KJIM

Derivation and validation of modified early warning score plus SpO$_2$/FiO$_2$ score for predicting acute deterioration of patients with hematological malignancies

Ju-Ry Lee[1],*, Youn-Kyoung Jung[1], Hwa Jung Kim[2], Younsuck Koh[3], Chae-Man Lim[3], Sang-Bum Hong[3], and Jin Won Huh[3]

[1]Medical Emergency Team, Departments of [2]Clinical Epidemiology and Biostatistics and [3]Pulmonary and Critical Care Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Correspondence to
Jin Won Huh, M.D.
Department of Pulmonary and Critical Care Medicine, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea
Tel: +82-2-3010-3985
Fax: +82-2-3010-6968
E-mail: jwhuh@amc.seoul.kr

*Current affiliation: Department of Nursing, Koje University, Geoje, Korea

Background/Aims: Scoring systems play an important role in predicting intensive care unit (ICU) admission or estimating the risk of death in critically ill patients with hematological malignancies. We evaluated the modified early warning score (MEWS) for predicting ICU admissions and in-hospital mortality among at-risk patients with hematological malignancies and developed an optimized MEWS.

Methods: We retrospectively analyzed derivation cohort patients with hematological malignancies who were managed by a medical emergency team (MET) in the general ward and prospectively validated the data. We compared the traditional MEWS with the MEWS plus SpO$_2$/FiO$_2$ (MEWS_SF) score, which were calculated at the time of MET contact.

Results: In the derivation cohort, the areas under the receiver-operating characteristic (AUROC) curves were 0.81 for the MEWS (95% confidence interval [CI], 0.76 to 0.87) and 0.87 for the MEWS_SF score (95% CI, 0.87 to 0.92) for predicting ICU admission. The AUROC curves were 0.70 for the MEWS (95% CI, 0.63 to 0.77) and 0.76 for the MEWS_SF score (95% CI, 0.70 to 0.83) for predicting in-hospital mortality. In the validation cohort, the AUROC curves were 0.71 for the MEWS (95% CI, 0.66 to 0.77) and 0.83 for the MEWS_SF score (95% CI, 0.78 to 0.87) for predicting ICU admission. The AUROC curves were 0.64 for the MEWS (95% CI, 0.57 to 0.70) and 0.74 for the MEWS_SF score (95% CI, 0.69 to 0.80) for predicting in-hospital mortality.

Conclusions: Compared to the traditional MEWS, the MEWS_SF score may be a useful tool that can be used in the general ward to identify deteriorating patients with hematological malignancies.

Keywords: Clinical deterioration; Hematologic neoplasms; Modified early warning score; Prediction; SpO2/FiO2 ratio

INTRODUCTION

The survival of patients with hematological malignancies has recently improved because of advances in chemotherapy protocols and transplantation conditioning regimens [1,2]. Aggressive treatment and improved

general care has also led to an increased demand for intensive care among hospitalized patients with hematological malignancies [1]. Favorable outcomes may be associated with an appropriate timing of transfer to the intensive care unit (ICU) [3], and previous studies have suggested that up to 50% of cardiopulmonary arrests in the general ward could be prevented by earlier treatment and transfer to the ICU [4]. Azoulay et al. [5] reported that earlier ICU admission was associated with improved survival in critically ill patients with hematologic malignancies. However, resource limitations in ICUs can lead to patients staying longer in the general ward and receiving inadequate treatment [6]. Thus, delayed ICU admission can lead to physiological deterioration, prolonged hospitalization, high costs, and poor outcomes [3,6,7].

Previous studies have revealed that the involvement of a medical emergency team (MET) can reduce the rates of unplanned ICU admissions, cardiac arrests, and in-hospital mortality [8,9]. The modified early warning score (MEWS) is used to identify patients in the general ward who will benefit from involvement of a MET, as well as to predict ICU admissions and in-hospital mortality [10-12]. The MEWS tool is based on physiological variables that predict patient deterioration in high-risk cases and several studies have revealed that the MEWS can facilitate early ICU admissions, which results in better patient outcomes [10,11,13,14].

The National Institute for Health and Clinical Excellence [15] recommends routinely using a system for patient monitoring, such as the MEWS, in the hematology ward. This system should be able to provide early identification of at-risk patients and facilitate their referral to receive critical care before their deterioration. Although critical illness is characterized by physiological deterioration, there are few data to support the suggestion that the traditional MEWS can predict outcomes among patients with hematological malignancies [6,16,17]. Moreover, little is known regarding the effectiveness of the traditional MEWS for predicting outcomes among patients with hematological malignancies in the general ward. Therefore, the present study was conducted to evaluate the ability of the traditional MEWS to predict ICU admissions and mortality among patients with hematological malignancies in the general ward and to develop a modified MEWS based on these patients' characteristics.

METHODS

Study cohort

This study was approved by the Institutional Review Board of Asan Medical Center, Korea (IRB no.: 2016-0857). The need for informed consent was waived by the ethics committee as this study involved routinely collected medical data that were anonymously managed. This study enrolled two separate cohorts of deteriorating adult patients (aged ≥ 18 years) who received treatment from our MET in the general ward for hematological malignancies. All patients had been treated at the Asan Medical Center, which is a university-affiliated tertiary-care hospital in Seoul, South Korea. The center has approximately 2,700 beds, including 28 medical ICU beds, and treats approximately 100,000 adult patients each year.

The derivation cohort from which data were retrospectively collected included 220 deteriorating adult patients who received treatment from our MET in the general ward for hematological malignancies between January 2014 and November 2015. The validation cohort from which data were prospectively collected and retrospectively analyzed included 320 deteriorating adult patients in the hematological general ward between March 2016 and September 2017 (Fig. 1). The exclusion criteria were MEWSs that could not be calculated because of missing data, the implementation of not-for-resuscitation (NFR) before MET contact or within 24 hours after MET contact, and the MET being contacted to perform cardiopulmonary resuscitation (CPR).

The medical emergency team

The MET nurse practitioners, medical ICU residents, fellows, and staff performed MET activities daily if pre-defined vital signs or the laboratory threshold were reached by EMR monitoring or if a general word nurse or resident called the MET by telephone or pager [18]. In our hospital, the MET decided whether to transfer deteriorating patients to the ICU after initial assessment and treatment in the ward.

Data collection

Data were collected using case forms that were completed by the MET nurse practitioners and the patient's electronic medical records in both the derivation and
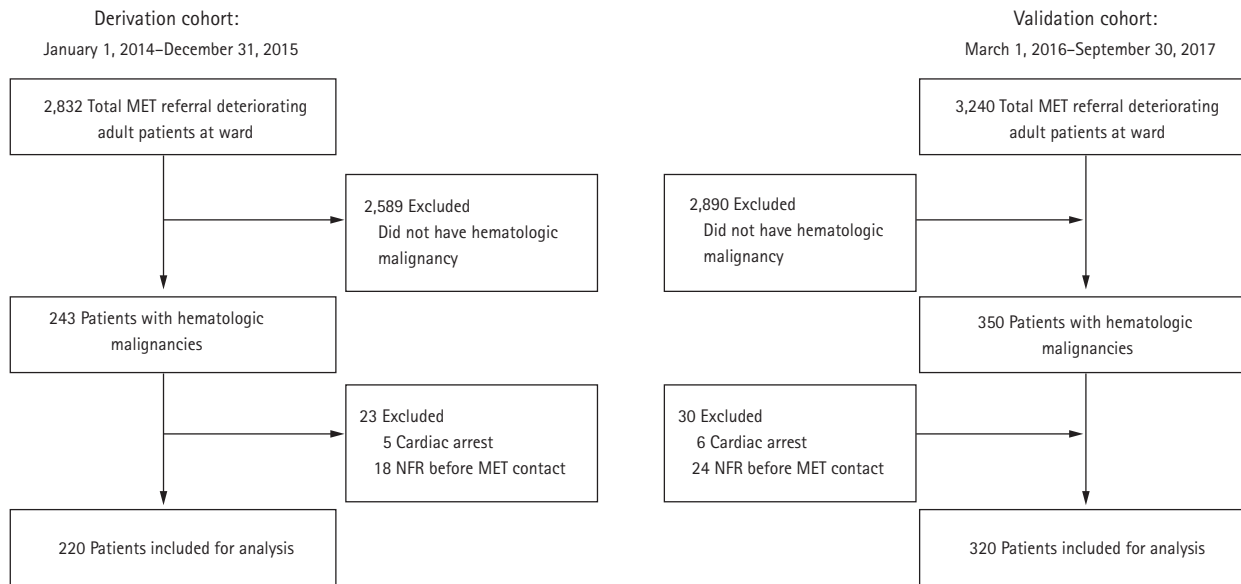
Derivation cohort:
January 1, 2014–December 31, 2015

Validation cohort:
March 1, 2016–September 30, 2017

2,832 Total MET referral deteriorating
adult patients at ward

3,240 Total MET referral deteriorating
adult patients at ward

2,589 Excluded
Did not have hematologic
malignancy

2,890 Excluded
Did not have hematologic
malignancy

243 Patients with hematologic
malignancies

350 Patients with hematologic
malignancies

23 Excluded
5 Cardiac arrest
18 NFR before MET contact

30 Excluded
6 Cardiac arrest
24 NFR before MET contact

220 Patients included for analysis

320 Patients included for analysis

Figure 1. Study flow chart. MET, medical emergency team; NFR, not for resuscitation.

validation cohorts. Variables were the demographic data, types of malignancies, comorbidities, disease status, bone marrow transplantation (BMT) or hematopoietic stem cell transplantation (HSCT) and type (autologous versus allogeneic), presence of graft-versus-host disease, presence of febrile neutropenia, performance status [19] at admission, reason for MET activation, physiological data, laboratory data, quick sequential organ failure assessment (qSOFA) score, sequential organ failure assessment (SOFA) score, NFR after MET activation, and MEWS. The traditional MEWS consisted of the systolic blood pressure, pulse rate, respiratory rate, body temperature, and mental status [11]. The components of the qSOFA [20], SOFA [21], and MEWS [11] are shown in Supplementary Table 1.

The SpO$_2$/FiO$_2$ (SF) ratio was derived noninvasively using pulse oximetry [19,22]. The SF ratio was scored based on a previous study [22]: SF scores of 0 points for > 315, 2 points for 236 to 315, and 3 points for ≤ 235. The primary outcome of this study was ICU admission. The secondary outcome was in-hospital mortality.

Statistical methods

Data are expressed as medians with interquartile ranges. Statistical analysis of the data was performed using chi-square analysis for categorical data and nonparametric

Wilcoxon tests for continuous data, as appropriate.

Univariate and multivariate logistic regression analyses were used to assess the MEWS and SF score as predictors of outcomes (ICU admission and in-hospital mortality). The multivariate analyses were adjusted for age, gender, comorbidities, underlying malignancies, disease status at admission, BMT recipients, performance status, the SOFA score, the qSOFA score, the reason for MET activation and NFR after MET activation, the MEWS, and the SF score. The results of these analyses were reported as odds ratios (ORs) with 95% confidence intervals (CIs).

Areas under the receiver-operating characteristic (AUROC) curves were calculated to evaluate the abilities of the MEWS, SF score, and MEWS plus SF (MEWS_SF) score to predict ICU admissions and in-hospital mortality. In these analyses, AUROC values of > 0.8 indicated good discrimination, values of 0.6 to 0.8 indicated moderate discrimination, and values of < 0.6 indicated poor discrimination [23]. We also calculated the sensitivities and specificities for predicting ICU admissions and in-hospital mortality.

Next, the prediction power of the MEWS, SF score, and MEWS_SF score were reassessed in the validation cohort. Differences with a p value of < 0.05 were considered statistically significant. All analyses were per-

Table 1. Baseline characteristic at admission in derivation and validation cohorts

Characteristic	Derivation cohort (n = 220)	Validation cohort (n = 320)	p
Age, yr	54 (42–63)	56 (45–65)	0.051
Male sex	135 (61.4)	197 (61.6)	1.000
Underlying malignancy			
Acute myeloid leukemia	91 (41.3)	118 (36.9)	0.098
Acute lymphoblastic leukemia	36 (16.4)	44 (13.8)	0.619
Chronic myeloid leukemia	1 (0.5)	4 (1.3)	0.653
Chronic lymphoblastic leukemia	5 (2.3)	0	0.011
Lymphoma	52 (23.6)	86 (26.8)	0.182
Myeloma	10 (4.5)	25 (7.8)	0.156
Aplastic anemia	6 (2.7)	6 (1.9)	0.765
Myelodysplasia	19 (8.7)	37 (11.6)	0.316
Comorbidity			
Chronic lung disease	5 (2.3)	9 (2.8)	0.788
Chronic heart disease	58 (26.4)	61 (19.1)	0.052
Chronic renal disease	4 (1.8)	8 (2.5)	0.769
Chronic liver disease	13 (5.9)	13 (4.1)	0.414
Cerebral vascular disease	14 (6.4)	14 (4.4)	0.055
Disease status at admission			
Newly diagnosis	48 (21.8)	54 (16.9)	0.179
Relapsed/refractory	141 (64.1)	213 (66.6)	0.581
Partial remission	4 (1.8)	16 (5.0)	0.064
Complete remission	28 (12.7)	37 (11.6)	0.688
BMT/HSCT recipient	91 (41.4)	116 (36.2)	0.242
Autologous	16 (7.3)	23 (8.1)	0.482
Allogeneic	75 (34.1)	90 (28.1)	0.172
GVHD	31 (14.1)	30 (9.4)	0.098
Reason for admission			0.301
Scheduled treatment	156 (70.9)	213 (66.6)	
Acute event	64 (29.1)	107 (33.4)	
ECOG[a] performance status, grade			< 0.001
0	38 (17.3)	88 (27.5)	0.007
1	56 (25.5)	75 (23.4)	0.610
2	99 (45.0)	90 (28.1)	< 0.001
3	27 (12.3)	55 (17.2)	0.143
4	0	12 (3.8)	0.002

Values are presented as median (interquartile range) or number (%).

BMT, bone marrow transplantation; HSCT, hematopoietic stem cell transplantation; GVHD, graft versus host disease; ECOG, Eastern Cooperative Oncology Group.

[a]Grade 0, fully active, grade 1 restricted in physically strenuous activity but ambulatory and able to carry out work of a light; grade 2, ambulatory and capable of all self care but unable to carry out any work activities; grade 3, capable of only limited self care, confined to bed or chair more than 50% of walking hours; grade 4, completely disabled. Totally confined to bed or chair.

Lee JR, et al. Usefulness of MEWS plus SpO_2/FiO score

KJIM

formed using IBM SPSS software version 20.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Derivation cohort

A total of 2,832 deteriorating ward patients had MET contact during the derivation period, and 243 patients with hematologic malignancies were included. Eighteen patients who received NFR after MET contact, and 5 patients who were MET-activated by CPR were excluded. Finally, 220 patients were enrolled in the derivation cohort.

The characteristics at admission of these 220 patients are shown in Table 1. The median patient age was 54 years (interquartile range [IQR], 42 to 63), and 61.4% were male. The most common hematological malignancies were acute myeloid leukemia (41.3%) and lymphoma (23.6%). The disease status at admission was relapsed or refractory in 64.1% of the patients.

Table 2 describes the laboratory and clinical outcomes at MET contact. The main reasons for MET contact were respiratory distress (55.5%), sepsis or septic shock (26.8%), and altered mental status (4.5%). The median MEWS and SF score were 6 (IQR, 4 to 7) and 2 (IQR, 0 to 3). The ICU admission rate and in-hospital mortality rate were 46.8% and 51.8%%, respectively.

The univariate analyses revealed that ICU admission was significantly associated with BMT/HSCT recipients (OR, 1.89; 95% CI, 1.10 to 3.25), the MEWS (OR, 1.89; 95% CI, 1.57 to 2.28), the SF score (OR, 1.59; 95% CI, 1.30 to 1.95), and the SOFA score (OR, 1.12; 95% CI, 1.02 to 1.24) (Supplementary Table 2). The multivariate analyses revealed that ICU admission was independently associated with the MEWS (OR, 2.20; 95% CI, 1.67 to 2.78) and SF score (OR, 2.11; 95% CI, 1.47 to 3.02) (Table 3).

The AUROC curves for predicting ICU admissions using the MEWS, SF score, and MEWS_SF score are shown in Fig. 2. The AUROC values were 0.69 for the SF score, 0.81 for the MEWS, and 0.87 for the MEWS_SF score; both the MEWS and MEWS_SF score were considered to have good discriminatory value. The cut-off value for predicting ICU admission using the MEWS was 6 (sensitivity: 77.7%, specificity: 74.4%, positive predictive value: 72.7%, negative predictive value: 79.1%), and the cut-

off value using the MEWS-SF score was 7 (sensitivity: 83.5%, specificity: 80.3%, positive predictive value: 79.0%, negative predictive value: 84.7%) (Table 4).

The univariate analyses revealed that in-hospital mortality was significantly associated with respiratory distress (OR, 2.08; 95% CI, 1.21 to 3.60), the MEWS (OR, 1.34; 95% CI: 1.20 to 1.57), the SF score (OR, 1.80; 95% CI, 1.45 to 2.22), the SOFA score (OR, 1.13; 95% CI, 1.02 to 1.24), and NFR after MET activation (OR, 2.00; 95% CI, 1.04 to 3.81) (Supplementary Table 3). The multivariate analyses revealed that ICU admission was independently associated with the MEWS (OR, 2.01; 95% CI, 1.48 to 2.72) and SF score (OR, 2.01; 95% CI, 1.48 to 2.72) (Table 5). The AUROC curves for predicting in-hospital mortality using the MEWS, SF score, and MEWS_SF score are shown in Fig. 3. The AUROC values were 0.69 for the SF score, 0.70 for the MEWS, and 0.76 for the MEWS_SF score. The cut-off value for predicting in-hospital mortality using the MEWS was 6 (sensitivity: 70.2%, specificity: 71.7%, positive predictive value: 72.7%, negative predictive value: 69.1%), and the cut-off value using the MEWS-SF score was 7 (sensitivity: 71.9%, specificity: 60.4%, positive predictive value: 66.1%, negative predictive value: 66.7%) (Table 6).

Validation cohort

A total of 3,240 deteriorating ward patients had MET contact during the validation period, and 350 deteriorating ward patients with hematologic malignancies were included. Twenty-four patients who received NFR before MET contact and six patients who were MET-activated by CPR were excluded. We evaluated this separate cohort of 320 patients to test the validity of the MEWS_SF score. Only the Eastern Cooperative Oncology Group performance status and rate of NFR after MET activation showed significant differences between the derivation and validation cohorts.

In the validation cohort, the AUROC curves for predicting ICU admissions using the MEWS, SF score, and MEWS_SF score are shown in Fig. 2. The AUROC values were 0.71 for the SF score, 0.71 for the MEWS, and 0.83 for the MEWS_SF score. The MEWS_SF score was considered to have good discriminatory value compared to the MEWS. The cut-off value for predicting ICU admission using the MEWS was 6 (sensitivity: 67.9%, specificity: 60.1%, positive predictive value: 63.6%, negative

Table 2. Characteristic and outcomes activated medical emergency team in derivation and validation cohorts

Characteristic	Derivation cohort (n = 220)	Validation cohort (n = 320)	p value
Major reasons for MET contact			
Respiratory distress	122 (55.5)	178 (55.6)	1.000
Sepsis/septic shock	59 (26.8)	65 (20.3)	0.095
Hypovolemic shock	7 (3.2)	10 (3.1)	1.000
Altered mental status	10 (4.5)	21 (6.6)	0.353
Metabolic acidosis	14 (6.4)	21 (6.6)	0.858
Others	8 (3.6)	25 (7.8)	0.104
Systolic blood pressure, mmHg	109 (88–131)	112 (88–140)	0.546
Heart rate, beats/min	123 (106–138)	120 (104–135)	0.207
Respiratory rate, breath/min	28 (24–32)	28 (22–34)	0.304
Body temperature, °C	37.4 (36.6–38.2)	37.5 (36.6–38.2)	0.989
Mental status (AVPU scale)			
Alert	164 (74.5)	219 (68.4)	0.148
Verbal	23 (10.5)	19 (5.9)	0.071
Pain	12 (5.5)	34 (10.6)	0.051
Unresponsive	21 (9.5)	48 (15.0)	0.067
SpO_2, %	96 (92–98)	96 (93–98)	0.454
Laboratory at MET contact			
Lactic acid, mmoL/L	2.6 (1.7–4.7)	2.2 (1.4–3.7)	0.104
Neutropenia[a]	95 (43.2)	83 (37.2)	0.209
Modified early warning score	6 (4–7)	6 (4–7)	0.208
SpO_2/FiO_2 ratio	297 (204–438)	270 (194–428)	0.216
SpO_2/FiO_2 score[b]	2 (0–3)	2 (0–3)	0.366
qSOFA score	1 (1–2)	1 (1–2)	0.141
SOFA score	6 (5–8)	6 (4–8)	0.376
ICU admission	103 (46.8)	162 (50.6)	0.431
NFR after MET activation	51 (23.2)	130 (40.6)	< 0.001
In-hospital mortality	114 (51.8)	169 (52.8)	0.861

Values are presented as number (%) or median (interquartile range).

MET, medical emergency team; AVPU, alert, verbal, pain, unresponsive; qSOFA, quick sequential organ failure assessment; SOFA, sequential organ failure assessment; ICU, intensive care unit; NFR, not for resuscitation.

[a]Neutropenia, absolute neutrophil count < 500/μL.

[b]SpO_2/FiO_2 score, 0 points for > 315, 2 points for ≤ 315 SpO_2/FiO_2 ratio < 235, 3 points for ≤ 235.

predictive value: 64.6%), and the cut-off value using the MEWS_SF score was 7 (sensitivity: 85.2%, specificity: 65.2%, positive predictive value: 71.5%, negative predictive value: 81.1%) (Table 4).

The AUROC curves for predicting in-hospital mortality using the MEWS, SF score, and MEWS_SF score are shown in Fig. 3. The AUROC values were 0.69 for the SF score, 0.64 for the MEWS, and 0.74 for the MEWS_SF score. The cut-off value for predicting in-hospital mortality using the MEWS was 6 (sensitivity: 62.1%, specificity: 55.0%, positive predictive value: 60.7%, negative predictive value: 56.5%), and the cut-off value using the MEWS_SF score was 7 (sensitivity: 80.5%, specificity: 62.3%, positive predictive value: 70.5%, negative predictive value: 74.0%) (Table 6).

Lee JR, et al. Usefulness of MEWS plus SpO$_2$/FiO score

KJIM

Table 3. Multivariate analyses for intensive care unit admission in derivation cohort and validation cohort

Variable	Derivation cohort[a]	Validation cohort[b]
	OR (95% CI)	OR (95% CI)
SpO$_2$/FiO$_2$ score[c]	2.11 (1.47–3.02)[d]	2.20 (1.64–3.00)[d]
MEWS	2.20 (1.67–2.78)[d]	1.70 (1.40–2.10)[d]

Adjusted for age, sex, comorbidity, underlying malignancies, disease status at admission, bone marrow transplantation/hematopoietic stem cell transplantation recipient, performance status, sequential organ failure assessment (SOFA) score, quick sequential organ failure assessment (qSOFA) score and major reason for medical emergency team (MET) activation. Performance status and major reason for MET activation.

OR, odds ratio; CI, confidence interval; MEWS, modified early warning score.

[a]Hosmer Lemishow test ($p = 0.377$).

[b]Hosmer Lemishow test ($p = 0.326$).

[c]SpO$_2$/FiO$_2$ score, 0 points for > 315, 2 points for ≤ 315 SpO$_2$/FiO$_2$ ratio < 235, 3 points for ≤ 235.

[d]$p < 0.001$.

	AUC	95% CI	p value
MEWS	0.81	0.76–0.87	< 0.001
MEWS_SF score	0.87	0.82–0.92	< 0.001
SF score	0.69	0.62–0.76	< 0.001

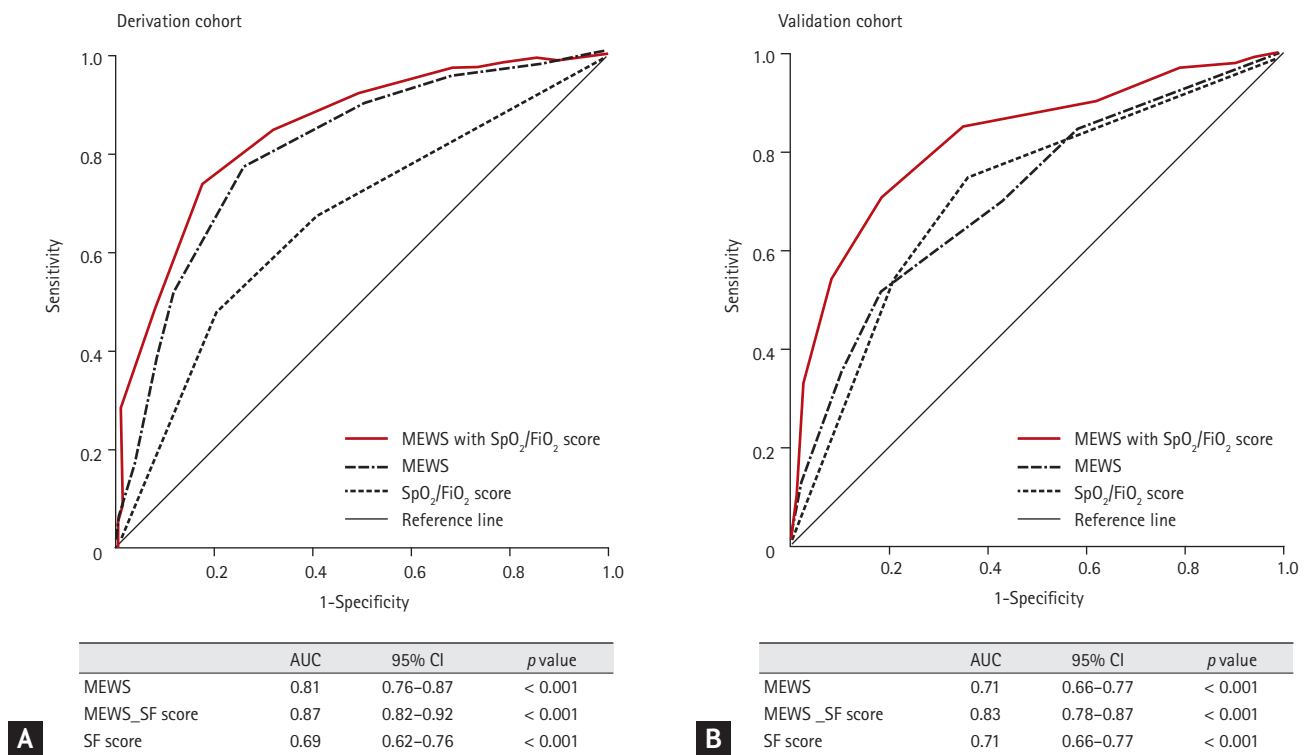|	AUC	95% CI	p value
MEWS	0.71	0.66–0.77	< 0.001
MEWS _SF score	0.83	0.78–0.87	< 0.001
SF score	0.71	0.66–0.77	< 0.001

Figure 2. The receiver operator characteristic curves of modified early warning score (MEWS) and MEWS plus SpO$_2$/FiO$_2$ to predict intensive care unit admission after medical emergency team activation (SpO$_2$/FiO$_2$ scores of 0 points for > 315, 2 points for ≤ 315 SpO$_2$/FiO$_2$ ratio < 235, 3 points for ≤ 235). (A) Derivation cohort. (B) Validation cohort. AUC, area under the curve; CI, confidence interval; SF score, SpO$_2$/FiO$_2$ score.

DISCUSSION

The present study revealed that the MEWS_SF score provided an improved ability to predict ICU admission and in-hospital mortality, compared to the traditional MEWS, among deteriorating patients in a hematology ward. In this study, we evaluated the effectiveness of the MEWS among this specific high-risk population and modified the MEWS based on the characteristics of patients who are at risk of deterioration in the general

Table 4. Multivariate analyses for in-hospital mortality in derivation cohort and validation cohort

Variable	Derivation cohort[a]	Validation cohort[b]
	OR (95% CI)	OR (95% CI)
SpO_2/FiO_2 score[c]	2.01 (1.48–2.72)[d]	2.01 (1.49–2.72)[d]
MEWS	1.50 (1.24–1.81)[d]	1.51 (1.23–1.85)[d]

Adjusted for age, gender, comorbidity, underlying malignancies, disease status at admission, bone marrow transplantation/hematopoietic stem cell transplantation recipient, performance status, sequential organ failure assessment (SOFA) score, quick sequential organ failure assessment (qSOFA) score, major reason for medical emergency team (MET) activation and not for resuscitation after MET activation.
OR, odds ratio; CI, confidence interval; MEWS, modified early warning score.
[a]Hosmer Lemishow test ($p = 0.521$).
[b]Hosmer Lemishow test ($p = 0.295$).
[c]SpO_2/FiO_2 score, 0 points for > 315, 2 points for ≤ 315 SpO_2/FiO_2 ratio < 235, 3 points for ≤ 235.
[d]$p < 0.001$.

Table 5. Sensitivity and specificity according to cutoff of risk score for intensive care unit admission in derivation and validation cohort

Score	Cut-off	Derivation cohort				Validation cohort			
		Sensitivity, %	Specificity, %	PPV, %	NPV, %	Sensitivity, %	Specificity, %	PPV, %	NPV, %
MEWS	5	90.3	50.4	61.6	85.5	84.5	41.1	59.6	72.2
	6	77.7	74.4	72.7	79.1	67.9	60.1	63.6	64.6
	7	52.4	88.9	80.6	68.0	51.9	81.6	74.3	62.3
MEWS_ SF score	6	92.2	59.0	66.4	89.6	90.7	38.6	60.2	80.3
	7	83.5	80.3	79.0	84.7	85.2	65.2	71.5	81.1
	8	59.2	89.7	83.6	71.4	71.0	81.6	79.9	73.3

PPV, positive predictive value; NPV, negative predictive value; MEWS, modified early warning score; SF, SpO_2/FiO_2.

hematology ward. Multivariate logistic regression analysis revealed that both the SF score and MEWS are independently associated with ICU admissions and in-hospital mortality.

Several previous studies have shown that > 30% of patients with hematological malignancies develop pulmonary complications and approximately 50% of these patients are admitted to an ICU [1,5,24,25]. Other studies have identified acute respiratory failure as a common reason for ICU admission among deteriorating patients with hematological malignancies [26,27]. Furthermore, previous studies have revealed that tachypnea, oxygenation parameters, and the PaO_2/FiO_2 ratio predict ICU admissions and mortality among patients with hematological malignancies [28,29]. However, arterial blood gas analysis in these patients with coagulopathy is difficult to perform routinely. The SF ratio provides a non-invasive measure of hypoxemia severity and has been proposed as a substitution for the PaO_2/FiO_2 ratio [22,30]. Sanz et al. [30] suggested that SpO_2 may be sufficient for estimating PaO_2/FiO_2, and an early assessment of oxygen status using the SF ratio can be used to screen for patients that should be admitted to the ICU. The present study showed that the most common reason for ICU admission is respiratory distress requiring oxygen support; thus, we suggest that the SF score can be used to identify deteriorating patients in the general ward.

Mulligan [31] evaluated 71 patients with hematological malignancies in the general ward using two tools: the "trust tool" (an observation chart in which a single abnormal parameter is used to identify at-risk patients) and early warning score (EWS) that was developed by Morgan et al. [32]. The EWS was the first reported track and triggering system (T&TS), and many T&TSs have
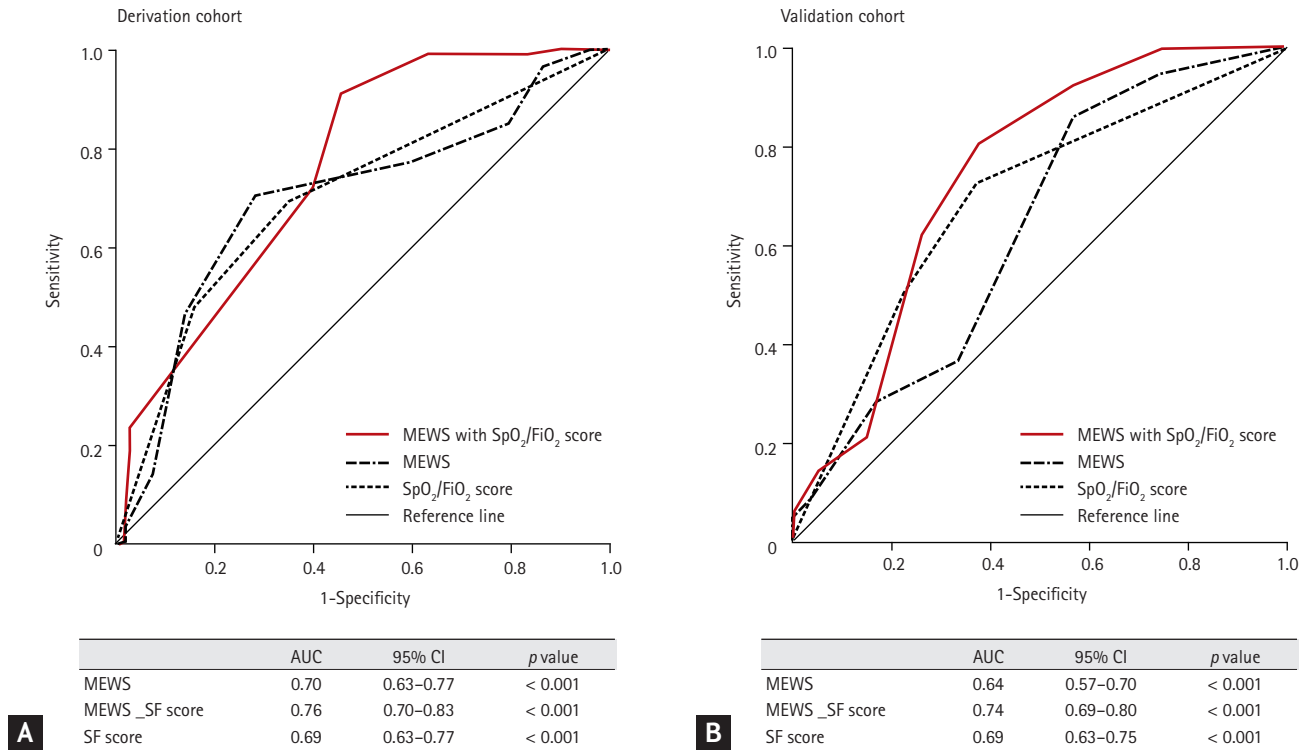
Lee JR, et al. Usefulness of MEWS plus SpO$_2$/FiO score

KJIM

	AUC	95% CI	p value
MEWS	0.70	0.63–0.77	< 0.001
MEWS _SF score	0.76	0.70–0.83	< 0.001
SF score	0.69	0.63–0.77	< 0.001

A

	AUC	95% CI	p value
MEWS	0.64	0.57–0.70	< 0.001
MEWS _SF score	0.74	0.69–0.80	< 0.001
SF score	0.69	0.63–0.75	< 0.001

B

Figure 3. The receiver operator characteristic curves of modified early warning score (MEWS) and MEWS plus SpO$_2$/FiO$_2$ to predict in-hospital mortality after medical emergency team activation (SpO$_2$/FiO$_2$ scores of 0 points for > 315, 2 points for ≤ 315 SpO$_2$/FiO$_2$ ratio < 235, 3 points for ≤ 235). (A) Derivation cohort. (B) Validation cohort. AUC, area under the curve; CI, confidence interval; SF score, SpO$_2$/FiO$_2$ score.

Table 6. Sensitivity and specificity according to cutoff of risk score for in-hospital mortality in derivation and validation cohort

Score		Derivation cohort				Validation cohort			
	Cut-off	Sensitivity, %	Specificity, %	PPV, %	NPV, %	Sensitivity, %	Specificity, %	PPV, %	NPV, %
MEWS	5	77.2	40.6	58.3	62.3	85.8	43.7	63.0	73.3
	6	70.2	71.7	72.7	69.1	62.1	55.0	60.7	56.5
	7	46.5	85.8	77.9	59.8	36.7	66.2	54.9	48.3
MEWS_ SF score	6	99.1	36.8	62.8	97.5	100.0	25.2	64.7	59.9
	7	71.9	60.4	66.1	66.7	80.5	62.3	70.5	74.0
	8	57.9	71.7	68.8	61.3	37.9	51.6	27.1	63.6

PPV, positive predictive value; NPV, negative predictive value; MEWS, modified early warning score; SF, SpO$_2$/FiO$_2$.

subsequently been developed (i.e., the MEWS) [16]. Mulligan's revealed that the Trust tool and EWS (using a trigger score of 3) have high sensitivities (both 82%), but low specificities (7% and 17%, respectively). Cooksley et al. [33] reported that the current T&TSs (the MEWS used at the Christie Hospital and National Early Warning Score) have poor discriminatory values for identifying patients with malignancies who are at-risk of deterio-

rating and requiring ICU admission. Moreover, several studies have shown that improved sensitivity and specificity for the MEWS could be achieved by modifying the measure reflecting the patients' characteristics and settings [6,15,16]. Because the findings of previous studies may have limited applicability to patients with hematological malignancies, we herein compared and analyzed the MEWS and SF score to improve the predictive power

of ICU admission in this specific patient group.

We modified the traditional MEWS using the SF score as an oxygenation index, given that respiratory failure is the main cause of ICU admissions among patients in the hematology ward. In our study, the estimation of FiO_2 in patients with spontaneous breathing was difficult. Indeed, FiO_2 depends not only on the oxygen flow rate, but also on several factors such as the respiratory rate, tidal volume, device used to deliver oxygen, and oxygen leaks [34]. However, because our study population comprised deteriorating ward patients who were not using a ventilator, they could not undergo correct FiO_2 measurements (they used a variety of O_2 devices, such as a nasal prong, venturi-mask, simple mask, etc.) Our study used the $SpO2/FiO_2$ score, which was validated as a noninvasive surrogate of the P/F ratio in mechanically ventilated patients in the ICU setting [22]. To minimize limitations, we performed a prospective validation study using a separate cohort. Our findings indicate that, compared to the traditional MEWS, the MEWS_SF score had a better ability to predict ICU admissions among patients with hematological malignancies.

The present study has several limitations. Our study was undertaken at a single center, which may have been associated with known risks of bias. Transfer to the ICU might have been affected by the attending clinician or occupancy rate of the ICU. Additionally, in-hospital mortality might have been affected by several factors, such as severity, disease status, and NFR after MET activation. However, we included and NFR after MET activation. However, we include the validation cohort to minimize these issues. Moreover, we performed multivariate analysis adjusted for baseline characteristics including severity, disease status, performance status, BMT/HSCT recipients and NFR after MET activation to improve causality.

In conclusion, the MEWS_SF score is superior to the traditional MEWS for identifying patients with hematological malignancies in the general ward who are at-risk for requiring intensive care and predicting in-hospital mortality. These findings suggest that oxygen monitoring is important in at-risk patients with hematological malignancies, and the MEWS_SF score may be a useful screening tool for determining ICU transfer and predicting in-hospital mortality in deteriorating patients with hematological malignancies.

KEY MESSAGE

1. The modified early warning score plus SpO_2/FiO_2 (MEWS_SF) score is superior to the traditional MEWS to identify patients with hematological malignancies in the general ward who are at-risk for requiring intensive care.
2. The MEWS_SF score is superior to the traditional MEWS to predict in-hospital mortality in deteriorating ward patients with hematological malignancies.
3. The MEWS_SF score may be a useful screening tool to determine intensive care unit transfer, and predict in-hospital mortality in deteriorating patients with hematological malignancies.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Lee JR, et al. Usefulness of MEWS plus SpO$_2$/FiO score

KJIM

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Lee JR, et al. Usefulness of MEWS plus SpO$_2$/FiO score

KJIM

Supplementary Table 1. Components of scoring systems in patients with critically ill

Scoring systems				Items			
qSOFA [20]	Respiratory rate ≥ 22/min						
	Altered mentation						
	Systolic blood pressure ≥ 100 mmHg						
MEWS [11]	3 Point	2 Point	1 Point	0 Point	1 Point	2 Point	3 Point
Systolic blood pressure, mmHg	≤ 70	71 to 80	81 to 100	101 to 199		≥ 200	
Heart rate, beats/min		≤ 40	41 to 50	51 to 100	101 to 110	111 to 129	≥ 130
Respiratory rate, breaths/min		< 9		9 to 14	15 to 20	21 to 29	≥ 30
Temperature, °C		< 35.0		35.0 to 38.4		≥ 38.5	
Conscious level				Alert	Reacting to voice	Reacting to pain	Unresponsive
SOFA [21]	0 Point	1 Point	2 Point	3 Point		4 Point	
PaO$_2$/FiO$_2$	≥ 400	< 400	< 300	< 200 with respiratory support		< 100 with respiratory support	
Platelet, × 10^3/μL	≥ 150	< 150	< 100	< 50		< 20	
Total bilirubin, mg/dL	< 1.2	1.2 to 1.9	2.0 to 5.9	6.0 to 12.0		> 12.0	
Cardiovascular (hypotension)	MAP ≥ 70	MAP < 70	Dopamine ≤ 5 or dobutamine	Dopamine > 5 or epinephrine ≤ 0.1 or norepinephrine ≤ 0.1		Dopamine > 15 or epinephrine > 0.1 or norepinephrine > 0.1	
GCS	15	13 to 14	10 to 12	6 to 9		< 6	
Creatinine (mg/dL) or urine output (mL/day)	< 1.2	1.2 to 1.9	2.0 to 3.4	3.5 to 5.0 Urine output < 500		> 5.0 Urine output < 200	

qSOFA, quick sepsis-related organ failure assessment; MEWS, modified early warning score; SOFA, sepsis-related organ failure assessment; MAP, mean arterial pressure; GCS, Glasgow coma scale.

Supplementary Table 2. Univariate analysis for intensive care unit admission in derivation and validation cohorts

Characteristic	Derivation cohort	Validation cohort
	OR (95% CI)	OR (95% CI)
Age, yr	1.00 (0.99–1.02)	1.00 (0.98–1.01)
Male sex	1.10 (0.64–1.90)	0.84 (0.54–1.32)
Underlying malignancies		
Acute myeloid leukemia	1.13 (0.67–1.93)	0.65 (0.41–1.04)
Acute lymphoblastic leukemia	1.54 (0.74–3.21)	1.66 (0.87–3.18)
Lymphoma	0.73 (0.37–1.44)	0.81 (0.50–1.30)
Myeloma	1.14 (0.32–4.10)	2.20 (0.92–5.25)
Aplastic anemia	0.28 (0.30–2.52)	0.98 (0.20–4.90)
Myelodysplasia	1.63 (0.63–4.22)	1.17 (0.59–2.32)
Comorbidity		
Chronic lung disease	0.28 (0.03–2.52)	0.78 (0.20–2.94)
Chronic heart disease	1.74 (0.95–3.18)	1.10 (0.63–1.91)
Chronic renal disease	1.14 (0.16–8.23)	3.00 (0.60–15.09)
Chronic liver disease	1.89 (0.60–6.00)	0.28 (0.08–1.03)
Cerebral vascular disease	1.15 (0.39–3.38)	0.38 (0.07–2.00)
Disease status at admission		
Newly diagnosis	0.95 (0.50–1.81)	2.22 (1.20–4.11)[a]
Relapsed/refractory	1.46 (0.85–2.51)	0.76 (0.48–1.21)
Partial remission	0.37 (0.04–3.64)	1.27 (0.46–3.49)
Complete remission	0.70 (0.31–1.58)	0.56 (0.28–1.12)
BMT/HSCT recipient	1.89 (1.10–3.25)[a]	1.49 (0.94–2.40)
ECOG performance status	1.12 (0.84–1.50)	1.07 (0.88–1.29)
Major reasons for MET activation		
Respiratory distress	1.15 (0.67–2.00)	1.22 (0.78–1.89)
Sepsis/septic shock	1.14 (0.63–2.07)	0.86 (0.50–1.49)
Hypovolemic shock	0.44 (0.08–2.33)	0.64 (0.18–2.32)
Altered mental status	4.84 (1.00–23.35)	2.59 (0.98–6.84)
Metabolic acidosis	0.32 (0.89–1.20)	0.58 (0.23–1.44)
Laboratory at MET activation		
Lactic acid, mmoL/L	0.98 (0.91–1.05)	1.08 (1.00–1.18)
Neutropenia[b]	1.04 (0.61–1.77)	1.16 (0.67–2.00)
Modified early warning score	1.89 (1.57–2.28)[c]	1.47 (1.30–1.66)[d]
SpO_2/FiO_2 score[e]	1.59 (1.30–1.95)[c]	1.87 (1.57–2.23)[d]
qSOFA score	1.07 (0.65–1.77)	0.83 (0.58–1.17)
SOFA score	1.12 (1.02–1.24)[a]	1.35 (1.22–1.50)[d]

OR, odds ratio; CI, confidence interval; BMT, bone marrow transplantation; HSCT, hematopoietic stem cell transplantation; ECOG, Eastern Cooperative Oncology Group; MET, medical emergency team; qSOFA, quick sequential organ failure assessment; SOFA, sequential organ failure assessment.

[a]$p < 0.05$.
[b]Neutropenia, absolute neutrophil count $< 500/\mu L$.
[c]$p < 0.01$.
[d]$p < 0.001$.
[e]SpO_2/FiO_2 score, 0 points for > 315, 2 points for ≤ 315 SpO_2/FiO_2 ratio < 235, 3 points for ≤ 235.

Supplementary Table 3. Univariate analysis for in-hospital mortality in derivation and validation cohorts

Characteristic	Derivation cohort OR (95% CI)	Validation cohort OR (95% CI)
Age, yr	1.00 (0.98–1.02)	1.00 (0.99–1.01)
Male sex	0.79 (0.46–1.36)	1.24 (0.79–1.95)
Underlying malignancies		
Acute myeloid leukemia	0.91 (0.53–1.54)	0.71 (0.45–1.14)
Acute lymphoblastic leukemia	1.21 (0.58–2.53)	1.50 (0.78–2.87)
Chronic lymphoblastic leukemia	0.61 (0.10–3.74)	1.12 (0.98–2.02)
Lymphoma	0.81 (0.41–1.59)	0.81 (0.50–1.30)
Myeloma	2.25 (0.57–8.92)	0.68 (0.30–1.56)
Aplastic anemia	0.23 (0.03–2.10)	0.89 (0.18–4.49)
Myelodysplasia	1.67 (0.63–4.40)	2.68 (0.98–5.74)
Comorbidity		
Chronic lung disease	0.61 (0.10–3.74)	3.22 (0.66–15.74)
Chronic heart disease	0.62 (0.34–1.14)	0.77 (0.44–1.34)
Chronic renal disease	0.30 (0.03–3.00)	0.89 (0.22–3.62)
Chronic liver disease	2.20 (0.65–7.32)	0.76 (0.25–2.31)
Cerebral vascular disease	0.93 (0.31–2.73)	0.66 (0.15–3.02)
Disease status at admission		
Newly diagnosis	0.66 (0.35–1.30)	1.82 (0.99–3.33)
Relapsed/refractory	1.55 (0.91–2.66)	0.78 (0.49–1.24)
Partial remission	2.84 (0.30–27.71)	1.16 (0.42–3.20)
Complete remission	0.78 (0.35–1.73)	0.73 (0.37–1.46)
BMT/HSCT recipient	1.68 (0.98–2.90)	1.23 (0.78–1.93)
ECOG performance status	0.87 (0.65–1.20)	1.70 (1.38–2.08)[a]
Major reasons for MET activation		
Respiratory distress	2.08 (1.21–3.60)[b]	1.67 (1.07–2.60)[b]
Sepsis/septic shock	0.86 (0.50–1.60)	0.61 (0.35–1.01)
Hypovolemic shock	0.36 (0.07–1.90)	2.13 (0.54–8.40)
Altered mental status	0.93 (0.26–3.30)	1.49 (0.60–3.70)
Metabolic acidosis	0.30 (0.07–1.00)	0.80 (0.33–1.94)
Laboratory at MET activation		
Lactic acid, mmoL/L	0.97 (0.89–1.04)	1.04 (0.96–1.13)
Neutropenia[c]	0.91 (0.54–1.56)	1.16 (0.67–2.00)
Modified early warning score	1.34 (1.20–1.57)[a]	1.28 (1.14–1.42)[a]
SpO$_2$/FiO$_2$ score[d]	1.80 (1.45–2.22)[a]	1.74 (1.47–2.10)[a]
qSOFA score	1.07 (0.65–1.77)	0.94 (0.66–1.33)
SOFA score	1.13 (1.02–1.24)[b]	1.27 (1.16–1.39)[b]
NFR after MET activation	2.00 (1.04–3.81)[b]	12.21 (6.93–21.53)[a]

OR, odds ratio; CI, confidence interval; BMT, bone marrow transplantation; HSCT, hematopoietic stem cell transplantation; ECOG, Eastern Cooperative Oncology Group; MET, medical emergency team; qSOFA, quick sequential organ failure assessment; SOFA, sequential organ failure assessment; NFR, not for resuscitation.

[a]$p < 0.001$.
[b]$p < 0.05$.
[c]Neutropenia, absolute neutrophil count $< 500/\mu L$.
[d]SpO$_2$/FiO$_2$ score, 0 points for > 315, 2 points for ≤ 315 SpO$_2$/FiO$_2$ ratio < 235, 3 points for ≤ 235.