Development and Validation of a New Risk Scoring System for Cancer Patients with Suspected Infection

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Abstract

Purpose: This study aimed to develop a new prognostic model for predicting 30-day 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 a single center. Adult active cancer patients with suspected infection were enrolled among visitors to the emergency room (ER). Logistic regression analysis was used to identify potential predictors for a new model.

Results: A total of 899 patients were included; 450 in the development cohort and 449 in the validation cohort. Six independent variables predicted 30-day mortality: Eastern Cooperative Oncology Group (ECOG) performance status (PS), peripheral oxygen saturation (SpO₂), creatinine, bilirubin, C-reactive protein (CRP), and lactate. The C-statistic of the new scoring system was 0.799 in the development cohort and 0.793 in the validation cohort. The C-statistics in the development cohort was significantly higher than those of SOFA [0.723 (95% CI: 0.663–0.783)], qSOFA [0.596 (95% CI: 0.537–0.655)], and SIRS [0.547 (95% CI: 0.483–0.612)].

Conclusions: The discriminative capability of the new cancer-specific risk scoring system was good in cancer patients with suspected infection. The new scoring system was superior to SOFA, qSOFA, and SIRS in predicting mortality.

Introduction

Patients with cancer are susceptible to infection, which can lead to poor outcomes. In a recent cohort study of 1 million sepsis hospitalizations in the United States, one in five cases was associated with malignancy, and in-hospital mortality was higher in cancer-related sepsis hospitalizations (27.9% vs. 19.5% in non-cancer-related sepsis).¹ The vulnerability of these patients to infection is driven by many factors, including their immunocompromised state caused by anti-cancer treatments, frequent use of broad-spectrum antibiotics, and indwelling catheters.^{2,3} Malnutrition caused by disruption of mucosal integrity and insufficient oral intake can also aggravate the immunosuppressive condition of these patients.⁴ Therefore, it is critical to recognize the severity of their condition and promptly provide appropriate treatment.

The clinical presentation of cancer patients with infection can differ from the typical signs and symptoms of infection alone. Immunomodulation can often prevent the onset of fever, even in severe cases of infection. Additionally, inflammatory markers can be elevated in both infectious and non-infectious patients with cancer.⁵ Organ dysfunction indicators such as elevated levels of creatinine or bilirubin, confused mentality, or respiratory distress are also often chronically held in patients with cancer regardless of infection. Such altered and inconstant clinical features can lead to an inaccurate understanding of the severity of the patient's condition and poor outcomes.

Existing severity scoring systems such as Systemic Inflammatory Response Syndrome (SIRS), Sequential Organ Failure Assessment (SOFA), and quick SOFA (qSOFA) have been used to predict the outcomes of critically ill patients.^{6,7} However, while studies have reported that SOFA is superior to qSOFA and SIRS, there have been few reports of the accuracy of these scoring systems to assess patients with cancer.^{8,9} There is no cancer-specific prognostic model that considers the characteristics of patients with cancer; therefore, to accurately risk-stratify these patients with suspected infection, a specialized, optimal prognostic model is needed. This study aimed to develop a new scoring system for predicting mortality in cancer patients with suspected infection.

Methods

Study design and patients

This study was retrospectively conducted in the emergency room (ER) of a tertiary referral center in Seoul, South Korea. Patients who attended the ER between August 1, 2019 and December 31, 2019 and met the following criteria were included in the study: 1) aged ≥ 18 years, 2) had active solid cancer, and 3) were suspected of having an infection and needed antibiotic treatment systemically by the physician. Active cancer was defined as any of the following; 1) cancer that has been newly diagnosed within 6 months of study initiation; 2) receiving anti-cancer treatment; and 3) cancer that has progressed within the past 6 months.⁸ All patients with suspected infection were performed with laboratory tests, blood and body fluid cultures, and imaging tests for detecting infection foci, and then administered antibiotics for therapeutic purposes. Patients diagnosed with hematologic malignancies, had already used antibiotics before the ER arrival, lost at follow-up, did not have adequate workup at the ER, or 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 ER visit, patients were divided into two groups: a development cohort from August 1st, 2019 to September 30th, 2019 and a validation cohort from October 1st, 2019 to December 31st, 2019. For multiple visits during the study period, only information on the first visit was collected. Any patient-identifying information was excluded from the study.

Data collection and evaluation

Data were collected retrospectively from the hospital's electronic medical records. Clinical variables included demographics, comorbidities, type of cancer, cancer stage, Eastern Cooperative Oncology Group (ECOG) performance status (PS)¹⁰, and initial vital signs, including mental status. Comorbidities, including hypertension, diabetes mellitus, chronic renal disease, chronic liver disease, chronic lung disease, and cardiovascular disease were analyzed based on the medical records at ER presentation. Mental status was assessed according to the Alert/responsive to Voice/responsive to Pain/Unresponsive (AVPU) scale. The AVPU values could be substituted to Glasgow Coma Scale (GCS) scores of 15, 13, 8, and 6, respectively.¹¹ A score of < 15 on the GCS was defined as an indication of 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 drawn from the catheter. Laboratory data included complete blood count, chemistry, electrolytes, coagulation battery, inflammatory markers such as C-reactive protein (CRP), and serum lactate. The first obtained value was used in cases with multiple test results. For lactate, the values higher than 15.0 mmol/L were reported as '>15.0 mmol/L'. The SIRS, qSOFA, and SOFA scores were calculated based on the ER's physiological and laboratory data.

Statistical analysis

The primary outcome was 30-day mortality. Data were reported as the mean $\pm$ standard deviation or median and inter-quartile range for continuous variables. They were compared between groups using the Student's *t*-test. Categorical variables were presented as the number and percentage and were compared using a chi-squared test.

To develop a new scoring system for 30-day mortality, univariate and multivariate logistic regression analyses were performed with an entering procedure in the development cohort. Results were summarized as odds ratios (OR) and respective 95% confidence intervals (CI). Variables with a *P*-value of < 0.1 in the univariate analysis and clinical relevance were considered for the multivariate analysis.

A simple risk score was devised using the penalized maximum likelihood estimates of the predictors in the multivariable model. The constant of the scoring system was defined as one-third of the regression coefficient of ECOG PS 3–4. 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 constant. The risk score's discrimination capability was assessed using the C-statistic. The calibration capability of the risk score was assessed by the Hosmer–Lemeshow test and calibration plot. Internal validation was performed by bootstrapping with 1000 iterations and calculated optimism-corrected C-statistic. The risk score was then categorized into low, intermediate, and high-risk groups based on the likelihood of 30-day mortality. A *P*-value of < 0.05 was considered statistically significant.^{12,13}

The predictive performances of the SOFA, qSOFA, SIRS scores, and the new scoring system were analyzed by using the area under the receiver operating characteristic (AUROC) values and compared with Delong's test. An AUROC 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 total population

Among the 1067 patients with cancer screened, 899 patients were included in the analysis: 450 in the development cohort and 449 in the validation cohort. The remaining 178 were excluded for the following

reasons: 111 patients had hematologic malignancies, 37 patients did not have adequate workup, 22 used antibiotics before ER arrival, and 8 were lost at follow-up (Supplementary S.1).

Baseline characteristics in total study subjects were shown in **Table 1**. The mean age was 63.0 ± 11.8 years, and the male was 55.6%. The most common cancer was lung cancer (19.2%), followed by biliary cancer (16.1%) and pancreatic cancer (13.9%). More than half of the total patients (55.6%) had distant metastasis, and 68.6% were under anti-cancer treatment. For ECOG PS, 29.9% had PS 0 to 1, 47.7% had PS 2, and 22.4% had PS 3 to 4. As lung and biliary cancer were dominant, lung and hepatobiliary infections were common in 24.4% and 25.1%, respectively. Between development and validation cohorts, there was no significant difference in baseline characteristics except anti-cancer treatment (64.2% vs. 73.1%, $P=0.004$). The overall 30-day mortality was 22.5%. There was a significant difference in the 30-day mortality rate between development and validation cohorts (19.3% and 25.6%, $P=0.024$).

Table 1. Baseline characteristics of total population

	Total (<i>n</i> = 899)	Development (<i>n</i> = 450)	Validation (<i>n</i> = 449)	<i>P</i> value
Age (years)	62.95 ± 11.80	63. 66 ± 11.92	62.24 ± 11.66	0.073
Sex- Male	500 (55.6)	262 (58.2)	238 (53.0)	0.116
Cancer type				
Lung	173 (19.2)	99 (22.0)	74 (16.5)	0.276
Biliary	145 (16.1)	71 (15.8)	74 (16.5)	
Pancreas	125 (13.9)	66 (14.7)	59 (13.1)	
Breast	86 (9.6)	41 (9.1)	45 (10.0)	
Liver	73 (8.1)	40 (8.9)	33 (7.3)	
Gynecology	69 (7.7)	29 (6.4)	40 (8.9)	
Stomach	47 (5.2)	23 (5.1)	24 (5.3)	
†Others	181 (20.1)	81 (18.0)	100 (22.3)	
Distant metastasis	499 (55.6)	248 (55.1)	251 (56.0)	0.782
Anti-cancer treatment	617 (68.6)	289 (64.2)	328 (73.1)	0.004
ECOG PS				
0 - 1	269 (29.9)	136 (30.2)	133 (29.6)	0.561
2	429 (47.7)	220 (48.9)	209 (46.5)	
3 - 4	201 (22.4)	94 (20.9)	107 (23.8)	
Infection focus				
Lung	219 (24.4)	114 (25.3)	105 (23.4)	0.181
Hepatobiliary	226 (25.1)	122 (27.1)	104 (23.2)	
GI & intra-abdominal	89 (9.9)	43 (9.6)	46 (10.2)	
UTI	79 (8.8)	45 (10.0)	34 (7.6)	
Unknown	140 (15.6)	63 (14.0)	77 (17.1)	
††Others	146 (16.2)	63 (14.0)	83 (18.5)	
30-day mortality	202 (22.5)	87 (19.3)	115 (25.6)	0.024

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

ECOG, Eastern Cooperative Oncology Group; GI, gastrointestinal; PS, performance status; UTI, urinary tract infection

† Others in cancer type: esophagus, duodenum, small bowel, colon, rectum, head & neck, prostate, renal, bladder, thymoma

†† Others in infection focus: bone & soft tissue, bacteremia, febrile neutropenia

Logistic regression analysis for 30-day mortality in the development cohort

Univariate and multivariate logistic regression analyses of a 30-day mortality were performed as shown in Table 2. In the univariate regression, age (OR 1.02; 95% CI: 1.00–1.04), male sex (OR 2.02; 95% CI: 1.22–3.36), distant metastasis (OR 2.07; 95% CI: 1.26–3.41), ECOG PS 2 (OR 4.87; 95% CI: 2.13–11.14), ECOG PS 3–4 (OR 10.44; 95% CI: 4.38–24.91), SpO₂ (OR 0.93; 95% CI: 0.87–0.99), altered mental status (OR 3.88; 95% CI: 1.37–11.02), creatinine (OR: 1.78; 95% CI: 1.41–2.24), total bilirubin (OR 1.07; 95% CI: 1.01–1.14), CRP (OR 1.07; 95% CI: 1.04–1.09), and lactate $\geq$ 2.0 mmol/L (OR 2.72; 95% CI: 1.69–4.39) were significantly associated with a 30-day mortality ($P < 0.05$ for all). In the multivariate regression analysis, ECOG PS 2 (OR 3.57; 95% CI: 1.60–7.96), ECOG PS 3–4 (OR 6.26; 95% CI: 2.67–14.71), SpO₂ (OR 0.90; 95% CI: 0.84–0.97), creatinine (OR 1.57; 95% CI: 1.25–1.98), total bilirubin (OR 1.09; 95% CI: 1.02–1.16), CRP (OR 1.06; 95% CI: 1.03–1.09), and lactate $\geq$ 2.0 mmol/L (OR 2.58; 95% CI: 1.49–4.48) were independent predictors of 30-day mortality.

Table 2
Logistic regression analysis of the 30-day mortality in the development cohort

	Univariate		Multivariate	
	OR (95% CI)	P value	OR (95% CI)	P value
Age	1.02 (1.00–1.04)	0.041		
Male	2.02 (1.22–3.36)	0.007		
Metastasis	2.07 (1.26–3.41)	0.004		
Anti-cancer treatment	0.66 (0.44–1.06)	0.088		
ECOG PS				
0–1	Reference		Reference	
2	4.87 (2.13–11.14)	< 0.001	3.57 (1.60–7.96)	0.002
3–4	10.44 (4.38–24.91)	< 0.001	6.26 (2.67–14.71)	< 0.001
SBP	0.99 (0.98–1.00)	0.208		
Heart rate	1.00 (0.99–1.02)	0.571		
SpO ₂	0.93 (0.87–0.99)	0.019	0.90 (0.84–0.97)	0.004
Altered mental status	3.88 (1.37–11.02)	0.011		
Creatinine	1.78 (1.41–2.24)	< 0.001	1.57 (1.25–1.98)	< 0.001
Total bilirubin	1.07 (1.01–1.14)	0.019	1.09 (1.02–1.16)	0.017
CRP	1.07 (1.04–1.09)	< 0.001	1.06 (1.03–1.09)	< 0.001
Lactate ≥ 2 mmol/L	2.72 (1.69–4.39)	< 0.001	2.58 (1.49–4.48)	0.001

CI, confidence interval; CRP, C-reactive protein; ECOG, Eastern Cooperative Oncology Group; OR, odds ratio; PS, performance status; SBP, systolic blood pressure; SpO₂, peripheral oxygen saturation

Development of a new risk scoring system

ECOG PS, SpO₂, creatinine, total bilirubin, CRP, and lactate were selected for the new scoring system. Allocated points for each variable were as follows; 1 point for each SpO₂ < 94%, creatinine ≥ 1.2 mg/dL, total bilirubin ≥ 1.2 mg/dL, CRP ≥ 10.0 mg/dL, 2 points for ECOG PS 2, lactate ≥ 2.0 mmol/L, and 3 points for ECOG PS 3–4. Finally, a 9-point risk scoring system with six variables was developed, as shown in Table 3. The calculation of the allocated point was described in Supplementary S.2.

Table 3
The new prognostic risk scoring
system for cancer patients with
suspected infection

Variables	score
ECOG PS 2	2
ECOG PS 3–4	3
SpO ₂ < 94%	1
Creatinine ≥ 1.2 mg/dL	1
Total bilirubin ≥ 1.2 mg/dL	1
CRP ≥ 10.0 mg/dL	1
Lactate ≥ 2.0 mmol/L	2
Total score	9

CRP, C-reactive protein; ECOG, Eastern Cooperative Oncology Group; PS, performance status; SpO₂, peripheral oxygen saturation;

The C-statistic of the new scoring system was 0.799 (95% CI: 0.752–0.846) in the development cohort and 0.793 (95% CI: 0.748–0.837) in the validation cohort. For internal validation, the optimism-corrected C-statistic was 0.784 (95% CI: 0.737–0.831). The calibration graphs show that the new scoring system's predicted and observed mortality risks in the development and validation cohorts were well-calibrated (Supplementary S.3). Additionally, the Hosmer–Lemeshow test did not indicate statistical significance for development ($\chi^2 = 3.84$, $df = 6$, $P = 0.698$) and validation cohorts ($\chi^2 = 5.40$, $df = 6$, $P = 0.493$). For predicting 30-day mortality in cancer patients with suspected infection, the new scoring system had a higher value of C-statistics than SOFA (0.723, 95% CI: 0.663–0.783, $P = 0.018$), qSOFA (0.596, 95% CI: 0.537–0.655, $P < 0.001$), and SIRS (0.547, 95% CI: 0.483–0.612, $P < 0.001$) (Fig. 1).

Discussion

We have developed a new cancer-specific scoring system for solid cancer patients with suspected infection. This new system had a strong discriminative power to predict 30-day mortality, showing a C-statistic of 0.799 in the development cohort and 0.793 in the validation cohort. In comparison with existing scoring systems, the new scoring system was superior to SOFA (C-statistic, 0.723), qSOFA (C-statistic, 0.596), and SIRS (C-statistic, 0.547). To our knowledge, our new prognostic model is the first cancer-specific scoring system to predict mortality for cancer patients with suspected infection.

This new scoring system was developed and validated in two groups of similar size, recruited at different times in the same hospital. There was no significant difference in baseline characteristics except anti-cancer treatment between the two development and validation cohorts. In our study, the overall 30-day

mortality rate was 22.5%. There was a difference in 30-day mortality between development and validation cohorts (19.3% vs. 25.6%, $P = 0.024$). However, the C-statistic (0.799 in the development cohort, 0.793 in the validation cohort) of our new scoring system showed a good discriminative capability to predict 30-day mortality in both groups. The Hosmer–Lemeshow goodness to fit test suggested that predicted mortality reflects true mortality, and thus our scoring system is well-calibrated. Several prognostic scoring systems have been used to predict prognosis in patients with infection.^{14–16} SOFA is one of the most frequently validated systems and is an excellent predictor of mortality.¹⁷ However, most of the SOFA studies were on non-cancer patients, and studies on those with cancer were limited with inconsistent results^{8,9,18}. In a recent study, SOFA had good discriminative power in patients with cancer and was superior to qSOFA.⁸ In two previous studies, both SOFA and qSOFA showed weak discriminative ability with a C-statistic of < 0.7 in predicting mortality for cancer patients with infection.^{9,18} As shown in this study, our new scoring system can be a good alternative to predict mortality in cancer patients with suspected infection.

The new cancer-specific scoring system consisted of six components: ECOG PS, SpO₂, creatinine, total bilirubin, CRP, and lactate. These six components reflect the underlying condition of patients with cancer and acute responses to infection. The ECOG PS of these patients has been considered as an essential prognostic factor.^{19,20} ECOG PS had the highest score distribution among the new scoring system variables in our study. Performance status is affected by many factors such as the patients' age, cancer stage, and side effects of anti-cancer treatment. Patients who have a poor PS and limited functional capacity tend to have more difficulty tolerating rigorous cancer treatments. These patients have less favorable outcomes than those with a better PS, regardless of distant metastasis or treatments given.²¹ In this study, ECOG PS was a significant prognostic factor in cancer patients with suspected infection, whereas advanced stage or anti-cancer treatment were not. Lactate represents tissue hypoperfusion, and lactate > 2 mmol/L was introduced as diagnostic criteria of septic shock.²² Furthermore, lactate has been shown to have prognostic power in cancer patients with sepsis.⁸ Increased CRP is an indicator of inflammation in patients with sepsis. A recent study reported that CRP carries significant independent prognostic information.²³, which was consistent with the results of our study; elevated CRP was associated with increased 30-day mortality in cancer patients with suspected infection. Creatinine and total bilirubin are indicators of hepatic and renal function, which are also components of SOFA.²⁴ SOFA included PaO₂/FiO₂ as a respiratory indicator. We used SpO₂ in place of PaO₂/FiO₂ given the ease to continuously and noninvasively obtain at the ER without drawing arterial blood. A previous study reported that SpO₂ was consistently associated with mortality in patients with septic shock.²⁵

This study has several limitations. First, it was conducted in a single hospital, which was a tertiary referral cancer center. There may have been a high proportion of severe disease. In our study, the 30-day mortality rate was 22.5%; however, in the US population report, cancer-related sepsis hospitalizations had high in-hospital mortality of 27.9%.¹ Second, this study used a retrospective design. However, there was very few missing data. In our hospital, there is a separate ER for patients with cancer²⁶, in which data collection

and the treatment process are standardized. Lastly, we included only solid tumors and excluded hematologic malignancies in this study. Generalization of applying the new scoring system to patients with hematologic malignancies is therefore difficult. Many studies have shown that prognosis of patients with solid tumors and hematologic malignancies is quite different.^{27,28} We consider that the prognostic model would have to be different to assess these two groups appropriately.

In conclusion, the new scoring system had a robust discriminative capability to predict prognosis in cancer patients with suspected infection. This new scoring system can be a good alternative for patients with cancer compared with existing scoring systems.

Conclusion

A new risk scoring system in active cancer patients with suspected infection consisted of six components: ECOG PS, SpO₂, creatinine, total bilirubin, CRP, and lactate. The new scoring system was superior to the existing scoring systems of SIRS, qSOFA, and SOFA in predicting 30-day mortality. We believe that our system can help physicians at the ER to predict prognosis for cancer patients more accurately and inform treatment decisions.

Declarations

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Authors' Contributions

Conceptualization: Yoon-Seon Lee, Methodology: Yoon-Seon Lee, Data acquisition and curation: Bora Chae, Formal analysis and investigation: Seonok Kim and Bora Chae, Writing the original draft: Bora Chae, Review and editing the manuscript: Yoon-Seon Lee and Bora Chae, Supervision: Yoon-Seon Lee

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Availability of data and material: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval: This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Institutional Review Board of of Asan medical center approved this study.

Consent to participate: Informed consent was waived by the Institutional Review Board of of Asan medical center in view of the retrospective nature of the study and all the procedures being performed

were part of the routine care.

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Figures

Figure 1

The AUROC of the new scoring system in the development cohort and the validation cohort (A) and comparison of the new scoring system with SOFA, qSOFA, and SIRS (B). The AUROC of the new scoring system was 0.799 (95% confidence interval, 0.752–0.846) in the development cohort and 0.793 (95% confidence interval, 0.747–0.838) in the validation cohort (A). The AUROC for the 30-day mortality was 0.723 (95% CI: 0.663–0.783, $P = 0.018$) for SOFA, 0.596 (95% CI: 0.537–0.655, $P < 0.001$) for qSOFA, and 0.547 (95% CI: 0.483–0.612, $P < 0.001$) for SIRS. AUROC, area under the receiver operating characteristic

curve; CI, confidence intervals; qSOFA, quick sequential organ failure assessment; SIRS, systemic inflammatory response syndrome; SOFA, sequential organ failure assessment

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