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Utility of a Clinical Risk Factor Scoring Model in Predicting Infection with Extended-Spectrum β -Lactamase-Producing Enterobacteriaceae on Hospital Admission

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Abstract

OBJECTIVE—To validate the utility of a previously published scoring model (Italian) to identify patients infected with community-onset extended-spectrum β -lactamase-producing Enterobacteriaceae (ESBL-EKP) and develop a new model (Duke) based on local epidemiology.

METHODS—This case-control study included patients 18 years of age or more admitted to Duke University Hospital between January 1, 2008, and December 31, 2010, with culture-confirmed infection due to an ESBL-EKP (cases). Uninfected controls were matched to cases (3 : 1). The Italian model was applied to our patient population for validation. The Duke model was developed through logistic-regression-based prediction scores calculated on variables independently associated with ESBL-EKP isolation. Sensitivities and specificities at various point cutoffs were determined, and determination of the area under the receiver operating characteristic curve (ROC AUC) was performed.

RESULTS—A total of 123 cases and 375 controls were identified. Adjusted odds ratios and 95% confidence intervals for variables previously identified in the Italian model were as follows: hospitalization (3.20 [1.62–6.55]), transfer (4.31 [2.15–8.78]), urinary catheterization (5.92 [3.09–11.60]), β -lactam and/or fluoroquinolone therapy (3.76 [2.06–6.95]), age 70 years or more (1.55 [0.79–3.01]), and Charlson Co-morbidity Score of 4 or above (1.06 [0.55–2.01]). Sensitivity and specificity were, respectively, more than or equal to 95% and less than or equal to 47% for scores 3 or below and were less than or equal to 50% and more than or equal to 96% for scores 8 or above. The ROC AUC was 0.88. Variables identified in the Duke model were as follows: hospitalization (2.63 [1.32–5.41]), transfer (5.30 [2.67–10.71]), urinary catheterization (6.89 [3.62–13.38]), β -lactam and/or fluoroquinolone therapy (3.47 [1.91–6.41]), and immunosuppression (2.34 [1.14–4.80]). Sensitivity and specificity were, respectively, more than or equal to 94% and less than or equal to 65% for scores 3 or below and were less than or equal to 58% and more than or equal to 95% for scores 8 or above. The ROC AUC was 0.89.

CONCLUSION—While the previously reported model was an excellent predictor of community-onset ESBL-EKP infection, models utilizing factors based on local epidemiology may be associated with improved performance.

Multidrug-resistant (MDR) organisms cause both healthcare-associated and community-acquired infections with increasing occurrence.^{1–6} Delays in initiating initial appropriate antibiotic therapy as a consequence of drug resistance contribute to the increased morbidity, mortality, length of stay, and treatment-related costs in patients with severe infections.^{7–14} To begin initial appropriate antibiotic therapy in a timely manner, many healthcare institutions have recognized the need for risk-stratification tools to identify patients at increased risk for infection due to MDR organisms at the time of admission.⁵

While recent reports have proposed prediction models and various risk factor scoring models, these have been created with specific patient populations and/or organisms without validation at other institutions.^{2,4–6,15} One report in particular proposed a novel scoring model to identify patients infected with extended-spectrum β -lactamase-producing Enterobacteriaceae (ESBL-EKP) on hospital admission.⁵ In this report, risk factors identified by a logistic regression model were converted to a point-based rule that assigned a weighted score to each risk factor. Risk factors identified included receipt of antibiotic therapy with β -lactams and/or fluoroquinolones (during the 3 months preceding the index admission), previous hospitalization (during the 12 months preceding the index hospitalization), transfer from another healthcare facility, Charlson Comorbidity Score of 4 or above, history of urinary catheterization (during the 30 days preceding the index admission), and age 70 years or more (Table 1). Diagnostic performance was described by reporting the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) at various point cutoffs. While the study utilized a validating cohort of patients, published reports of its application in patient populations outside of Italy are lacking. Therefore, the generalizability and utility of this model and others like it in other clinical settings are unknown. The primary objective of this study was to assess the ability of this novel scoring model (Italian model) to identify patients with community-onset infection due to ESBL-EKP at our institution. The secondary objective was to develop a new model (Duke model) based on the local epidemiology of such infections at our institution.

METHODS

We conducted a single-center case-control study. The study was approved by the Duke University Hospital (DUH) Institutional Review Board. Potential subjects were identified through a search of DUH electronic medical records and the DUH infection control database. Subjects were included if they were 18 years of age or more and admitted to DUH between January 1, 2008, and December 31, 2010. Cases were defined as patients with an ESBL-EKP obtained from a clinical culture within 48 hours of admission and signs and/or symptoms consistent with active clinical infection. Surveillance cultures consisting of rectal swabs and nasal swabs were excluded. In light of this definition, all cases were labeled as “community onset.” If more than 1 isolate was reported for the same patient, only the initial (ie, index) culture was included in the study. ESBL phenotype was determined on the basis of Clinical and Laboratory Standards Institute–approved methods and interpretative criteria.¹⁶ Uninfected controls (subjects with no reports of culture positivity for Enterobacteriaceae during their hospitalization) were matched to cases at a 3 : 1 ratio based on hospital ward and month of admission. Patients were excluded if medical records were incomplete.

Data collected from both electronic and paper-based medical records included patient demographics (birth date, sex, admission date, admission ward), culture and susceptibility results, antibiotic therapy with a β -lactam (including β -lactam/ β -lactamase inhibitor combinations) and/or fluoroquinolone more than 48 hours within 3 months preceding the index admission, hospitalization during the 12 months preceding the index hospitalization, transfer from another healthcare facility, urinary catheterization during the 30 days

preceding the index admission, and comorbidities included in the Charlson Comorbidity Score.¹⁷ Single doses of antimicrobials were not included except in the setting of renal failure and/or hemodialysis. Additional variables collected and analyzed included total parenteral nutrition (during the 30 days preceding the index admission), immunosuppressive therapy during the 3 months preceding the index admission (defined as glucocorticoids [equivalent to prednisone at 20 mg or above for at least 2 weeks] or more than 48 hours of any of the following: tacrolimus, sirolimus, cyclosporine, mycophenolate, or antithymocyte globulin), and chemotherapy (defined as alkylating agents) during the 3 months preceding the index admission.

Standard descriptive statistics were used to describe the study cohort and to compare cases and controls. Continuous variables were expressed as means or medians, as appropriate, and were compared by the Student *t* test for normally distributed variables and by the Mann-Whitney *U* test for non-normally distributed variables. Categorical variables were analyzed by the χ^2 test or the 2-tailed Fisher exact test. Odds ratios and 95% confidence intervals were calculated to evaluate the strength of any association that emerged. Data were collected using Microsoft Access. JMP 8 statistical software (SAS Institute) was used to perform the statistical analyses.

For the primary objective, the Italian model was utilized and scores were given to subjects on the basis of the model's 6 preidentified risk factors (Table 1). Diagnostic performance was described by reporting the sensitivity, specificity, PPV, NPV, and accuracy calculated at various point cutoffs. The discriminatory power of the model was evaluated through determination of the area under the receiver operating characteristic curve (ROC AUC).¹⁸

A newly created Duke model from this study was developed by analyzing the 6 preidentified variables in the Italian model (receipt of antibiotic therapy with β -lactams and/or fluoroquinolone, previous hospitalization, transfer from another healthcare facility, Charlson Comorbidity Score of 4 or above, history of urinary catheterization, and age 70 years or more) and additional variables collected (total parenteral nutrition therapy, immunosuppression exposure, and chemotherapy exposure). However, the Charlson Comorbidity Score was evaluated by looking at all possible score cutoffs (not just 4 or above). Furthermore, age was evaluated at all possible cutoffs (not just 70 years or more). Variables associated with ESBL-EKP isolation in the univariate analysis ($P \leq .10$) were included into a logistic regression model, with a backward stepwise approach utilized to identify independent predictors of ESBL-EKP isolation. Any variable with a *P* value of less than or equal to .05 was retained in the final model. The final regression model was converted into a point-based rule with weighted scores assigned to each variable. Weighted scores were calculated by dividing each regression coefficient by one-half of the smallest coefficient and rounding to the nearest integer.¹⁹ Study patients received a score based on weighted points assigned to each variable from the Duke model. Diagnostic performance was also performed on the Duke model by reporting the sensitivity, specificity, PPV, NPV, and accuracy calculated at various point cutoffs. The discriminatory power of the model was evaluated through determination of the ROC AUC.¹⁸

RESULTS

A total of 498 subjects met the inclusion criteria. Fifty subjects were excluded due to incomplete medical records. Therefore, 448 subjects (110 cases and 338 controls) were included. Clinical, laboratory, and demographic characteristics of the study population are summarized in Table 2. Most patients were female (60% and 55% of cases and controls, respectively), and the median age was 67.22 and 58.21 years, respectively. *Escherichia coli* and *Klebsiella* species were the causative microorganism in case patients (55% and 45%,

respectively). *E. coli* and *Klebsiella* species were most commonly isolated from the urinary tract (76% of case subjects).

In the Italian model, 95% of scores 3 or below were associated with controls, and 80% of scores 8 or above were associated with cases. Furthermore, scores of 4 or below were associated with a relatively high sensitivity (90% or higher) but low specificity and accuracy (less than or equal to 62% and less than or equal to 69%, respectively). However, when the cutoff is raised to a score of 8 or above, the sensitivity decreases to approximately 50%, and a corresponding increase in specificity and accuracy (96% and 85%, respectively) occurred. The ROC AUC was 0.88.

All of the variables used in the Italian model were significantly more associated with cases than controls in the univariate analysis. In the multivariate analysis, all variables remained significantly more associated with cases than controls except age 70 years or more (including ages at all cutoffs) and Charlson Comorbidity Score of 4 or above (including scores at all cutoffs). Of the additional variables analyzed, only immunosuppressive therapy was found to be significantly more associated with ESBL-EKP isolation. Therefore, 5 variables were identified and incorporated in the Duke model on the basis of the multivariate regression model (Table 3). The points accompanying the variables similar to those of the Italian model were also different. The Duke model followed a pattern similar to that of the Italian model, with 94% of scores 3 or below associated with controls and 79% of scores 8 or above associated with cases. Similarly, scores of 4 or below were associated with a relatively high sensitivity (more than or equal to 87%) but low specificity and accuracy (less than or equal to 69% and less than or equal to 73%, respectively). Likewise, when the cutoff is raised to a score of 8 or above, the sensitivity decreases to approximately 58%, and a corresponding increase in specificity and accuracy (95% and 86%, respectively) occurred. The ROC AUC was 0.89.

Table 4 summarizes the evaluation of the variables used in both models. The diagnostic performance of various score cutoffs for the 2 models is summarized in Table 5. Scores of 0 were found exclusively among controls for both models. Recent urinary catheterization followed by admission from another healthcare facility were associated the highest adjusted odds ratios in both models. The prevalence of ESBL-EKP at scores of 8 or above was 50% and 58% for the Italian and Duke models, respectively.

DISCUSSION

The need to identify patients at increased risk for MDR organisms on hospital admission is particularly relevant to those with infections caused by ESBL-producing organisms. The incidence of both community-acquired and healthcare-associated ESBL-EKP is increasing.^{20–23} In addition, inappropriate empiric antimicrobial drug therapy is the main risk factor for mortality in patients with severe infections caused by ESBL-EKP.^{7,11} However, in nonsevere infections (eg, urinary tract infections) the need to identify those with ESBL-EKP remains critical in order to employ effective strategies to prevent and/or limit outbreaks of these infections.⁹ To address this need, various prediction tools have been created to identify those harboring MDR organisms.^{2,4–6,15,24–26}

While some scoring models aid in the identification of risk factors for specific MDR organisms, others have been developed to identify risk factors for specific MDR pathogens in specific disease states.^{2,4–6,15,27} To date, most risk factor assessment scoring and prediction models have targeted gram-positive organisms, specifically methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE).^{2,15,25} Conversely, few studies evaluating risk factors for the isolation of ESBL-EKP exist. In

contrast to other models, the scoring model (Italian⁵) used in this study is the only published model that identifies patients infected with a community-onset infection likely due to an ESBL-EKP on the basis of information available on hospital admission. Studies examining the risk of MDR organisms within 48 hours of hospital admission depend largely on medical history to provide targeted active surveillance and guide empiric therapy.^{2,5,15}

The elements of the Italian and Duke models are similar to those employed in MRSA and VRE models.^{2,15} The models frequently include previous hospitalization, transfer from another healthcare facility, previous antibiotics, advanced age, and urinary catheterization as risk factors.^{2,15} Elements of these models are similar to risk factors identified for colonization or infection with ESBL-EKP in previous studies.^{4,28–30} Risk factors for colonization with ESBL-EKP in the intensive care unit (ICU) on admission include antibiotic use during hospitalization prior to ICU admission, along with a higher infectious disease-specific Chronic Disease Score and age more than 60 years.⁴ Previous hospitalization (in the past 12 months) and previous exposure to antibiotics have also been reported as risk factors for urinary tract infections due to ESBL-EKP.²⁸ Finally, antibiotic use has also been reported to be a risk factor for infection due to ESBL-producing *Klebsiella pneumoniae*.²⁹

On the basis of this study, the utility of these risk scoring models and the choice of optimal score “cutoff” values depend on its intended application. The clinical relevance of a scoring model is not based purely on the AUC; it is also based on the expected utility linked with that AUC.^{31,32} If the desired application is a screening tool, choosing a cutoff score with a high sensitivity at the expense of lower specificity may be acceptable. Withholding empiric antimicrobial therapy with in vitro activity against ESBL-EKP could therefore be considered in patients with scores below the cutoff. In the Italian model, when a risk score of 4 or above was used, the sensitivity and NPV were 90% and 95%, respectively, at the cost of low specificity and PPV (62% and 44%, respectively). In the Duke model, when a risk score of 4 or above was used, the sensitivity and NPV were 87% and 94%, respectively, at the cost of low specificity and PPV (69% and 48%, respectively). In contrast, empiric use of antibiotic therapy directed at ESBL-producing organisms would likely require a threshold score with a higher specificity and PPV, with acceptance of the “cost” of lower sensitivity. In this study, a threshold score of 8 or above was associated with a specificity and PPV of 96% and 80%, respectively, with corresponding reductions in sensitivity (50%) for the Italian model. In the Duke model, a threshold score of 8 or above was associated with a specificity and PPV of 95% and 79%, respectively, with corresponding reductions in sensitivity (58%). Therefore, if only subjects with a score of 8 or above were given empiric therapy directed at ESBL-producing organisms (such as carbapenems), 85% of patients would have received appropriate initial therapy, 3% would have been treated too broadly, and 12% would have failed to receive the necessary initial empiric ESBL-directed therapy if the Italian model was utilized. If the Duke model was utilized, 86% of patients would have received appropriate initial therapy, 4% would have been treated too broadly, and 10% would have failed to receive the necessary initial empiric ESBL-directed therapy.

Like the hospitals included in the Italian model, our hospital is a large, full-service teaching hospital. However, European Antimicrobial Resistance Surveillance System (<http://www.ecdc.europa.eu>) data in 2009 showed a higher prevalence of ESBL-producing *E. coli* in Italian hospitals (17%) than predicted in our institution. In 2011, the DUH microbiology laboratory identified 1,606 individual patients with cultures positive for EKP. Of these, 175 (11%) were ESBLs. The DUH laboratory receives specimens from DUH and more than 160 outpatient clinics. Therefore, this is a reasonable marker of prevalence in our community, not just in the hospital.

Our study has limitations. Data were unavailable if not present in the DUH medical history. This limitation, however, applied equally to both cases and controls. Furthermore, it is reasonable to assume that there are differences between the Italian institutions and Duke with regard to availability of outside medical records, which may explain differences in Charlson Comorbidity Score findings. The conduct of the study at a tertiary medical center may also limit applicability to smaller institutions. Consequently, the exact score threshold cutoff values that should be used may vary between institutions and purpose of the model. We did not evaluate subjects with hospital-acquired infections. Therefore, applicability of these models to hospital-acquired infections is unknown. Furthermore, we did not differentiate between community-onset healthcare-associated and community-acquired infections. We also did not evaluate all known or possible risk factors. This may have led to an improved Duke model. However, our primary goal was to validate the Italian model. Last, the Duke model has not undergone external validation.

The previously published Italian model displayed good discrimination and is an excellent predictor of ESBL-EKP isolation. However, the multivariate analysis showed that not all variables in the model were applicable (age 70 years or more and Charlson Comorbidity Score of 4 or above [including all possible age and Charlson Score cutoffs]) to our institution and that another variable (immunosuppressive therapy) would be. Therefore, the creation of a new model for our institution would be appropriate and may be performed by other institutions to reflect local epidemiology when adapting published models for their use. Both models displayed similar accuracy and were associated with similar discriminatory power. However, the declining sensitivity and increased specificity with escalating scores necessitates further determination of application-specific interpretive cutoffs for both models.

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TABLE 1Italian Model (Tumbarello et al⁵)

Attribute	No. of points
Recent antibiotic therapy with β -lactams and/or fluoroquinolones ^a	2
Previous hospitalization ^b	3
Transfer from another healthcare facility	3
Charlson Comorbidity Score of ≥ 4	2
Recent history of urinary catheterization ^c	2
Age ≥ 70 years	2

^aDuring the 3 months preceding the index hospitalization.^bDuring the 12 months preceding the index hospitalization.^cDuring the 30 days preceding the index admission.

TABLE 2

Demographic and Infection Characteristics of the Study Population

Characteristic	Cases	Controls	P
Patient characteristics			
Male	44 (40)	152 (45)	.646
Age, mean $\pm$ SD, years	62 $\pm$ 17.85	56 $\pm$ 17.49	.0006
ESBL pathogen			
<i>Escherichia coli</i>	60 (55)	...	
<i>Klebsiella</i> species	50 (45)	...	
Isolate source			
Blood	16 (15)	...	
Urinary tract	84 (76)	...	
Lower respiratory tract	2 (2)	...	
Surgical wound	6 (5)	...	
Skin and soft tissue	2 (2)	...	
Comorbidities			
Myocardial infarction	9 (8)	19 (6)	.365
Heart failure	19 (17)	28 (8)	.0115
Peripheral vascular disease	9 (8)	18 (5)	.2589
Dementia	8 (7)	8 (2)	.0324
Cerebrovascular disease	16 (15)	23 (7)	.0184
Chronic lung disease	24 (22)	50 (15)	.3923
Connective tissue disease	9 (8)	17 (5)	.2412
Peptic ulcer disease	5 (5)	10 (3)	.5406
Chronic liver disease	10 (9)	21 (6)	.2877
Hemiplegia	9 (8)	6 (2)	.0031
Kidney disease	40 (36)	56 (17)	.0001
Diabetes	54 (49)	89 (26)	.0001
Diabetes with end-organ damage	8 (7)	10 (3)	.0538
Solid tumor	7 (6)	32 (9)	.4357
Leukemia	3 (3)	10 (3)	.7435
Lymphoma	3 (3)	8 (2)	.7355
Metastatic solid tumor	2 (2)	22 (7)	.0843
AIDS	2 (2)	2 (1)	.2537
Recent immunosuppressive therapy	28 (25)	36 (11)	.0003
Recent chemotherapy	3 (3)	15 (4)	.5805
Recent total parenteral nutrition therapy	2 (2)	1 (0.3)	.1506

NOTE. Data are no. (%), unless otherwise indicated. ESBL, extended-spectrum β -lactamase; SD, standard deviation.

TABLE 3

Duke Model

Attribute	No. of points
Recent antibiotic therapy with β -lactams and/or fluoroquinolones ^a	3
Previous hospitalization ^b	2
Transfer from another healthcare facility	4
Recent history of urinary catheterization ^c	5
Immunosuppression ^d	2

^aDuring the 3 months preceding the index hospitalization.

^bDuring the 12 months preceding the index hospitalization.

^cDuring the 30 days preceding the index admission.

^dDuring the 3 months preceding the index admission.

TABLE 4

Evaluation of Risk Factors in the Models

Evaluable points in scoring model	Cases, no. (%)	Controls, no. (%)	Italian model				Duke model			
			Unadjusted OR (95% CI) ^a	Unadjusted <i>p</i> ^a	Adjusted OR (95% CI) ^b	Adjusted <i>p</i> ^b	Unadjusted OR (95% CI) ^a	Unadjusted <i>p</i> ^a	Adjusted OR (95% CI) ^b	Adjusted <i>p</i> ^b
Recent hospitalization	93 (85)	147 (43)	7.11 (4.06–12.44)	<.0001	3.20 (1.62–6.55)	.0007	7.11 (4.06–12.44)	<.0001	2.63 (1.32–5.41)	.0059
Admission from another healthcare facility	47 (43)	26 (8)	8.95 (5.16–15.52)	<.0001	4.31 (2.15–8.78)	<.0001	8.95 (5.16–15.52)	<.0001	5.30 (2.67–10.71)	<.0001
Recent urinary catheterization	59 (54)	24 (7)	15.14 (8.65–26.48)	<.0001	5.92 (3.09–11.60)	<.0001	15.14 (8.65–26.48)	<.0001	6.89 (3.62–13.38)	<.0001
Recent antibiotic therapy	79 (72)	81 (24)	8.09 (4.98–13.13)	<.0001	3.76 (2.06–6.95)	<.0001	8.09 (4.98–13.13)	<.0001	3.47 (1.91–6.41)	<.0001
Age 70 years	43 (39)	67 (20)	2.60 (1.63–4.14)	<.0001	1.55 (0.79–3.01)	.2013	...	...	...	...
Charlson Comorbidity Score of 4	36 (33)	64 (19)	2.08 (1.29–3.37)	.0029	1.06 (0.55–2.01)	.8611	...	...	...	...
Immunosuppression	28 (25)	36 (11)	...	...	...	...	2.60 (1.63–4.14)	.0003	2.34 (1.14–4.80)	.0209

NOTE. CI, confidence interval; OR, odds ratio.

^aObtained through univariate logistic regression.

^bObtained through multivariate logistic regression, adjusted for other factors.

TABLE 5

Distribution of Scores with Diagnostic Cutoff Performance

Score	Italian mode								Duke model									
	TP	FP	TN	FN	Se	Sp	PPV	NPV	Acc	TP	FP	TN	FN	Se	Sp	PPV	NPV	Acc
0	110	338	0	0	100	0	25	0	25	110	338	0	0	100	0	25	0	25
2	110	214	124	0	100	37	34	100	52	108	189	149	2	98	44	36	99	57
3	104	179	159	6	95	47	37	96	59	103	119	219	7	94	65	46	97	72
4	99	127	211	11	90	62	44	95	69	96	106	232	14	87	69	48	94	73
5	95	100	228	15	86	67	49	94	72	89	87	251	21	81	74	51	92	76
6	77	53	285	33	70	84	59	90	81	78	42	296	32	71	88	65	90	83
7	76	48	290	34	69	86	61	90	82	74	37	301	36	67	89	67	89	84
8	55	14	324	55	50	96	80	85	85	64	17	321	46	58	95	79	87	86
9	45	10	328	65	41	97	82	83	83	62	16	322	48	56	95	79	87	86
10	34	8	330	76	31	98	81	81	81	51	11	327	59	46	97	82	85	84
11	20	6	332	90	18	98	77	77	79	38	6	332	72	35	98	86	82	83
12	17	4	334	93	15	99	81	78	78	34	6	332	76	31	98	85	81	82
13	17	4	334	93	15	99	81	78	78	24	4	334	86	22	99	86	80	80
14	6	2	336	104	5	99	75	76	76	23	4	334	87	21	99	85	79	80
16	...	...	...	...	...	...	...	...	...	6	0	338	105	5	100	100	76	77

NOTE. Acc, accuracy; FN, false negatives; FP, false positives; NPV, negative predictive value; PPV, positive predictive value; Se, sensitivity; Sp, specificity; TN, true negatives; TP, true positives.