factors such as patients' age, cancer stages, and side-effects of anticancer treatment. Patients who have a worse PS and limited functional capacity tend to have more difficulty tolerating rigorous cancer treatments. These patients have less favorable outcomes than more fit patients with better PS, regardless of the

treatments given.[46] ECOG PS ranges from 0 to 5. The measurement of performance is highly dependent on the physician's subjective judgment. In this study, the five PS scales were reclassified into three groups. Intermediate PS allocated point 2, and poor PS assigned point 3 in the new model.

In the new model, there are five laboratory components. The use of laboratory values is objective and reproducible. Among the five components, albumin was allocated the highest scores of 2 to 4 according to its levels. Albumin is generally known as a value reflecting nutritional state, liver function, and oncotic pressure in cancer patients. Albumin is also related to immunity by maintaining skin barrier against infection and acting as a radical scavenger.[47] Therefore, decreased serum albumin levels can be observed in malnutrition status and an inflammatory process. Previous studies have exhibited that the low serum albumin level is a significant predictor of high mortality in various cancer types.[48-51] In this study, albumin was the most robust variable showing a negative correlation with mortality (HR, 0.503; 95% CI, 0.412-0.614). The highest point was allocated to albumin, and values were divided into three groups in a new prognostic model. In comparison to the global cancer distribution, biliary and pancreatic cancer were highly common in this study.[52, 53] Such a skewed distribution may have caused the impact of albumin to be overestimated. The fact that hepato-biliary origin was the second most common infection focus can be explained in the same context.

Lactate is an indicator of tissue hypoperfusion and a useful prognostic biomarker in several critical diseases.[54-56] In cancer patients, lactate is increased in tumor glycolysis, and it is essential in promoting malignant cell invasion, immune response evasion, and resistance to apoptosis.[57-59] Therefore, hyperlactatemia is common in cancer patients due to cancer itself or the infectious process. Hyperlactatemia is associated with cancer progression and higher overall mortality in previous studies.[60, 61] In this study, hyperlactatemia was significantly associated with mortality in Cox proportional-hazards regression (HR, 1.626; 95% CI, 1.100-2.402). The lactate cut-off value of 4 mmol/L was commonly used in septic shock patients to initiate early goal-directed therapy before sepsis-3 definition. However, recent studies have shown that lactate in the intermediated levels of 2 to 4 mmol/l had a similar correlation with poor outcomes in patients with suspected infection.[62] Moreover, it turns out that the lactate level increases from occult tissue hypoperfusion without

hypotension or hypoxia, and there have been many attempts to lower the cut-off. There is a lack of evidence on the optimal cut-off value of serum lactate in cancer patients. However, higher mortality than doubling was observed in the increased lactate levels above 4 mmol/L than in the intermediate range between 2 and 4 mmol/L in cancer patients.[56] Therefore, the lactate values above 4 mmol/L was set to hyperlactatemia in this study.

The new model includes creatinine. Elevated creatinine levels were associated with higher mortality in cancer patients with suspected infection. Impairment of kidney function is frequently seen in cancer patients. The impaired kidney function is caused by hypovolemia from insufficient oral intake, intra-renal injury from hypoperfusion or chemo agents, and obstruction due to local invasion.[63] Many anticancer agents are cleared by the kidney or affect the renal function [64-67], so the renal function is an essential factor to determine a drug dose or treatment itself.[68] Moreover, although the mechanism is still poorly understood, the creatine/creatinine metabolism has been related to carcinogenesis and cancer progression. Chronic low-grade inflammation may also induce intrinsic renal dysfunction that can elevate serum creatinine levels. So, serum creatinine levels may reflect a chronic inflammatory state from the underlying malignancy.[69, 70] Recent evidence reported that impaired kidney function is associated with poor prognosis in cancer patients.[67, 71-73] It has been evident that kidney dysfunction is correlated with cancer-related outcomes, whether acute or chronic.[74, 75] Therefore, careful monitoring of renal function is critical and renal function has great clinical significance in cancer patients. Creatinine is the prognostic variable with clinical relevance rather than statistical significance in this new prognostic model.

PT was one of the predictors of mortality in cancer patients with suspected infection in this study. The hypercoagulable and thrombophilic state of cancer can cause frequent complications such as deep vein thrombosis (DVT) or pulmonary thromboembolism (PTE). Procoagulants released from tumor cells activate a cascade of coagulopathy and result in thrombocytopenia or thrombocytosis, elevated d-dimer, PT, and FDP. Because of this cascade, interesting co-existence of anti-coagulation and thrombophilic state occurs in cancer patients.[76] Previous studies have reported that coagulopathy is related to the prognosis of various malignancies.[77-80] Moreover, infection insult induces the procoagulants' release, which affects thrombo-modulation.[81] In other words, cancer and

infection share some tendencies in terms of coagulopathy. PT is generally thought to be prolonged in cancer patients, but it is erratic because of a mixed state of anti-coagulation and thrombophilic conditions.[82] The actual tri-quartile value of PT INR was 1.28, and the average value was 1.22 in this study. They were not far higher than the reference cut-off value, so PT was categorized according to INR's normal range. The PT INR $\geq$1.2 was associated with two times higher mortality in this study.

Lastly, leukocytosis is one of the components in the new model. Leukocytosis is usually interpreted as a representative inflammatory marker. Through the studies of the relationship between cancer and inflammation, leukocytosis is related to tumor development and progression.[83, 84] Cancer-related inflammation has tumor-promoting effects and suppressing anti-tumor immunity.[83, 85] So, many studies have reported that leukocytosis correlates with cancer-related poor outcomes in various cancer types.[86-90] Leukopenia is commonly seen in cancer patients due to myelosuppression by malignant infiltration and anticancer treatment [19, 91] but did not significantly correlate with mortality in this study. The cut-off level was set along with the upper limit of reference value because nonlinear distribution contributed to not raising the cut-off value. WBC $\geq$ 1,000/mm^3 was associated with a 26% increase in cancer patients' mortality with suspected infection in this study.

Several prognostic scoring systems have been developed to predict prognosis in sepsis patients. SOFA is one of the most commonly validated models and shown to be accurate in many studies.[27] However, there has been a lack of studies on their accuracy, specifically in cancer patients. This study's new model was a robust prognostic model for mortality in cancer patients with suspected infection compared to existing predictive models. The AUCs of 30-day and 180-day mortalities for the new model were more than 0.8, while the AUCs for SIRS, qSOFA, and SOFA were lower than 0.7. The new prognostic model included cancer-specific characteristics such as ECOG PS or distant metastasis. Such factors as disease progression and functional status are critical determinants of prognosis in cancer patients. Therefore, it seems reasonable to have cancer-specific factors reflected in a prognostic system. A more reliable and objective model of the prognosis for

active cancer with suspected infection can help a physician determine the appropriate clinical decision.

This study has several limitations. It was conducted in a single center. The cancer distribution in the study subjects was quite different compared to global statistics. In the future, the standardization of the study subjects can be considered. Second, this study was designed as a retrospective study. Data were collected by reviewing a medical record. There were a few missing data, but the missing values were negligible. In conclusion, the new prognostic model showed high accuracy in predicting mortality in active cancer patients with suspected infection. In the future, more intensive studies are needed to validate the new model in various sub-groups.

Conclusion

A new prognostic model in active cancer patients with suspected infection consisted of seven components: ECOG PS, distant metastasis, WBC, PT, albumin, creatinine, and lactate. The new model was superior to existing prognostic scoring systems such as SIRS, qSOFA, and SOFA. It can help physicians at ER to predict prognosis early and make a proper decision.

Reference

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국문요약

응급실에 내원한 감염이 의심되는 암환자의 예후 예측을 위한 새로운 예측 모델 개발과 타당성 검증

연구목적

전 세계적으로 암은 사회경제적 영향이 막대한 주요 질환이다. 최근 암의 유병률은 감소하고 있으나 항암 치료의 발전으로 인해 생존율과 함께 그로 인한 합병증 발생은 더 증가하고 있는 추세이다. 암환자들은 항암치료의 영향, 영양 불량, 잦은 카테터 삽입, 그리고 암 자체의 영향 등으로 면역력이 저하되어 일반 환자들보다 감염에 취약하다. 더불어 감염에 따른 패혈증, 패혈성 쇼크, 사망 등 불량한 예후 발생도 일반 환자에 비해 높은 편이다. 따라서, 암환자들의 감염을 조기에 인지하고 필요하다고 판단되는 경우 신속하고 적극적인 치료 개입을 하는 것은 매우 중요하다. 이에 본 연구는 임상적으로 감염이 의심되는 암환자의 예후 예측을 위한 새로운 모델을 개발하여 그것을 토대로 환자들의 위험도를 구분하여 검증하여 보다 빠르고 정확한 치료 방침을 제시하는 것을 목표로 하였다.

연구방법

본 연구는 2019 년 8 월부터 2019 년 12 월까지 서울아산병원 응급실로 내원한 임상적으로 감염이 의심되는 18 세 이상 활동성 암환자 998 명을 대상으로 진행되었다. 시간 순서대로 2019 년 8 월 1 일부터 9 월 30 일 사이 방문한 500 명의 환자 군을 대상으로 모델 개발을 하였고, 2019 년 10 월 1 일부터 12 월 18 일 사이에 방문한 498 명의 환자 군을 통하여 개발된 모형을 검증하였다.

환자들의 응급실 방문 당시의 인구통계학적 자료, 임상 자료 및 진단검사 자료들을 후향적으로 조사하여 사용하였다. 일차 결과는 장기사망률로 콕스 비례 위험 모형 분석으로 부트스트랩 재배열을 통하여 예측 변수들을 선택하였다. 선택된 변수들의 점수는 회귀 계수를 기준 값으로 나누어 계산하였다. 개발된 모델은 기존의 중증도 평가 도구들과 수신자 조작 특성 분석에 따른 곡선 하 면적을 이용하여 예측력을 비교 분석하였다.

연구결과

새로운 예후 예측 모델에 포함된 요인들은 전신 활동도 2 (2 점), 전신 활동도 3-4 (3 점), 원격 전이 (2 점), 백혈구 ≧ 10,000/mm^3 (1 점), 프로트롬빈 시간 ≧ 1.2 INR (1 점), 크레아티닌 ≧ 1.2 mg/dL (1 점), 젖산 ≧ 4.0 mmol/L (1 점), 알부민 2.5-3.5 g/dL (2 점), 알부민 < 2.5 g/dL (4 점) 이었다. 개발된 모델의 총점 분포는 0 점에서 13 점까지의 범위를 가진다.

각 점수 마다 분포된 환자수를 토대로 하여 저 위험군, 중간 위험군, 고 위험군 등 3 개의 위험군으로 분류하였다. 저 위험군 (총점 0-4)의 30 일 예측 사망률은 3.0-9.8%, 180 일 예측 사망률은 12.3-35.7%, 중간 위험군 (총점 5-8)의 30 일 예측 사망률은 13.0-29.3%, 180 일 예측 사망률은 45.0-77.4%, 고 위험군 (총점 9-13)의 30 일 예측 사망률은 37.5-79.5%, 180 일 예측 사망률은 86.7-99.9%로 서로 현저한 차이를 보였다. 개발된 새 예측 모델의 내부 검증 일치 인덱스는 0.729, 외부 검증의 일치 인덱스는 0.759 로 실제 사망률과 예측된 사망률 비교 시 검정 그래프가 유의하게 신뢰 구간을 벗어나지 않았다. 30 일 사망률에 대한 새 예측 모델과 기존의 중증도 및 예후 평가 기준들의 수신자 조작 특성 분석에 따른 곡선 하 면적을 비교해 보았을 때, 새 모델은 0.828 (95% 신뢰구간 0.790-0.867), SIRS 는 0.612 (95% 신뢰구간 0.556-0.669), qSOFA 는 0.681 (95% 신뢰구간 0.624-0.738), SOFA 는 0.752 (95% 신뢰구간 0.703-0.801)로 새 모델이 가장 높았다. 180 일 사망률에 대한 새 예측 모델과 기존의 중증도 및 예후 평가 기준들의 수신자 조작 특성 분석에 따른 곡선 하 면적은 새 모델이 0.810 (95% 신뢰구간 0.770-0.849), SIRS 0.531 (95% 신뢰구간 0.473-0.583), qSOFA 0.637 (95% 신뢰구간 0.587-0.686), SOFA 0.678 (95% 신뢰구간 0.630-0.725)로 역시 새 모델이 가장 높았다.

결론

본 연구에서는 감염이 의심되는 활동성 암환자들의 사망률 예측을 위해 개발된 모델에는 2 개의 암 특이적 특성으로 전신 수행 상태와 원격 전이, 5 개의 혈액검사 결과 변수로 백혈구, 프로트롬빈 시간, 알부민, 크레아티닌, 그리고 젖산이 포함되었다. 새 예후 예측 모델은 현재 사용되는 예후 예측 도구들과 비교하여 가장 우수한 예측력을 보였다.

중심단어

Suspected infection; Cancer; Mortality; ECOG PS; Distant metastasis; WBC; PT; Creatinine; Albumin; Lactate