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Identifying Patients Harboring Extended-Spectrum-β-Lactamase-Producing *Enterobacteriaceae* on Hospital Admission: Derivation and Validation of a Scoring System▽

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Increases in community-acquired infections caused by extended-spectrum-β-lactamase (ESBL)-producing *Enterobacteriaceae* have important implications for hospital infection control and empirical antibiotic therapy protocols. We developed and validated a tool for identifying patients harboring these organisms at hospital admission. We retrospectively analyzed chart data for 849 adult inpatients. The derivation cohort included 339 patients admitted to a large hospital in Rome during 2008, with ($n = 113$) or without ($n = 226$) culture positivity for ESBL-producing *Escherichia coli*, *Klebsiella* spp., or *Proteus mirabilis* within 48 h after admission. Logistic-regression-based prediction scores were calculated based on variables independently associated with the outcome. The model was validated in a second cohort ($n = 510$) selected with identical criteria in hospitals in Genoa and Turin during 2009. Prediction scores were based on the following six variables (reported with odds ratio for study outcome and the 95% confidence intervals in brackets): recent (≤12 months before admission) hospitalization (5.69 [2.94 to 10.99]), transfer from another health care facility (5.61 [1.65 to 19.08]), Charlson comorbidity score ≥ 4 (3.80 [1.90 to 7.59]), recent (≤3 months before admission) β-lactam and/or fluoroquinolone treatment (3.68 [1.96 to 6.91]), recent urinary catheterization (3.52 [1.96 to 6.91]), and age ≥ 70 years (3.20 [1.79 to 5.70]). The model displayed good calibration and good-to-excellent discrimination in the derivation and validation sets (Hosmer-Lemshow $\chi^2 = 15.28$ and 14.07; $P = 0.17$ and 0.23; areas under the receiver-operating characteristic curve, 0.83 and 0.92). It reliably identified patients likely to be harboring ESBL-producing *Enterobacteriaceae* at hospital admission who may need special infection control measures. Further study is needed to confirm this model's potential as a guide for prescribing empirical antibiotic therapy.

In the last 2 decades, intensive use of broad-spectrum cephalosporins has led to the emergence of antibiotic-resistant strains of *Enterobacteriaceae* (predominantly *Klebsiella pneumoniae* and *Escherichia coli*) that produce extended-spectrum β-lactamases (ESBLs) (8, 12, 20, 21, 27). These strains are widespread throughout the world, but the prevalence and phenotypic characteristics of clinical isolates varies from area to area (7, 9).

Several studies suggest that infections caused by ESBL-producing bacteria have an important clinical impact, and the increasing prevalence of these organisms in hospitals has been well documented (9, 12, 34). In addition, they have recently been reported to cause urinary tract and bloodstream infections in nonhospitalized patients (1–3, 10, 14, 16, 18, 23, 24). An unrecognized influx of community-acquired ESBL-producing organisms into hospital settings could have important consequences. For one thing, patients admitted with these infections require special monitoring and infection control measures to prevent the spread of these organisms within the healthcare facility. Furthermore, there is obviously a substantial risk that the infecting pathogen will be resistant to empirically prescribed antimicrobial protocols normally used for community-acquired infections, which often include oxyimino cephalosporins. Many ESBL-producing organisms contain plasmids (sometimes the same ones encoding ESBL production) that confer resistance to other antimicrobial agents as well. In these cases, carbapenems are often the only drugs that are effective (9, 31–33). Failure to provide adequate treatment in the initial stages of bloodstream infections caused by ESBL-producing *Enterobacteriaceae* has already been linked to a markedly increased risk of mortality (26, 31). Our aim was to develop and validate a reliable, easy-to-use clinical prediction rule that could be used at hospital admission to identify patients likely to harbor these organisms.

MATERIALS AND METHODS

Setting and study design. To identify risk factors for isolation of ESBL-producing *Enterobacteriaceae* (i.e., *E. coli*, *Klebsiella* spp., or *Proteus mirabilis*) (ESBL-EKP) from clinical samples shortly after hospital admission, we conducted a case-control study. Patient cohorts were identified via databases main-

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tained by the microbiology laboratories in three large, full-service teaching hospitals in Italy, each with a yearly admission rate of about 50,000 patients: the Catholic University Hospital, a 1,600-bed hospital located in Rome; San Martino University Hospital, a 1,500-bed hospital in Genoa; and the San Giovanni Battista-Molinette Hospital, a 1,200-bed facility located in Turin.

The derivation cohort consisted of adult inpatients admitted to the Catholic University Hospital between 1 January and 31 December 2008. The case group comprised those whose records showed at least one isolation of an ESBL-EKP from samples collected within 48 h of hospital admission. Rectal swab screening was not routinely performed in any of the hospitals included in the study. Therefore, the study focused on the isolation of ESBL-EKP from clinical culture samples. If more than one isolation was reported for the same patient, only the first was included in the study (index culture). Patients admitted with a known history of ESBL-EKP infection were excluded. For each case identified, we included two controls (matched for hospital ward and month of admission) with no reports of culture positivity for *Enterobacteriaceae* during their hospitalization. These individuals were randomly selected from lists of patients admitted to the hospital during the study period.

The validation cohort (cases and controls) consisted of hospitalized individuals that were prospectively enrolled in San Martino University Hospital or San Giovanni Battista-Molinette Hospital between 1 June and 31 December 2009. The inclusion and exclusion criteria were identical to those used for the derivation cohort, with the exception that four control subjects were chosen for each case patient.

Variables analyzed. Data were collected from patients' medical records and computerized hospital databases. For consistency's sake, the variables recorded for each cohort were defined in accordance with recent publications in this field (31–34). These variables included (i) patient demographics, (ii) source of admission (in particular, whether or not the patient had been transferred from another healthcare facility [acute care, long-term care, or nursing home]), (iii) underlying diseases and comorbidities present on admission (including solid tumors, hematological malignancies, liver disease, chronic renal failure, diabetes mellitus, chronic obstructive pulmonary disease, heart failure, cerebrovascular disease, solid organ transplantation, and AIDS), and (iv) recent medical history, including hospitalization for >2 days during the 12 months preceding admission, surgery or invasive procedures within the 30 days preceding admission (including the insertion of central venous catheters [CVCs], a nasogastric tube, or Foley catheters or endoscopy), immunosuppressive and/or corticosteroid therapy within the 3 months before admission, and antimicrobial therapy lasting >48 h during the 3 months preceding admission. For risk-factor analysis, the latter variable was dichotomized (any therapy versus no therapy). The impact of comorbidities was determined based on the Charlson comorbidity index (5).

Microbiological analyses. Isolates were identified at the species level with the Vitek 2 (bioMérieux, Inc., Hazelwood, MO) and/or the Phoenix (Becton Dickinson Microbiology Systems) systems. ESBL production was detected by broth microdilution method according to the Clinical and Laboratory Standards Institute guidelines (6). *K. pneumoniae* ATCC 700603 and *E. coli* ATCC 25922 were used as positive and negative controls, respectively.

Statistical analysis. Continuous variables were compared by using the Student *t* test for normally distributed variables and the Mann-Whitney U test for nonnormally distributed variables. Categorical variables were evaluated with the χ^2 or two-tailed Fisher exact test. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to evaluate the strength of any association that emerged. Values are expressed as means ± the standard deviations (SD) (continuous variables) or as percentages of the group from which they were derived (categorical variables). Two-tailed tests were used to determine statistical significance; a P value of <0.05 was considered significant.

Variables associated with ESBL-EKP isolation in the univariate analysis ($P \leq 0.10$) were included in a logistic regression model, and a backward stepwise approach was used to identify independent predictors of ESBL-EKP isolation. Variables were retained in the final model if the P value was ≤0.05. The final regression model was transformed into a point-based rule. The weighted scores assigned to each variable were obtained by dividing each regression coefficient by half of the smallest coefficient and rounding to the nearest integer (28). The discriminatory power of the prediction rule in the derivation group was expressed as the area under the receiver-operator characteristic curve (ROC AUC). An AUC of 0.5 indicates no discriminative ability, and perfect discrimination (i.e., a test with 100% sensitivity and 100% specificity) is reflected by an AUC of 1. An AUC exceeding 0.8 is usually indicative of good to excellent prediction; those in the 0.7 to 0.8 and 0.6 to 0.7 ranges reflect moderate and low predictive power, respectively. The sensitivity and specificity of the prediction rule—each with 95% CIs—were calculated at different cutoff values. Positive and negative predictive values (PPV and NPV, respectively) were obtained with standard methods. Calibration was assessed by using the Hosmer-Lemeshow test for goodness of fit, which evaluates expected and observed probabilities in population deciles. The same methods were used to assess model discrimination and calibration in the validation cohort.

All statistical analyses were performed using the Intercooled Stata program, version 10, for Windows (Stata Corp., College Station, TX).

RESULTS

Derivation cohort. A total of 115 patients with culture positivity for ESBL-EKP met the inclusion criteria for the derivation set study. Two were excluded because of missing data, leaving a total of 113 cases for analysis. Two control subjects were enrolled for each case, bringing the total number of patients in the derivation cohort to 339. The ESBL-EKP isolates (*E. coli* [$n = 77$, 68.1%], *K. pneumoniae* [$n = 19$, 16.8%], and *P. mirabilis* [$n = 17$, 15.1%]) were mainly recovered from urine specimens ($n = 72$, 63.7%). Blood ($n = 19$, 16.8%), skin and soft tissue ($n = 14$, 12.4%), respiratory tract ($n = 8$, 7.1%), biliary tract ($n = 4$, 3.5%), and surgical wound ($n = 2$, 1.8%) specimens accounted for the remaining isolates. In six cases the same microorganism was isolated simultaneously from two different sites.

The mean (± the SD) age of the patients in the case group was 65.9 ± 20.3 years, and more than half were older than 70 years (59/113, 52.2%). Sixty (53.1%) were women. The proportion of cases hospitalized on medical wards (80/113, 70.8%) was significantly higher than that for surgical wards (28/113, 24.7%) or intensive care units (5/113, 4.4%). Table 1 summarizes the main clinical and demographic characteristics of case patients included in the derivation cohort.

In univariate analysis, ESBL-EKP culture positivity within 48 h of hospital admission was significantly associated with age >70 years ($P < 0.001$), previous hospitalization ($P < 0.001$), and transfer from another healthcare facility ($P < 0.001$). Compared to controls, the case group had higher rates of diabetes ($P = 0.01$), chronic pulmonary obstructive diseases ($P < 0.001$), cerebrovascular disorders ($P < 0.001$), renal failure ($P = 0.001$), and Charlson comorbidity scores ≥ 4 ($P < 0.001$). Patients in this group were also more likely to have a recent history of urinary catheterization ($P < 0.001$) and of the following: steroid therapy ($P < 0.001$), antibiotic therapy (any drug) ($P < 0.001$), antibiotic therapy with β-lactams and/or fluoroquinolones ($P < 0.001$), immunosuppressive therapy ($P = 0.02$), or radiotherapy ($P = 0.07$).

In logistic regression analysis, six variables were independently associated with isolation of ESBL-EKP within 48 h of hospital admission: previous hospitalization ($P < 0.001$), admission from another healthcare facility ($P = 0.006$), Charlson comorbidity score ≥ 4 ($P < 0.001$), previous therapy with β-lactams and/or fluoroquinolones ($P < 0.001$), recent history of urinary catheterization ($P < 0.001$), and age ≥70 years ($P < 0.001$) (Table 2).

Validation cohort. From June through December 2009 in the two hospitals involved in the validation study, ESBL-EKPs were isolated within 48 h of hospitalization in 102 patients. For each case, four control patients were included, bringing the number of patients in the validation cohort to 510. Their baseline characteristics are summarized in Table 1. Compared to the derivation cohort, the validation cohort contained a higher percentage of *E. coli* (87.2% versus 68.1% in the derivation

TABLE 1. Comparison of characteristics of case patients in the derivation and validation groups

Characteristics[a]	No. (%) of patients		*P*
	Derivation set (n = 113)	Validation set (n = 102)	
Microorganism isolated			
Escherichia coli	77 (68.1)	89 (87.2)	<0.001
Klebsiella spp.	19 (16.8)	10 (9.8)	0.13
Proteus mirabilis	17 (15.1)	5 (4.9)	0.01
Isolate source			
Blood	19 (16.8)	27 (26.5)	0.08
Urinary tract	72 (63.7)	54 (52.9)	0.11
Lower respiratory tract	8 (7.1)	11 (10.8)	0.33
Surgical wound	2 (1.8)	5 (4.9)	0.19
Skin and soft tissues	14 (12.4)	13 (12.8)	0.94
Biliary tract	4 (3.5)	6 (5.9)	0.42
Patient characteristics			
Male patients	53 (46.9)	55 (53.9)	0.30
Patients >70 years old	59 (52.2)	66 (64.7)	0.06
Ward			
Medicine	80 (70.8)	79 (77.5)	0.27
Surgery	28 (24.8)	21 (20.6)	0.46
Intensive care units	5 (4.4)	2 (1.9)	0.31
Comorbidities			
Solid tumor	29 (25.7)	34 (33.3)	0.22
Hematological malignancy	8 (7.1)	8 (7.8)	0.83
Liver disease	17 (15.0)	13 (12.8)	0.63
Chronic renal failure	23 (20.4)	23 (22.6)	0.69
Diabetes mellitus	29 (25.7)	23 (22.6)	0.59
Chronic obstructive pulmonary disease	20 (17.7)	16 (15.7)	0.69
Heart failure	56 (49.6)	52 (50.9)	0.83
Cerebrovascular disease	33 (29.2)	30 (29.4)	0.97
Solid organ transplantation	7 (6.2)	2 (1.9)	0.12
AIDS	4 (3.5)	1 (0.9)	0.21
Charlson comorbidity index ≥ 4	37 (32.7)	60 (58.8)	<0.001
History			
Recent hospitalization*	92 (81.4)	78 (76.5)	0.37
Admission from another healthcare facility	14 (12.4)	30 (29.4)	0.002
Recent bacterial infections†	62 (54.9)	36 (35.3)	0.004
Dialysis	2 (1.7)	3 (2.9)	0.56
Surgical procedures‡	30 (26.6)	29 (28.4)	0.76
Central venous catheter‡	12 (10.6)	22 (21.6)	0.03
Urinary catheterization‡	44 (38.9)	53 (51.9)	0.06
Surgical drainage tube(s)‡	12 (10.6)	6 (5.9)	0.21
Nasogastric tube‡	5 (4.4)	6 (5.9)	0.63
Total parenteral nutrition‡	10 (8.9)	18 (17.7)	0.06
Endoscopy[b]	15 (13.3)	9 (8.8)	0.30
Immunosuppressive therapy†	8 (7.1)	5 (4.9)	0.50
Corticosteroid therapy†	24 (21.2)	24 (23.5)	0.69
Radiotherapy†	5 (4.4)	3 (2.9)	0.57
Chemotherapy†	13 (11.5)	14 (13.7)	0.62
Recent antibiotic therapy†			
In general (any drug)	69 (61.1)	56 (54.9)	0.36
By drug class			
Aminoglycosides	6 (5.3)	6 (5.9)	0.92
β-Lactam-β-lactamase inhibitor	8 (7.1)	17 (16.7)	0.04
Fluoroquinolones	24 (21.2)	31 (30.4)	0.18
Oxyimino cephalosporins	27 (23.9)	13 (12.8)	0.02
Carbapenems	9 (7.9)	6 (5.9)	0.49
Others	9 (7.9)	14 (13.7)	0.21

[a] *, During the 12 months preceding index hospitalization; †, during the 3 months preceding index blood culture; ‡, during the 30 days preceding index blood culture.

[b] This category includes esophagogastroduodenoscopy, colonoscopy, and endoscopic retrograde cholangiopancreatography, during the 30 days preceding index blood culture.

cohort, $P < 0.001$). The two cohorts were similar in terms of isolate sources, but significant differences were noted in mean Charlson comorbidity scores ($P < 0.001$), admission rates from other health care institutions ($P = 0.002$), and recent histories of the bacterial infections ($P = 0.004$), CVCs ($P = 0.03$), or treatment with β-lactam-β-lactamase inhibitors ($P = 0.04$) and/or oxyimino-cephalosporins ($P = 0.02$) (Table 1).

TABLE 2. Multivariate logistic regression analysis of risk factors for ESBL-producing *Enterobacteriaceae* isolation within 48 h of hospital admission in the derivation set, with corresponding point values

Parameter	Regression coefficient	*P*	OR (95% CI)	Score
Recent hospitalization[a]	1.73	<0.001	5.69 (2.94–10.99)	3
Admission from another healthcare facility	1.72	0.006	5.61 (1.65–19.08)	3
Charlson comorbidity index ≥ 4	1.33	<0.001	3.80 (1.90–7.59)	2
Previous therapy with β-lactams and/or fluoroquinolones[b]	1.30	<0.001	3.68 (1.96–6.91)	2
History of urinary catheterization[c]	1.25	<0.001	3.52 (1.96–6.91)	2
Age ≥70 years	1.16	<0.001	3.20 (1.79–5.70)	2

[a] During the 12 months preceding index hospitalization.

[b] Includes treatment with β-lactam/β-lactamase inhibitor combinations, oxyiminocephlosporins, and/or fluoroquinolones during the 3 months preceding index admission.

[c] During the 30 days preceding index blood culture.

Construction and validation of the predictive scoring system. (i) Derivation set. A weighted score was assigned to each risk factor found to be independently associated with isolation of ESBL-EKP within 48 h of hospital admission in the derivation set, as follows: previous hospitalization, 3 points; admission from another healthcare facility, 3 points; previous antibiotic therapy with β-lactams and/or fluoroquinolones, 2 points; Charlson comorbidity score ≥ 4, 2 points; age ≥70 years, 2 points; and recent history of urinary catheterization, 2 points (Table 2). The individual scores were added together to produce an overall score ranging from 0 to 14 points.

The distribution of overall scores among the cases and controls of the derivation cohort is summarized in Table 3. Scores of 0 were found exclusively among controls, as were the vast majority (85.1%) of scores of 2. The ROC AUC for these data was 0.83 (95% CI = 0.79 to 0.88), indicating that the model is

TABLE 3. Distribution of scores in the derivation and validation sets

Points	No. (%) of patients					
	Derivation set			Validation set		
	Cases	Controls	Total	Cases	Controls	Total
0	0	52 (100)	52	4 (1.9)	204 (98.1)	208
2	7 (14.9)	40 (85.1)	47	3 (3.1)	96 (96.9)	99
3	14 (19.2)	59 (80.8)	73	4 (10.3)	35 (89.7)	39
4	5 (23.8)	16 (76.2)	21	7 (35)	13 (65)	20
5	25 (35.7)	45 (64.3)	70	10 (20)	40 (80)	50
6	4 (66.7)	2 (33.3)	6	5 (62.5)	3 (37.5)	8
7	34 (82.9)	7 (17.1)	41	20 (55.6)	16 (44.4)	36
8	1 (50)	1 (50)	2	2 (66.7)	1 (33.3)	3
9	14 (82.4)	3 (17.7)	17	19 (100)	0	19
10	2 (100)	0	2	8 (100)	0	8
11	3 (75)	1 (25)	4	5 (100)	0	5
12	3 (100)	0	3	7 (100)	0	7
14	1 (100)	0	1	8 (100)	0	8
Total	113 (33.3)	226 (66.7)	339	102 (20)	408 (80)	510

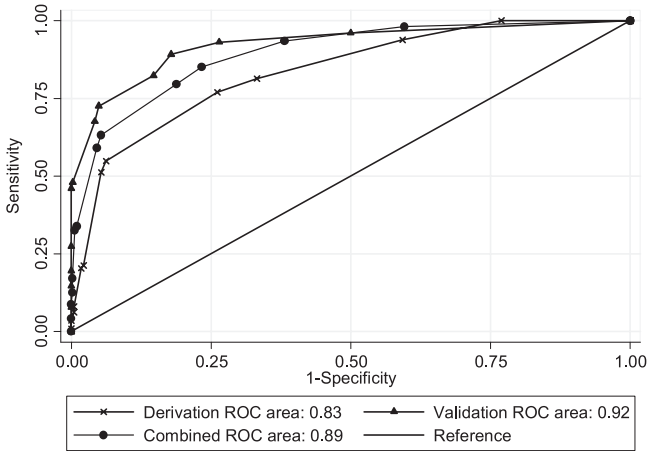

FIG. 1. Receiver-operator characteristic curves (ROC AUC) for the scoring system in the derivation set, validation set, and combined populations.

an excellent predictor of ESBL-EKP isolation within the first 48 h of hospitalization (Fig. 1). The results of Hosmer-Lemshow chi-squared testing ($\chi^2 = 15.28$; $P = 0.17$) were indicative of good calibration.

Table 4 shows the prediction rules derived from this scoring system. Diagnostic performance parameters are reported for different cutoffs.

When high risk was defined as an overall score of ≥ 3, the scoring system had excellent sensitivity (94%), low specificity (41%), and an PPV and NPV of 44 and 93%, respectively, and an overall accuracy of 58%. Scores of ≥3 points were associated with an OR for early ESBL-EKP isolation of 10.39 (95% CI = 4.55 to 27.54, $P < 0.001$). When the cutoff was raised to 6, the sensitivity dropped (55%) and the specificity increased appreciably (94%). This cutoff level was associated with an PPV and NPV of 82 and 81%, an overall accuracy of 81%, and an OR for ESBL-EKP isolation of 18.40 (95% CI = 9.21 to 38.10, $P < 0.001$).

(ii) Validation set. As shown in Table 3 and Fig. 1, when the prediction rule was applied in the validation cohort, the model once again exhibited excellent predictive power (ROC AUC = 0.92; 95% CI = 0.89 to 0.95), as well as good calibration (Hosmer-Lemeshow $\chi^2 = 14.07$; $P = 0.23$).

TABLE 4. Model and risk score performance: derivation set ($n = 339$)

Score	Model and risk score performance[a]								
	TP	FP	TN	FN	Se	Sp	PPV	NPV	Acc
≥2	113	174	52	0	100	23	39	100	49
≥3	106	134	92	7	94	41	44	93	58
≥4	92	75	151	21	81	67	55	88	72
≥5	87	59	167	26	77	74	60	87	75
≥6	62	14	212	51	55	94	82	81	81
≥7	58	12	214	55	51	95	83	80	80
≥8	24	5	221	89	21	98	83	71	72
≥9	22	4	222	91	19	98	85	71	72
≥10	9	1	225	104	8	100	90	68	69
≥11	7	1	225	106	6	100	88	68	68
≥12	4	0	226	109	4	100	100	67	68

[a] TP, number of true positives; FP, number of false positives; FN, number of false negatives; TN, number of true negatives; Se, % sensitivity; Sp, % specificity; PPV, % positive predictive value; NPV, % negative predictive value; Acc, rate of accuracy (%) of the risk score model.

TABLE 5. Model and risk score performance: validation set ($n = 510$)

Score	Model and risk score performance[a]								
	TP	FP	TN	FN	Se	Sp	PPV	NPV	Acc
≥2	98	204	204	4	96	50	32	98	59
≥3	95	108	300	7	93	74	47	98	77
≥4	91	73	335	11	89	82	55	97	84
≥5	84	60	348	18	82	85	58	95	85
≥6	74	20	388	28	73	95	79	93	91
≥7	69	17	391	33	68	96	80	92	90
≥8	49	1	407	53	48	100	98	88	89
≥9	47	0	408	55	46	100	100	88	89
≥10	28	0	408	74	27	100	100	85	85
≥11	20	0	408	82	20	100	100	83	84
≥12	15	0	408	87	15	100	100	82	83

[a] TP, number of true positives; FP, number of false positives; FN, number of false negatives; TN, number of true negatives; % Se, sensitivity; % Sp, specificity; PPV, % positive predictive value; NPV, % negative predictive value; Acc, rate of accuracy (%) of the risk score model.

The prediction rules derived from the scoring system in the validation set are listed in Table 5 with diagnostic performance parameters for the main cutoffs. The ORs for ESBL-EKP isolation within 48 h of hospital admission were even higher than those observed in the derivation cohort: 37.69 (95% CI = 16.76 to 98.55, $P < 0.001$) for scores ≥ 3 and 51.27 (95% CI = 26.30 to 100.90, $P < 0.001$) for scores ≥ 6. The lower cutoff displayed excellent sensitivity but lost specificity; use of the higher cutoff markedly increased specificity and diminished sensitivity to some extent, but the overall accuracy was better than that associated with a cutoff of 3 (91% versus 77%).

Application of the model in the combined cohort. When we combined the two cohorts ($n = 849$), the predictive effects of the model were similar to those observed in the derivation set. The ORs for early isolation of ESBL-producing *Enterobacteriaceae* associated with scores of ≥3 and ≥6 were 23.25 (95% CI = 13.11 to 44.18, $P < 0.001$) and 30.37 (95% CI = 19.10 to 48.66, $P < 0.001$), respectively. The lower cutoff displayed a sensitivity, specificity, PPV, NPV, and overall accuracy of 93%, 62, 45, 97, and 70, respectively. The corresponding figures for the 6-point cutoff were 63, 95, 80, 88, and 87%, respectively. In the combined cohort, the prediction rule had an ROC AUC of 0.89 (95% CI = 0.87 to 0.92) (Fig. 1) and a Hosmer-Lemeshow χ^2 of 10.19 ($P = 0.51$).

DISCUSSION

In recent years, ESBL-EKPs have been increasingly implicated as causes of both hospital and community-acquired infections (1–3, 9, 7, 10, 14, 16, 18, 22–24, 34,). Their role in the latter type of infections implies that reservoirs of these pathogens exist outside hospitals and not only among individuals with frequent healthcare contacts. Indeed, Mesa et al. reported relatively high isolation rates in livestock, food, and human sewage, with a general prevalence of 6.6% (19). The prevalence of fecal carriers varies, with reports up to 13.1 and 15.4% among healthy individuals and outpatients, respectively (15,

35). A recent study found ESBL-producing *E. coli* in the feces of 67.9% of patients with community-acquired urinary tract infections (UTIs) caused by these organisms, and fecal carriage was also increased in these patients' relatives (27.4% for those living in the same household, 15.6% for those living in other households, and 7.4% in nonrelatives) (25).

This widespread occurrence of ESBL-EKP in the community has important implications for the management of infections in hospital settings. For one thing, current policies on the empirical treatment of serious community-acquired infections that might be caused by *Enterobacteriaceae* (e.g., complicated UTIs and intra-abdominal infections) might need to be revised. Second, early identification of patients likely to be colonized and/or infected with these bacteria is also an important step in the prevention or containment of their spread among hospitalized patients. There is a pressing need for an easy-to-use risk stratification tool that can be used at hospital admission. However, while the clinical impact of serious infections caused by ESBL-producing *Enterobacteriaceae* in inpatient populations has been well documented (1, 16, 23), few studies have analyzed risk factors for the entry of ESBL-producing organisms into hospitals (2–4, 10, 14, 18, 24).

Our study was conducted in three medical centers where serious infections caused by strains of ESBL-EKP are increasing in frequency. The results demonstrated that patients harboring these organisms can be reliably identified on admission by the application of a simple clinical prediction rule. This type of risk stratification has proved to be an important strategy for improving clinical decisions and infection control (11, 13, 17, 29, 30). Our score is, to the best of our knowledge, the first one that specifically identifies probable carriers of ESBL-EKP among new admissions.

The multivariate model identified six factors associated with the isolation of ESBL-EKP within the first 48 h of hospitalization. They include previous therapy with β-lactams and/or fluoroquinolones, previous hospitalization, transfer from another healthcare facility, a Charlson comorbidity score of ≥4, recent history of urinary catheterization, and an age of ≥70 years.

Predictors of admission with ESBL-EKP infection/colonization that were identified by our multivariate models include factors associated with healthcare-related environmental exposure to ESBL-producing organisms and others reflecting increased susceptibility to bacterial colonization of the gastrointestinal tract, i.e., the recent use of antibiotic therapy. However, the emergence of ESBL-producing bacteria (particularly those producing CTX-M-type β-lactamases) in patients who have not had recent contact with the healthcare system can confuse the strategies based solely on such risk factors. Our score also includes important variables such as patient age, recent history of urinary catheterization, and the presence of comorbidities.

The score is simple to calculate and constructed from variables that are readily available at the time of admission, such as demographic characteristics, elements of the patient history, and routine clinical findings. This enhances its practical value in clinical settings, and its consistent use might conceivably reduce the subsequent need for surveillance cultures. It provided good discrimination of risk in both the derivation and validation sets, with similar ROC AUCs, and the fact that the two cohorts came from different hospitals and were hospitalized during different time periods increases the likelihood that our findings can be generalized to a broad range of patients and acute-care facilities.

When a threshold of ≥6 was used, the specificity of prediction was more than 94% in both the derivation and validation sets, and the PPV and NPV were, respectively, 82 and 81% in the derivation set and 79 and 93% in the validation set. Although sensitivity was low (55 and 73% in the derivation and validation sets, respectively), the high specificity of the prediction could improve targeting of high-risk patients. Conventional measures used to identify inpatients colonized by antibiotic resistant strains of bacteria (e.g., rectal swabs) could be limited to this subset of individuals, thereby reducing workloads as well as costs. In addition, high-risk patients could be empirically subjected to appropriate infection control measures while the screening cultures are being processed.

Inappropriate antimicrobial drug therapy during the empirical phase of treatment is the main risk factor for mortality in patients with severe infections caused by ESBL-EKP (8, 12, 21, 31–33), including those that are community acquired (1, 23). Use of our scoring system with the lower threshold (≥3) could provide useful information for prescribing empirical therapy. In the derivation set, the sensitivity (94%) and NPV (93%) of our model were very high, while the specificity (41%) and PPV (44%) were low. Similar figures emerged in the validation set. If patients with scores ≥ 3 initially receive broad-spectrum antibiotic treatment that includes an agent active against ESBL-EKP (e.g., carbapenems), the probability of inappropriate therapy should be very low (<10%). However, because the PPV associated with this cutoff is low, this type of treatment would also be administered to about half the patients with infections caused by bacteria other than ESBL-producing *Enterobacteriaceae*. Therefore, a more appropriate strategy might be to use drugs likely to be effective against ESBL producers when the patient's score is ≥3 and (i) the infection is suspected to be serious and/or (ii) the patients are already severely ill, situations in which initially inappropriate antibiotic therapy carries a high risk of mortality. In either case, however, as soon as microbiological data become available, antibiotic treatment should be de-escalated whenever appropriate to prevent the subsequent emergence of multidrug-resistant bacteria. It is important to note that application of the scoring system in empirical treatment decision-making processes needs further validation against a different type of control population, i.e., hospitalized patients suspected of infection (including more severe infections such as bacteremia) whose cultures did not grow ESBL-EKPs.

Our study has a number of other limitations. First, the data set we used included relatively few patients harboring ESBL-EKP isolates. This may have led us to underestimate the role of certain factors and, although our findings are statistically significant, our conclusions do need to be confirmed in a larger clinical trial. Second, because rectal swab screening for ESBL-EKP was not performed on admission in any of the hospitals involved in the present study, the control group might conceivably have included some colonized patients without clinical manifestations. This might also have facilitated the underestimation of some risk factors. Third, considerable variability in community-onset ESBL-EKP infections has been observed between different countries and within different subregions of the

same area. Consequently, our results might not be applicable in all parts of the world (18, 22). For example, international travel has been reported as a major risk factor for developing an ESBL-producing *E. coli* infection in certain parts of the world (e.g., Canada and New Zealand) (18), but this variable was not even analyzed in our scoring system.

In conclusion, we have developed and validated a novel scoring system that can reliably identify patients likely to be harboring ESBL-producing *Enterobacteriaceae* on hospital admission. The score is based on six easy-to-define variables that are readily available at the time of hospital admission. Proper use of this tool should minimize the time required to identify patients harboring these organisms and allow more rapid application of measures designed to prevent the spread of these resistant strains within the inpatient population. Future efforts should focus on quantifying its value as a risk assessment tool compared to the clinical judgment of hospitalists, which is likely to be highly variable from one setting to another.

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