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Major Article

Validation of a carbapenem-resistant *Enterobacteriaceae* colonization risk prediction model: A retrospective cohort study in Korean intensive care units

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Key Words:
Statistical model
Calibration

Background: To assess the external validity of a carbapenem-resistant *Enterobacteriaceae* colonization risk prediction model (CREP-model).

Methods: This retrospective cohort study included 414 patients admitted to the intensive care units of a tertiary hospital from November 1, 2017 to May 31, 2018. Data were collected via medical record review, and we analyzed the performance of the CREP-model by assessment of calibration, discrimination, clinical usefulness, and uniformity-of-fit.

Results: The validation subjects showed differences in age, Acute Physiology and Chronic Health Evaluation II score, mechanical ventilation days, and carbapenem-resistant *Enterobacteriaceae* colonization rate from those of the CREP-model development subjects. The calibration-in-the-large was 0.069 (95% confidence interval [CI], 0.065-0.074), and calibration slope was 1.114 (95% CI, 1.091-1.136). The area under the receiver operating characteristic curve was 0.883 (95% CI, 0.838-0.928). At the predicted risk of 0.25, the sensitivity, specificity, and correct classification rates were 81.3%, 79.8%, and 80.0%, respectively, and the net benefit according to the model was 0.035 with 64 fewer false-positive results per 100 patients. The calibration, discrimination, and clinical usefulness showed similar results among subjects stratified according to sex, age group, medical department, and admission source.

Conclusions: The CREP-model showed good performance in the validation sample; therefore, we recommend introducing the CREP-model into intensive care units of tertiary hospitals to improve decision-making.

Carbapenem-resistant *Enterobacteriaceae* (CRE) is regarded as one of the most urgent threats because of broad resistance to β-lactam antibiotics including carbapenem and a high mortality rate from infection.[1] Both the US Centers for Disease Control and Prevention (CDC) and the Korea CDC (KCDC) have introduced several preventive actions in the guidance for CRE control, including hand hygiene, contact precaution, environmental cleaning, et cetera.[2,3] Among them, active surveillance test is helpful to identify unrecognized colonized patients who might not be on contact precaution and are a potential source of CRE transmission.[2] Particularly, for patients transferred from hospital or facilities where CRE is epidemic and patients hospitalized in high-risk environments like intensive care units, early detection of CRE colonization based on a quick active surveillance test can help control and prevent the spread of CRE.[2,4,5]

However, the active surveillance test has accompanying practical difficulties such as high test cost, requirement of testing personnel, and considerable time taken until reporting of the test results.[5] Therefore, our research team developed a CRE colonization prediction model (CREP-model) to screen the high-risk population of CRE colonization based on the active surveillance culture test among 444 adult patients (89 CRE carriers and 355 non-CRE carriers) hospitalized in intensive care units at a 1,200 bed high-level general hospital in Yangsan, South Korea, between October 1, 2016, and October 31, 2017.[6] Considering that the prediction model is developed from subjects who exist at a certain temporal point, geographical region or domain, and is used for other targets who exist at a different temporal point, geographical region or domain, it is necessary to evaluate the predictive accuracy of the model across new samples from the same target population.[7] This external validation process is composed of 3 steps: investigating the relatedness between development

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and validation samples to confirm transportability of the model, assessing the model performance, and interpreting the model validation results.[7] Among them, model performance evaluation computes indicators like calibration, discrimination, and clinical usefulness.[7-9]

Calibration is the degree of matching between the probability (occurrence of an event) predicted by the model and the probability observed, whereas discrimination is the ability to discriminate between persons who experience the event and persons who do not. Clinical usefulness is the ability to make a better decision when using a model compared to when not using a model, and is calculated determining the sensitivity, specificity, predictability, and the net benefit (NB) of using the prediction model.[10-12] Because calibration, discrimination, and clinical usefulness of the prediction model can differ by the subjects' characteristics, uniformity-of-fit is also evaluated to confirm each subgroup of the subjects.[13,14] This study aimed to evaluate the model performance on 4 aspects of the CREP-model, by selecting subjects having temporal characteristics different from those of the model development subjects.

METHODS

Study setting and population

This study included patients hospitalized in intensive care units of a high-level general hospital located in Yangsan, South Korea, between November 1, 2017 and May 31, 2018. These units have a longstanding CRE active surveillance program, and every patient admitted to these units provides a perirectal swab to check for CRE colonization within 7 days of hospitalization (baseline screening), and weekly thereafter until 7 days after discharge. Patients without confirmatory findings of CRE colonization until the end of this study were excluded. Patients who did not have CRE colonization at baseline screening but did have CRE colonization at the weekly test were classified as the CRE colonized group. CRE colonization was confirmed by carbapenem antimicrobial susceptibility testing (imipenem, ertapenem) by disk diffusion method, which was done in accordance with the legal communicable disease diagnostic criteria of the KCDC.[15] The definition of the CRE colonized group and CRE colonization was the same as those in the development stage of the CREP-model.[6]

The sample size was calculated using an online program called Open Source Epidemiologic Statistics for Public Health.[16] We considered a significance level (α) of 0.05, power ($1\text{-}\beta$) = 0.80, 16.0% of CRE colonization cases with Acute Physiology and Chronic Health Evaluation (APACHE) II scores <21, and 29.5% of CRE colonization cases with APACHE Ⅱ scores >21 based on a previous study.[8] Among the risk factors for CRE colonization, the APACHE Ⅱ score that showed the lowest odds ratio was used. When the ratio of the CRE colonized group to the noncolonized group was defined as 1 to 4, the minimum number of subjects required was 82 persons for the colonized group and 326 persons for the noncolonized group for a total of 408 subjects. Among the 414 subjects who satisfied the inclusion criteria, 48 were assigned to the CRE colonized group and 366 to the noncolonized group.

CRE colonization prediction model

The CREP-model used in this study was: E (logit of CRE colonization) = −2.821 + 1.606 (separation of multidrug-resistant organism [MDRO]) + 1.347 (cephalosporin antibiotic used for 15 days or longer) + 0.980 (carbapenem antibiotic used for 15 days or longer) + 0.544 (APACHE Ⅱ score of 21 points or above).[6] This model was composed of 4 CRE colonization risk factors identified in the model development stage: whether MDROs were isolated or not, whether cephalosporin antibiotics were used for not less than 15 days, whether carbapenem antibiotics were used for not less than 15 days, and whether APACHE II scores were 21 or more.[6] The area under the receiver operating characteristic curve (AUROC) of the CREP-model confirmed among the subjects in the development stage was 0.80 (95% confidence interval [CI], 0.74-0.85; $P < .001$). When probabilities of 0.20, 0.25, and 0.30 were used as the cutoff points to distinguish between the CRE colonized group and noncolonized group, the sensitivity was 79.8%, 61.8%, and 60.7%, respectively; the specificity was 66.2%, 84.5%, and 85.1%, respectively; the positive predictive value was 37.2%, 50.0%, and 50.5%, respectively; the negative predictive value was 92.9%, 89.8%, and 89.6%, respectively; and the classification accuracy was 68.9%, 80.0%, and 80.2%, respectively.[6] For the internal validation test, 3 sets of validation test samples were made by random allocation, and AUROC in the samples ranged from 0.77 (95% CI, 0.67-0.87) to 0.78 (95% CI, 0.68-0.89).

Data collection

Data were collected for 2 months from June 1 to July 31, 2018, after obtaining the approval of the Pusan National University Yangsan Hospital institutional review board (05-2018-050). First, we made a list of the patients selected as the subjects among patients in the intensive care units from November 1, 2017 to May 31, 2018. These subjects were divided into the CRE colonized and noncolonized groups according to CRE surveillance culture test results from the laboratory department of the institution. Afterward, electronic medical records of the subjects were reviewed to collect data from the date of hospitalization until the date of CRE colonization for the CRE colonized group, and until the date of discharge from intensive care units for the noncolonized group. The APACHE Ⅱ score was calculated using physiological parameters recorded on the critical patient record form. If a test was repeated within 24 hours after hospitalization, the worst physiological parameter value was used.

Data analysis

The collected data were analyzed using SPSS version 21.0 (IBM Corporation, Armonk, NY). A 2-tailed test was performed with a significance level (α) of 0.05. Frequencies, percentages, means, and standard deviations were calculated for the characteristics of the subjects. The t test and the χ^2 test were conducted to compare the characteristics of the subjects and CRE colonization rate between the model development and validation stages. Logistic regression analysis was used to predict the regression coefficient of the prediction factor included in the CREP-model. Calibration of the CREP-model was assessed with the χ^2 and P values by the Hosmer-Lemeshow goodness-of-fitness test (H-L test), and with the calibration-in-the-large and calibration slope from a calibration plot.[7,10] The H-L test only presents the P value for the difference in the observed and predicted values between the randomly assigned groups. Considering that the direction of discordance is unknown and the P value is dependent on sample size, it is recommended to use the calibration-in-the-large and calibration slope.[9,10]

Discrimination of the CREP-model was assessed with the AUROC and its 95% CI.[7,10] For the clinical usefulness of the CREP-model, the cutoff points ranged from 0.1-0.5 to include CRE colonization risks of 0.20, 0.25, and 0.30 presented as the cutoff points during model development. A 2×2 decision-making matrix was created to calculate sensitivity, specificity, positive predictive value, negative predictive value, and correct classification rate.[10,11] The NB was calculated at each cutoff point and the decision curve was created.[12] The equation used to calculate NB was as follows: $NB = (true\ positive/N) - \{(false\ positive/N) \times (P/1-P)\}$*true positives*, *false positives*, P_t /1-P_t, N is the total sample size, and P_t the thereshold probability.[11,12] For uniformity-of-fit of the CREP-model, indicators for calibration, discrimination, and clinical usefulness were calculated in each

subgroup according to sex, age group, medical department, and admission source.

RESULTS

Characteristics of the subjects

As is evident from Table 1, the subjects of this study showed a significantly higher mean age (54.27 years vs 46.48 years; $P = .001$), admission from emergency room (ER) (72.9% vs 43.2%; $P < .001$), mean APACHE Ⅱ score (18.61 points vs 17.12 points; $P = .001$), lower mechanical ventilator use for 15 days or longer (18.4% vs 23.9%; $P = .048$) and CRE colonization rate (11.6% vs 20.0%; $P = .001$) than the model development subjects. Among the subjects of this study, CRE colonizers had higher admission from ward ($P = .006$), mean length of stay ($P < .001$), Charlson Comorbidity Index score ($P = .008$), mean APACHE Ⅱ score ($P < .001$), MDROs isolated ($P < .001$), use of medical devices for 15 days or more such as urinary catheter ($P = .004$), central venous catheter ($P = .001$), mechanical ventilator ($P = .001$), tracheostomy ($P = .005$), nasogastric tube ($P < .001$), and drainage tube ($P = .004$), and use of antibiotics such as penicillin ($P = .012$), cephalosporin ($P < .001$), and vancomycin ($P = .047$) for 15 days or more than the non-CRE colonized subjects.

Performance of CRE colonization prediction model

For calibration of the CREP-model, the H-L test yielded a χ^2 value of 4.16 and a P value of .244, indicating its goodness-of-fit. The calibration-in-the-large, evaluated from the calibration plot, was 0.069 (95% CI, 0.065-0.074) and the calibration slope was 1.114 (95% CI, 1.091-1.136) (Fig 1). For discrimination, the AUROC was calculated using the CRE colonization score calculated by the CREP-model and the actual CRE colonization rate observed, was 0.883 (95% CI, 0.838-0.928).

For clinical usefulness, the correct classification rate was 71.0%, 80.0%, and 81.6%; sensitivity was 93.8%, 81.3%, and 79.2%; and specificity was 68.0%, 79.8%, and 82.0%; for a CRE colonization risk of 0.20, 0.25, and 0.30, respectively (Table 2). Table 2 presents the NB results considering the benefits and harms of CRE preventive interventions when all patients hospitalized in intensive care units are assumed to be at high risk of CRE colonization, and when patients with threshold probability above a certain value are assumed as a high-risk group. The NB was observed to be 0.038, 0.035, and 0.023 when interventions were applied after sorting the high-risk group based on the model at a threshold probability of 0.20, 0.25, and 0.30, respectively. In other words, 3.8 patients with true-positive results can be found among every 100 hospitalized patients without increasing the number of false-positive results, which may reduce unnecessary

Table 1
Characteristics of subjects between development and validation stages

Variables		Development stage* (n = 444)	Validation stage (this study)			P_1†	P_2†
			Total (n = 414)	CRE colonizers (n = 48)	Non-CRE colonizers (n = 366)		
General characteristics							
Sex	Female	189 (42.6)	162 (39.1)	15 (68.8)	147 (40.2)	.306	.234
	Male	255 (57.4)	252 (60.9)	33 (31.3)	219 (59.8)		
Age (years)	M±SD	46.48 ± 29.67	54.27 ± 25.40	50.81 ± 23.72	54.72 ± 25.60	.001	.108
Medical department	Surgical	158 (35.6)	160 (38.6)	18 (37.5)	142 (38.8)	.244	.981
	Medical	202 (45.5)	193 (46.6)	23 (47.9)	170 (46.4)		
	Pediatric	84 (18.9)	61 (14.7)	7 (14.6)	54 (14.8)		
Admission source	ER	192 (43.2)	302 (72.9)	27 (56.3)	275 (75.1)	<.001	.006
	Ward	252 (56.8)	112 (27.1)	21 (43.7)	91 (24.9)		
LOS in ICU (days)	M±SD	14.16 ± 12.94	15.13 ± 22.24	20.83 ± 17.26	14.38 ± 22.73	.711	<.001
Presence of comorbidity	No	115 (25.9)	122 (29.5)	13 (27.1)	109 (29.8)	.243	.700
	Yes	329 (74.1)	292 (70.5)	35 (72.9)	257 (70.2)		
CCIS	M±SD	1.40 ± 1.46	1.40 ± 1.30	2.00 ± 1.68	1.33 ± 1.23	.440	.008
APACHE Ⅱ score	≤20	312 (70.3)	241 (58.2)	12 (25.0)	229 (62.6)	<.001	<.001
	≥21	132 (29.7)	173 (41.8)	36 (75.0)	137 (37.4)		
	M±SD	17.12 ± 6.79	18.61 ± 7.06	22.90 ± 6.40	18.05 ± 6.95	.001	<.001
MDROs isolated	No	261 (58.8)	262 (63.8)	4 (8.3)	258 (70.5)	.177	<.001
	Yes	183 (41.2)	152 (36.2)	44 (91.7)	108 (29.5)		
Use of therapeutic devices ≥15 days							
Urinary catheter		148 (33.3)	131 (31.6)	24 (50.0)	107 (29.2)	.597	.004
Central venous catheter		158 (35.6)	133 (32.1)	26 (54.2)	107 (29.2)	.285	.001
Mechanical ventilator		106 (23.9)	76 (18.4)	17 (35.4)	59 (16.1)	.048	.001
Tracheostomy		48 (10.8)	37 (8.9)	10 (20.8)	27 (7.4)	.359	.005
Nasogastric tube		137 (30.9)	123 (29.7)	26 (54.2)	97 (26.5)	.715	<.001
Drainage tube		62 (14.0)	45 (10.9)	11 (22.9)	34 (9.3)	.170	.004
CRRT		31 (7.0)	34 (8.2)	6 (12.5)	28 (7.7)	.496	.261
Antibiotics administered ≥15 days							
Penicillin		57 (12.8)	43 (10.4)	10 (20.8)	33 (9.0)	.263	.012
Carbapenem		30 (6.8)	21 (5.1)	5 (10.4)	16 (4.4)	.297	.082
Cephalosporin		65 (14.6)	56 (13.5)	24 (50.0)	32 (8.7)	.640	<.001
Fluoroquinolone		64 (14.4)	51 (12.3)	9 (18.8)	42 (11.5)	.368	.149
Vancomycin		27 (6.0)	24 (5.8)	6 (12.5)	18 (4.9)	.860	.047
CRE colonization	No	355 (80.0)	366 (88.4)			.001	
	Yes	89 (20.0)	48 (11.6)				

APACHE, Acute Physiology and Chronic Health Evaluation; *CCIS*, Charlson Comorbidity Index score; *CRE*, carbapenem-resistant *Enterobacteriaceae; CRRT*, continuous renal replacement therapy; *ER*, emergency room; *ICU*, intensive care unit; *LOS*, length of stay; *M±SD*, mean ± standard deviation; *MDROs*, multidrug-resistant organisms.
*This was adapted from a study conducted by Song and Jeong.[6]
†*P* values were estimated between the development and validation stages.
‡*P* values were estimated between CRE colonizers and non-CRE colonizers.

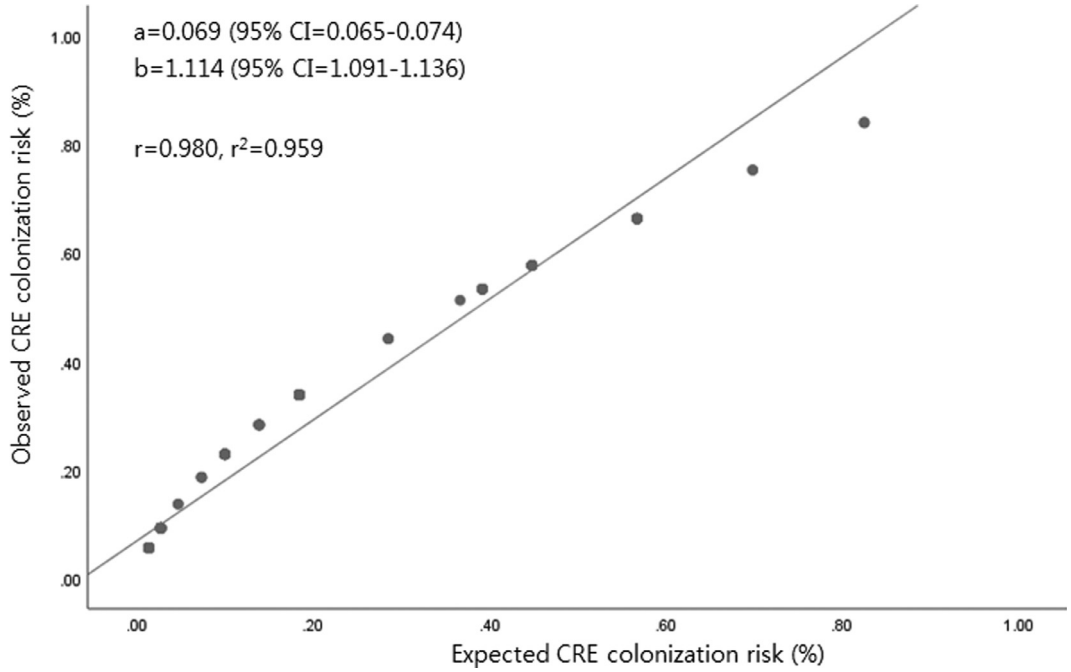

Fig 1. Calibration plot of the CRE colonization prediction model. *a*, calibration-in-the-large; *b*, calibration slope; *CI*, confidence interval; *CRE*, carbapenem-resistant *Enterobacteriaceae; r*, Pearson's correlation coefficient.

preventive interventions in approximately 57 patients at a threshold probability of 0.20. According to the decision-making curve on the use of the CREP-model, the application of CRE-preventive interventions to the high-risk group with a threshold probability between 0.05 and 0.50 was found to yield greater NB compared with the cases in which preventive interventions were applied to all hospitalized patients, or to none of the patients (Fig 2).

Uniformity-of-fit of the performance of CRE colonization prediction model

Table 3 presents the results of analysis of calibration, discrimination, and clinical usefulness of the CREP-model for each subgroup according to sex, age, medical department, and admission source of the subjects. In the calibration plot, the calibration slope ranged from 1.056-1.203. The χ^2 value of the H-L test ranged from 1.03-5.84 and satisfied the null hypothesis that the value predicted by the CRE colonization prediction model and the observed value were the same in all subgroups. The AUROC ranged from 0.847-0.914, showing a high degree of discrimination. The correct classification rate ranged from 73.2%-86.3% at a threshold probability of 0.25, and this rate was higher among women, patients aged 45-64 years, patients in the department of surgery, and patients transferred from ERs. The unnecessary interventions were reduced by applying the model in all subgroups and the reduction was higher among women, patients aged 65 years and older, patients in the department of surgery, and patients transferred from ERs, ranging from 32-68 per 100 patients.

DISCUSSION

Based on the external validation approach,[7] we assessed the differences in case mix and prediction factors between the CREP-model development subjects and validation subjects. The CRE colonization rate was 11.6% in this study, showing a significant difference of 20.0% among the model development subjects.[8] In addition, there were significant differences in age, APACHE Ⅱ score, and mechanical ventilation for 15 days or longer. Among the 4 risk factors found in the model development stage, the use of carbapenem antibiotics for 15 days or longer was not a risk factor in the study. The prediction factorial effect (regression coefficient) estimated from the subjects of

Table 2
Predictive accuracy of and net benefit from the use of the carbapenem-resistant *Enterobacteriaceae* colonization prediction model

	Threshold probability (P_t)						
	0.10	0.15	0.20	0.25	0.30	0.40	0.50
Sensitivity (%)	95.8	95.8	93.8	81.3	79.2	52.1	52.1
Specificity (%)	66.4	66.9	68.0	79.8	82.0	91.8	92.6
(+) Predictive value (%)	27.2	27.5	27.8	34.5	36.5	45.5	48.1
(−) Predictive value (%)	99.2	99.2	98.8	97.0	96.8	93.6	93.6
Correct classification (%)	69.8	70.3	71.0	80.0	81.6	87.2	87.9
Net benefit from all (a)	0.018	−0.040	−0.105	−0.179	−0.263	−0.473	−0.768
Net benefit from model (b)	0.078	0.060	0.038	0.035	0.023	0.012	−0.005
True net benefit (b-a)	0.060	0.100	0.143	0.214	0.286	0.485	0.763
Reduction in unnecessary interventions per 100 patients*	54.0	56.7	57.2	64.2	66.7	72.8	76.3

*Reduction in unnecessary interventions per 100 patients is calculated as: (net benefit of the model − net benefit of all)/(P_t/(1− P_t)) × 100.[16]

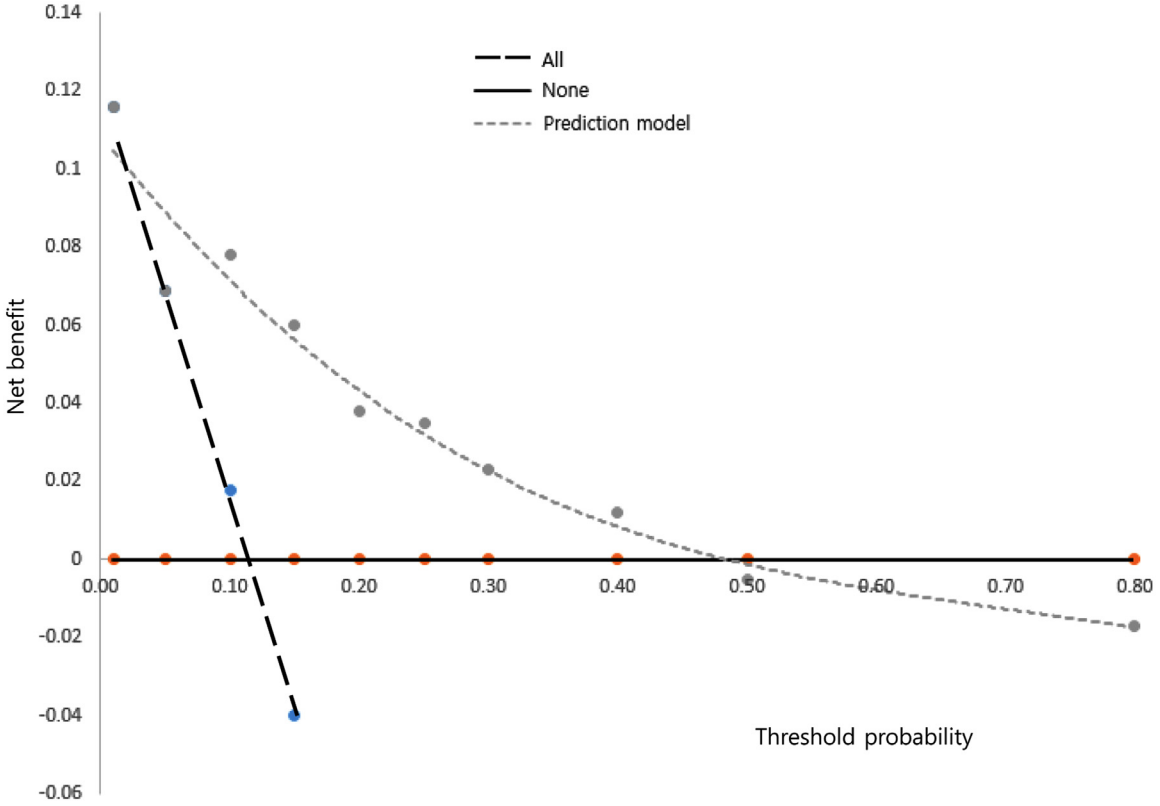

Fig 2. Decision curve for a model to predict carbapenem-resistant *Enterobacteriaceae* (CRE) colonization among patients in intensive care units. Thick dotted line: assuming all patients have CRE-preventive interventions. Thin dotted line: assuming patients at high risk of CRE colonization based on the prediction model have CRE-preventive interventions. Thick line: assuming no patients have CRE-preventive interventions.

this study was clearly different from the prediction factorial effect of the model development subjects. Based on these results, the subjects of this study were found to have different characteristics compared with the model development subjects, although they were taken from the same target population.

The required minimum sample size for the study was predicted as 82 persons for the colonized group and 326 persons for the noncolonized group for a total of 408 subjects. However, in this study, 48 of the 414 subjects were assigned to CRE colonized group, and 366 to the noncolonized group. Therefore, we met the total sample size for the study, but failed to meet the sample size for CRE colonized subjects. However, the statistical power based on the APACHE II score and CRE carrier risk in the study was 100%, which means the sample size was appropriate.

The CREP-model showed good calibration from the H-L test and the calibration-in-the-large and calibration slope from the calibration plot. The *P* value of the H-L test was greater than the significance level of .05, satisfying the null hypothesis and demonstrating fitness of the CREP-model. The calibration-in-the-large is the *Y*-intercept of the calibration plot that compares the mean predicted risk with the mean observed risk, and the ideal value is 0.[7] It assesses whether the predicted risk is consistently too high or too low.[9] The calibration slope is the slope of the calibration plot, and the ideal value is 1. Values >1 indicate that the range of the predicted risk is narrow. Values between 0 and 1 indicate that the prediction factorial effect does not agree between the predicted risk and observed risk.[7] In this study, the calibration-in-the-large was 0.069 and the calibration slope was 1.114. Although there was a slight difference between CRE

Table 3
Uniformity-of-fit of the carbapenem-resistant *Enterobacteriaceae* colonization prediction model according to the general characteristics of the subjects

		Calibration plot		Hosmer-Lemeshow test		AUROC (95% CI)	At threshold probability = 0.25				
		a	b	χ^2	*P*		Sen (%)	Spe (%)	CC (%)	NB	RIU
Sex	Female	0.065	1.143	5.11	.164	0.914 (0.863-0.964)	86.7	81.6	82.1	0.010	66
	Male	0.072	1.098	1.03	.795	0.867 (0.805-0.929)	78.8	78.5	78.6	0.025	55
Age (years)	<45	0.071	1.089	1.78	.776	0.910 (0.844-0.975)	91.7	78.0	79.8	0.012	53
	45-64	0.065	1.149	2.59	.459	0.886 (0.812-0.960)	77.3	83.1	82.2	0.023	49
	≥65	0.072	1.103	1.14	.769	0.866 (0.786-0.947)	78.6	77.9	78.0	−0.001	66
Medical department	Surgical	0.060	1.203	4.14	.247	0.928 (0.885-0.971)	83.3	86.6	86.3	0.021	61
	Medical	0.074	1.094	3.24	.519	0.847 (0.763-0.931)	78.3	75.9	76.2	0.010	55
	Pediatric	0.075	1.056	1.52	.679	0.894 (0.796-0.992)	85.7	74.1	75.4	0.003	55
Admission source	ER	0.066	1.114	2.70	.440	0.872 (0.808-0.936)	74.1	83.3	82.5	0.011	68
	Ward	0.080	1.099	5.84	.322	0.885 (0.819-0.952)	90.5	69.2	73.2	0.023	32

a, calibration-in-the-large; *b*, calibration slope; *AUROC*, area under the receiver operating characteristic curve; *CC*, correct classification; *CI*, confidence interval; *ER*, emergency room; *NB*, net benefit of the model; *RIU*, reduction in unnecessary interventions per 100 patients; *Sen*, sensitivity; *Spe*, specificity.

colonization risk predicted by the CREP-model and CRE colonization risk observed, they were very close to the ideal values. When calibration of the prediction model was analyzed for each subgroup, the *P* value of the H-L test exceeded .05 for sex, age, department, and course of hospitalization. Therefore, the null hypothesis was adopted, and the fitness of the CREP-model was shown. The calibration-in-the-large was relatively similar and ranged from 0.060-0.080. The calibration slope ranged from 1.056-1.203, showing small differences among subgroups. Uniformity-of-fit was maintained in the calibration domain.

The AUROC was used for assessment of discrimination of the CREP-model. This is an effective indicator for evaluating overall discrimination regardless of cutoff points.[17] The AUROC has a value of 1 when the sensitivity is 100% and the false-positive fraction is 0% (or when specificity is 100%), meaning that all subjects can be discriminated properly between the CRE colonization and noncolonization group. In general, an AUROC of 0.5 is considered as no discrimination, 0.7-0.8 as acceptable, 0.8-0.9 as excellent, and 0.9 as outstanding.[18,19] The AUROC of the CREP-model showed excellent discrimination. In terms of subgroups, higher discrimination was shown by women, patients aged <45 years, patients in the department of surgery, and patients transferred from wards. However, uniformity-of-fit was maintained in the discrimination domain with excellent discrimination ranging from 0.847-0.928 in all subgroups.

On the contrary, the AUROC only focuses on the prediction accuracy of the model and does not consider the results of using the model. Therefore, it fails to provide information about the clinical usefulness of the model and what kind of model is preferrable.[11] For instance, if patients are classified into the low-risk group by the CREP-models but actually belong to the high-risk group, CRE may become prevalent in the health care setting owing to failure in taking appropriate preventive interventions. In this case, it can be risky to select a model with a large AUROC, extremely high specificity, and slightly low sensitivity. If patients are classified as the high-risk group by the CREP-model but actually belong to the low-risk group, they can undergo unnecessary preventive interventions such as contact isolation, chlorhexidine gluconate bathing, and wearing of gloves or gowns[2,3] that may result in financial stress or psychological anxiety[20] among the subjects. In this case, it can be risky to choose a model with high sensitivity. As such, even if the AUROC is large, the decision of whether the model can be used clinically depends on whether the sensitivity or specificity is higher. Accordingly, clinical usefulness is confirmed by calculating the NBs for 2 cases, one in which interventions are applied to the high-risk group using the CREP-model (NB from model) and the other in which interventions are applied to all subjects (NB from all).[11,12] In the present study, the NB difference (true NB) was >0 for all threshold probabilities ranging from 0.10-0.50. Also, using the prediction model was found to reduce 54-76 unnecessary preventive interventions per 100 patients hospitalized in intensive care units. Thus, the results of our study may support the hypothesis that targeted intervention was not inferior to the universal intervention regarding the rate of intensive care unit–acquired MDRO infections.[21-23] Based on the results of the uniformity-of-fit in clinical usefulness, the number of unnecessary preventive interventions reduced by using the model may be greater among women, patients aged 65 years or older, patients in the department of surgery, and patients transferred from ERs than counterparts, as the sensitivity and specificity were higher among those subjects.

This study is meaningful because model performance was established after confirming the transportability of the CREP-model[6] that was developed for the first time in South Korea for patients hospitalized in intensive care units according to the external validation procedure. In particular, according to statistical data announced by the KCDC, the number of cases of CRE isolated from blood samples increased rapidly from 1,830 in 2013 to 4,596 in 2016.[24] Considering the fact that the necessity of CRE-preventive interventions is increasing in various medical institutions, this study has significance in verifying the multi-institutional applicability of the CREP-model. As the CREP-model showed good calibration and discrimination, it may be applied to screen CRE high-risk patients who need preemptive isolation in hospitals without an active surveillance program.

However, this study has 2 limitations. First, because validation was carried out on patients hospitalized in intensive care units of a high-level general hospital located in the Yangsan region, it is difficult to apply this study to patients hospitalized in other types of intensive care units. Each hospital may have a different case mix and CRE preventive activities from those of the hospital in which our studies were carried out. For example, this hospital has adopted various CRE prevention programs, as per the recommendation of KCDC[3] and US CDC[2]: hand hygiene, contact precaution, health care personnel education, minimal use of devices, laboratory notification, antimicrobial stewardship, environmental cleaning, patient cohorting or isolation at the facility level, and active surveillance testing at the intensive care unit level. The CRE prevention programs performed at the facility or intensive care unit level can be different according to the hospital characteristics such as size, location, and patient distribution, which can affect the CRE colonization risk factors and external validity of the CREP-model. Therefore, each hospital should compare their case mix and CRE colonization pattern to those of the study hospital before using the CREP-model directly. Second, this study was a retrospective study that examined medical records. Patients who did not undergo the CRE surveillance culture on hospitalization and discharge were excluded from the study, and their characteristics were not reflected.

CONCLUSIONS

The CREP-model showed good calibration and excellent discrimination. The NB was >0 when the CREP-model was used at a threshold probability of 0.10 or above, reducing at least 54 unnecessary preventive interventions per 100 patients. Such results showed similar tendencies according to sex, age, department, and admission route of the subjects, verifying uniformity-of-fit of the CREP-model. Therefore, we suggest active use of the CREP-model in intensive care units with CRE colonization rates of approximately 10%-20%, and additional studies to evaluate the external validation of the CREP-model in other hospitals with different characteristics compared with the subjects of this study.

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