Journal of Hospital Infection 102 (2019) 8–16

Available online at www.sciencedirect.com

Journal of Hospital Infection

journal homepage: www.elsevier.com/locate/jhin

Review

Clinical prediction models for ESBL-Enterobacteriaceae colonization or infection: a systematic review

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ARTICLE INFO

Article history:
Received 12 November 2018
Accepted 10 January 2019
Available online 14 January 2019

Keywords:
ESBL
Extended-spectrum beta-lactamases score
Prediction
Risk stratification

SUMMARY

Background: β-Lactamase resistance among certain Gram-negative bacteria has been associated with increased mortality, length of hospitalization, and hospital costs.
Aim: To identify and critically appraise existing clinical prediction models of extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBL-EKP) infection or colonization.
Methods: Electronic databases, reference lists, and citations were searched from inception to April 2018. Papers were included in any language describing the development or validation, or both, of models and scores to predict the risk of ESBL-EKP infection or colonization.
Findings: In all, 1795 references were screened, of which four articles were included in the review. The included studies were carried out in different geographical locations with differing study designs, and inclusion and exclusion criteria. Most if not all studies lacked external validation and blinding of reviewers during the evaluation of the predictor variables and outcome. All studies excluded missing data and most studies did not report the number of patients excluded due to missing data. Fifteen predictors of infection or colonization with ESBL-EKP were identified. Commonly included predictors were previous antibiotic use, previous hospitalization, transfer from another healthcare facility, and previous procedures (urinary catheterization and invasive procedures).
Conclusion: Due to limitations and variations in the study design, clinicians would have to take these differences into consideration when deciding on how to use these models in clinical practice. Due to lack of external validation, the generalizability of these models remains a question. Therefore, further external validation in local settings is needed to confirm the usefulness of these models in supporting decision-making.

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https://doi.org/10.1016/j.jhin.2019.01.012

Introduction

Several studies have suggested that infections caused by extended-spectrum β-lactamase-producing Enterobacteriaceae (i.e. *Escherichia coli*, *Klebsiella* spp., and *Proteus mirabilis*) (ESBL-EKP) have an important clinical impact, and the increasing prevalence of these organisms in hospitals has been well documented [1–3]. β-Lactamase resistance among certain Gram-negative bacteria has been associated with increased mortality, length of hospitalization, and hospital costs. A study by Schwaber *et al.* concluded that infection with an ESBL-producing organism was associated with an adjusted 3.6-fold increased risk of in-hospital mortality, an unadjusted 2.3-fold increased risk of infection-related mortality, an adjusted 1.6-fold increase in length of stay, an adjusted 25-fold increased risk of delay in appropriate therapy, and an unadjusted 4-fold-increased likelihood of discharge to a long-term care facility for those who survived [4]. In view of these potential complications, it is important to implement measures to combat resistance, develop treatment strategies to overcome the adverse consequences of resistance, and to identify patients at risk of resistance early and accurately, so that effective antibiotic therapy can be given.

Precise determination of risk factors for ESBL-EKP infection may assist in accurate targeting of empirical carbapenem therapy; with appropriate therapy, there should be a decline in treatment failure, infectious complications, antibiotic costs, and the risk of selecting carbapenem resistance [5,6]. A risk discrimination tool that can identify patients likely to harbour ESBL-EKP might therefore assist with rational antibiotic prescribing and the early implementation of infection control precautions [7].

Several clinical scoring tools have been published since 2011 [7–10]. Attempts to develop or validate these scoring tools have been made by different study groups in different populations and their findings have been heterogeneous. To our knowledge, no previous systematic review of clinical risk scoring systems for predicting ESBL-EKP colonization or infection in hospitalized patients has been published. Therefore, we aimed to carry out a systematic review, to describe and give an overview of these scoring systems, and to compare and contrast the scores to assist clinicians in their use in clinical practice.

Methods

The Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies (CHARMS) Checklist was followed to guide the framing of the review aim, search strategy, and study inclusion and exclusion criteria [11]. The review was prospectively registered in PROSPERO [12]. Reporting of the review was consistent with PRISMA guidelines [13].

Search strategy

Models for review were identified by searching: Medline, Embase, CINAHL, and the Cochrane Database of Systematic Reviews (CDSR) from inception to April 2018, and by searching the reference lists and citations of included studies. Articles published in any language were included. We used a mixture of MeSH terms and free text for the keywords 'beta-Lactamases' (MeSH), 'beta-Lactam Resistance' (MeSH), 'lactamases', 'extended spectrum beta-lactamase', 'extended spectrum beta lactamase producing enterobacteriaceae', 'ESBL-E', 'ESBLE', ESBL, 'Risk Assessment' (MeSH), 'Risk' (MeSH), 'Risk Assessment' (MeSH), 'risk function', 'risk equation', 'risk chart', 'risk tool', 'risk assessment function', 'risk assessor', 'risk appraisal', 'risk calculation', 'risk calculator', 'risk factor calculator', 'risk factor calculation', 'risk engine', 'risk equation', 'risk table', 'risk threshold', 'risk disc', 'risk disk', 'risk scoring method', 'scoring scheme', 'risk scoring system', 'risk prediction', 'predictive instrument', 'project risk', 'scoring model', 'scoring system', 'prediction model'. The authors also conducted an additional search on the references of relevant papers.

Selection criteria

Studies attempting to develop a scoring model/score for the prediction of ESBL-EKP colonization or infection in hospitalized patients were included. Studies on the associations between clinical variables and ESBL-EKP colonization or infection were excluded. Studies in which the study setting was in the community were also excluded.

Populations for this review were broadly inclusive, involving any country and both sexes. The target population comprised individuals admitted to hospital, aged ≥18 years, with active infection or colonization with ESBL-EKP.

Study selection

Four independent reviewers performed the study selection (S.M.S.L. and N.A. screened search results obtained from two databases; P.L.W. and H.S. screened search results from another two databases) based on the predefined inclusion and exclusion criteria. They screened all titles and abstracts of the articles to identify potentially eligible studies. The full text of these potentially eligible studies was then evaluated to determine eligibility for inclusion into the systematic review. Disagreements were resolved through discussion (S.M.S.L., N.A., P.L.W., and H.S.).

Quality assessment

The full text versions of articles that met the study inclusion criteria were then sought and independently rated for methodological quality by all team members (two raters per article). Quality assessment of the included studies was done according to the Critical Appraisal Skills Programme checklist for clinical prediction rule (CASP-CPR) [14].

Data extraction process

Four reviewers extracted data from each article (S.M.S.L., N.A., P.L.W., and H.S.). Discrepancies between the reviewers were resolved by consensus. The following data were extracted from the included trials: source of data or study design, participant eligibility and recruitment method, description of participants, study date and setting, definition and method for measurement of the outcome to be predicted, time of outcome occurrence, predictors included in the clinical prediction rule, definition and method for measurement of predictors, timing

of predictor measurement, number of participants, number of participants with any missing value, handling of missing data, modelling method, method for selection of predictors for inclusion in multivariable modelling, calibration and discrimination measures with confidence intervals, method used for testing model performance (development dataset only or separate external validation, whether model was adjusted or updated, model performance measures, interpretation of presented models, comparison with other studies, and discussion of generalizability, strengths and limitations). To gather missing data, we attempted to contact the corresponding authors of the included studies.

Results

Study selection

Our search identified 1795 articles after removal of duplicates. Only four articles meeting the inclusion criteria were included in the systematic review (Figure 1) [7–10]. The earliest study was published in 2011 and the most recent was published in 2017.

Study design and participants

Two types of study design were used: retrospective matched case–control studies [8,9] and cohort studies [7,10]. Only one study performed an external prospective validation of the prediction model derived from their derivation study [9]. All studies were done in the hospital setting, whereby three used inpatient cohorts [7–9] and one used emergency department patient cohort [10]. The prediction models were developed in Italy [9], USA [8], Thailand [7], and Taiwan [10]. Sample sizes in the derivation cohorts varied widely, ranging from 339 to 1141. Three of the derivation studies were done in a single centre [7–9]. The one validation study was carried out in two centres in Italy [9]. Three of the studies recruited patients admitted from 2008 onwards [8–10]. The period for patient recruitment ranged from two to five years.

The inclusion and exclusion criteria differed between the four studies. Three out of four studies included patients with ESBL-EKP [8–10], whereas one study included patients with ESBL-EC only [7]. One study only included positive blood cultures [10], whereas the others included any clinical specimens. All but one study included patients with signs and symptoms of active infection [9]. All four studies excluded patients with missing data. Other reasons for exclusion include known history of ESBL-EKP, readmission within 30 days and hospital-onset or polymicrobial bacteraemia. The number of excluded patients ranged from two to 2349. The breakdown of excluded patients according to the reason of exclusion was not documented.

The mean age of the study participants ranged from 63 to 68 years. In all studies, the majority of patients (53–57%) were female. The ESBL-EKP isolates were mainly recovered from

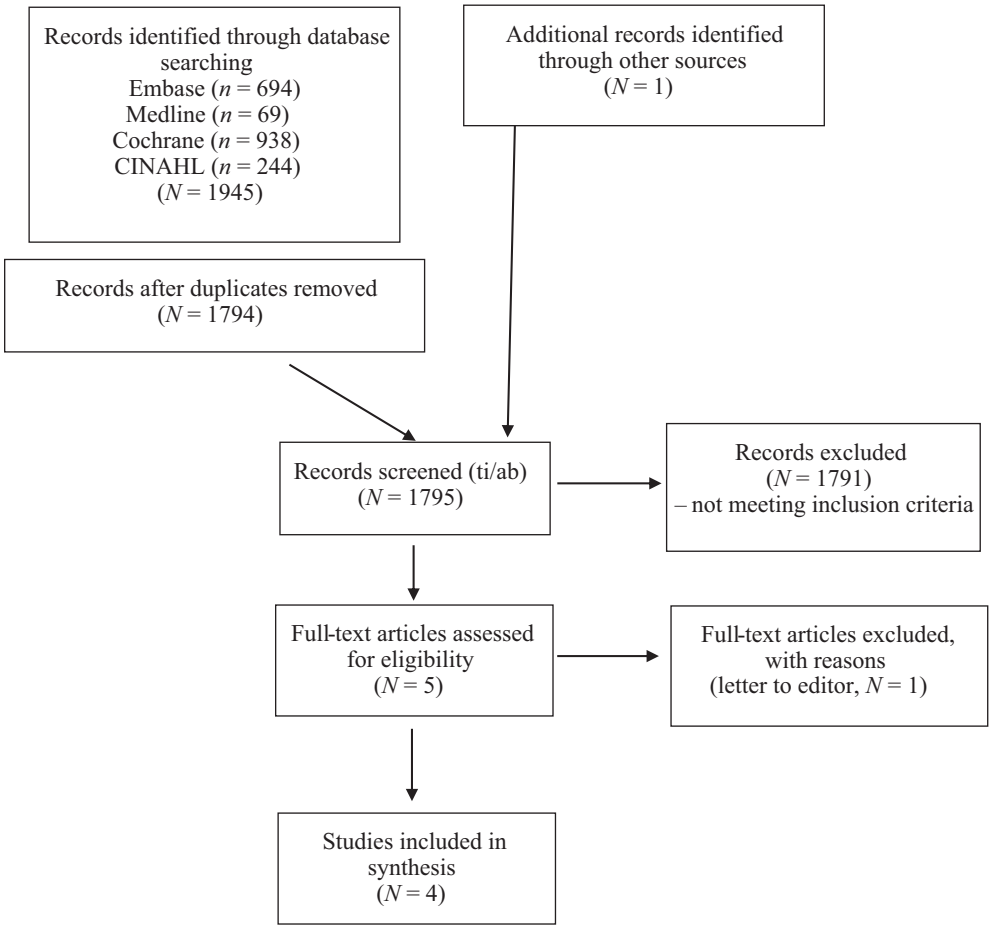

Figure 1. PRISMA flowchart detailing the search strategy.

urine specimens in all studies (52–76%). For the three studies including ESBL-EKP specimens, EC was the organism most frequently isolated (55–72%). Table I summarizes the characteristics of the included studies.

Outcome of interest

All studies looked at a single outcome. Three out of four studied infection with ESBL-EKP or ESBL-EC [7,8,10], whereas the remaining study examined either infection or colonization with ESBL-EKP [9]. ESBL phenotype was determined on the basis of Clinical and Laboratory Standards Institute-approved methods and interpretative criteria in all except one study, in which it was not mentioned. The term 'infection' was not clearly defined in all four studies. No study stated what outcomes were measured without knowledge of candidate predictor variables (i.e. blinded). No study stated whether candidate predictor variables were part of the outcome (e.g. in panel or consensus diagnosis) in any of the identified models. Time of specimen collection is either at presentation to hospital or any period during the hospital admission.

Risk predictors

The final number of risk predictors ranged from four to nine (Table II). All models included previous antibiotic use (either three months or four weeks prior to index admission) and most models included transfer from another healthcare facility and previous procedures (urinary catheterization or invasive procedure) 30 days prior to index admission [8–10]. Two studies included previous hospitalization 12 months prior to index admission [8,9] and age [7–9]. Other risk predictors included by some models were hospitalization >7 days, previous ESBL-EC infection one year prior to index admission, Charlson comorbidity index ≥4, use of immunosuppression three months prior to index admission, male gender, having hospital- or healthcare-associated infection, presence of sepsis, and three or more visits to the emergency department one year prior to index admission.

The methods of selection of predictor variables for inclusion in multivariable modelling was described for all models. Predictor variables were identified using significance testing. Timing of predictor measurement was at initial presentation in three studies [8–10]. It was not stated whether researchers assessing predictor variables were blinded to outcome and to other predictors (where relevant) in any of the identified studies. Handling of predictors in the modelling were similar in three studies for both continuous and categorical variables [8–10].

Predictor variables were defined and described in most studies. Immunosuppression was defined as use of (i) glucocorticoids that is equivalent to prednisone at ≥20 mg for at least two weeks or (ii) >48 h of any of the following: tacrolimus, sirolimus, cyclosporine, mycophenolate, or antithymocyte globulin, and chemotherapy (defined as alkylating agents) [8]. Hospital-acquired infection was defined as infection that occurred >48 h after admission to the hospital [7]. Healthcare-associated infection was defined as infection that occurred within 48 h of admission with more than one of the following criteria: (i) was receiving intravenous therapy at home; (ii) had attended a hospital or haemodialysis clinic, or received intravenous chemotherapy, in the preceding 30 days; (iii) had been hospitalized for two or more days within 90 days before onset of the infection; (iv) resident in a nursing home or long-term care facility [7]. Sepsis was defined as systemic inflammatory response to infections, manifested by two or more of the following: temperature >38 or <36°C, heart rate >90 bpm, respiratory rate >20 bpm or $PaCO_2$ <32 mmHg, and white blood cell count >12,000 or <4000 cells/mm^3 in a patient with suspected infection [7].

Sample size and missing data

None of the included studies considered a sample size calculation. Only one study reported the total number of participants with missing data (it was the only exclusion criterion for that study) (Table I) [8]. Most of the studies did not specify the number of participants with missing data for each predictor variable or outcome. Handling of missing data was described in all four studies but their justification was not documented. Three studies excluded participants with missing data [7–9]. One study performed complete case analysis if the missing values were <5%, or imputation if the missing values were ≥5% [10].

Model development

All studies used stepwise logistic regression to develop the identified prediction models, but only two described having used the backward method [9,10]; the other two did not specify [7,8]. No study reported whether modelling assumptions were satisfied or whether any investigations were undertaken to test assumptions. Shrinkage of predictor weights or regression coefficients was described in all but one of the identified models [10].

Model performance and evaluation

Only two studies reported calibration using Hosmer–Lemeshow test (Table III) [7,9]. All models illustrated discrimination using receiver–operating characteristic curves, but the 95% confidence interval was not reported for one model [8]. The discrimination of prediction models validated in their development population ranged from 0.74 to 0.92. One study was externally validated (temporally and geographically) with recalibration done for both the validation and combined (derivation and validation) cohorts [9]. The discrimination of the externally validated model was 0.92. One of the identified models was updated to adjust for alternate populations or to improve accuracy [8]. Sensitivity (74–94%), specificity (41–91%), positive predictive value (PPV) (40–73%) and negative predictive value (NPV) (68–99%) were reported in all studies.

Appraisal of models included

Quality assessment of the included studies was done according to CASP-CPR (Table IV) [14]. This assessment tool, however, was not developed to provide a score but it revealed that all studies lacked external validation and blinding of

Table I
Characteristics of included studies

Study	Years of study	Country	Study design	Validation	Patients (*N*) (case:control)	Inclusion	Exclusion	Excluded patients	Aim of study
Tumbarello *et al.* [9]	2008–2009	Italy	Matched case–control; derivation: retrospective; validation: prospective	External and temporal	Derivation: 339 (1:2); validation: 510 (1:4)	Positive cultures for ESBL-EKP in any specimen, collected within 48 h of hospital admission. Matched control: matched for hospital ward and month of admission, with no reports of culture positivity for EKP during their hospitalization.	(1) Known history of ESBL-EKP infection; (2) Missing data	Derivation: 2/115	To develop a clinical prediction rule. For identifying patients likely to harbour ESBL-EKP
Johnson *et al.* [8]	2008–2010	USA	Matched case–control; retrospective	Not applicable	448 (1:3)	Positive cultures for ESBL-EKP in any specimen, collected within 48 h of admission, with signs and/or symptoms consistent with active clinical infection. Matched control: matched for hospital ward and month of admission, with no reports of culture positivity for EKP during their hospitalization.	Missing data	50/498	To develop a score for identifying patients with infection due to ESBL-EKP
Kengkla *et al.* [7]	2011–2014	Thailand	Cohort; retrospective	Not applicable	810	Positive cultures for EC in any specimen throughout the period of admission, with signs and/or symptoms consistent with active clinical infection	(1) Missing data; (2) Readmitted to hospital within 30 days	2349/3159	To develop a score for predicting ESBL-EC infection
Lee *et al.* [10]	2008–2013	Taiwan	Cohort; retrospective	Not applicable	1141	Positive blood cultures for EKP, with signs and/or symptoms consistent with active clinical infection	(1) Hospital-onset bacteraemia. (2) Polymicrobial bacteraemia. (3) Bacteraemia before arrival to the ED	25/1166	To develop a score for identifying patients at high risk for ESBL-EKP infections

ESBL, extended-spectrum β-lactamase; ED, emergency department.

Table II
Identified variables and authors' recommendations

Reference	Previous antibiotic use	Previous hospitalization	Prolonged hospitalization	Transfer from other healthcare facilities	Previous procedures	Comorbidities	Previous ESBL infection	Age (years)	Gender	HAI or HCAI	Presence of sepsis	ED visits	Range of score	Threshold score	Authors' recommendation
Tumbarello *et al.* [9]	3 months prior	12 months prior		Yes	Urinary catheterization 30 days prior	Charlson score ≥4		≥70					0–14	3	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.
Johnson *et al.* [8]	3 months prior	12 months prior		Yes	Urinary catheterization 30 days prior	Immunosuppression 3 months prior							0–16	8	Consider withholding empiric antimicrobial therapy with in-vitro activity against ESBL-EKP in patients with scores ≤4. Consider giving empiric antimicrobial therapy with in-vitro activity against ESBL-EKP in patients with scores ≥8.
Kengkla *et al.* [7]	3 months prior		>7 days				1 year prior	≥55	Male	Yes	Yes		0–39	12	Do not give empiric therapy to cover for ESBL-EC in patients with score ≤8. Use BLBLI or fluoroquinolones as empiric therapy for patients with score between 9 and 11. Use carbapenems as empiric therapy for patients with score of ≥12.
Lee *et al.* [10]	4 weeks prior			Nursing home resident	Invasive procedure 30 days prior							≥3 visits one year prior	0–4	2	Consider giving empiric antimicrobial therapy with in-vitro activity against ESBL-EKP in patients with scores ≥2

ESBL, extended-spectrum β-lactamase; HAI, hospital-associated infection; HCAI, healthcare-associated infection; ED, emergency department; BLBLI, β-lactam/β-lactamase inhibitor.

Table III
Model performance and evaluation

Study	Calibration[a]	Discrimination[b] (95% CI)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Overall accuracy (%)
Tumbarello *et al.* [9]							
Derivation cohort	χ^2 =15.28; $P = 0.17$; good calibration	0.83 (0.79–0.88)	94	41	44	93	58
Validation cohort	$\chi^2 = 14.07$; $P = 0.23$; good calibration	0.92 (0.89–0.95)	93	74	47	98	77
Combined cohort	$\chi^2 = 10.19$; $P = 0.51$	0.89 (0.87–0.92)	93	62	45	97	70
Johnson *et al.* [8]	Not recorded	0.89	87	69	48	94	73
Kengkla *et al.* [7]	$\chi^2 = 13.29$; $P = 0.065$	0.773 (0.742–0.805)	74	66	73	68	70
Lee *et al.* [10]	NR	0.92 (0.88–0.96)	84.6	92.5	40.4	99	NR

CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.
[a] Hosmer–Lemeshow test.
[b] Receiver–operating characteristic area under the curve.

reviewers. It is also unclear whether any of the prediction models could be applied locally and how they might impact local clinical management, as each model would first need to be validated in our own population before being applied in clinical practice.

Discussion

In the last two decades, extensive use of broad-spectrum β-lactams has led to the emergence of antibiotic-resistant strains of Enterobacteriaceae, including ESBL-EKP [1,15,16]. β-Lactams are most commonly used for the treatment of bacterial infections. The persistent exposure of bacterial strains to a multitude of β-lactams has induced dynamic and continuous production, and mutation of the β-lactamase enzymes in these bacteria, expanding their activity to newly developed β-lactam antibiotics. ESBLs are now widespread throughout the world, but the prevalence and phenotypic characteristics of clinical isolates varies according to geographical areas [2,17].

Carbapenems therefore become the antimicrobial of choice for the treatment of infections due to ESBL-EKP, but they come at a cost [18]. Excessive use of carbapenems for empirical treatment of suspected ESBL-EKP infection may promote carbapenem resistance in bacteria such as *E. coli*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*, as well as adding to antibiotic costs [19,20]. This needs to be balanced against the risks of delay in initiating appropriate antibiotic therapy in hospitalized cases of infection with ESBL-EKP, which may be associated with increased rates of complications and mortality [4,21–23].

Precise determination of risk factors for ESBL-EKP infection may assist in accurate targeting of empirical carbapenem therapy. A scoring system provides end-users with a predictive tool as well as a way to stratify and identify populations at risk by taking into account patients' characteristics as well as the size effect accorded by each selected variable [24]. However, such a system at should be appraised and validated at each centre prior to its use due to possible inherent issues of each published model. These issues may limit respective tools' external validity and use. This review shows that there is only a handful of ESBL-EKP infection prediction models for patients who are hospitalized. There are few external validation studies for most of these developed models, therefore their generalizability remains a question.

Most studies included in this review had one or more limitations. All studies were done retrospectively, which has its own disadvantages. There were differences in the study design and inclusion criteria. Some models omitted reporting of key statistical properties such as calibration values that would allow a clinician to judge the practical value of the score. With variations in the study design, inclusion criteria, and outcome to be predicted – such as inpatient vs emergency department patients; inclusion of ESBL-EKP vs ESBL-EC; bacteraemic vs non-bacteraemic patients; patients with active infection vs without infection; or infection vs colonization – clinicians would have to take these differences into account before deciding on which population of patients to apply these scores on or which cut-off points to use. We have not selected a single risk score that we favoured, as we are unclear of the significance of these models in our own local setting due to the lack of external validation of these models.

There is no universal ideal risk score, as the utility of any score depends not merely on its statistical properties but also on its context of use [25]. Even when a risk model has excellent discrimination (and especially when it does not) the balance between sensitivity and specificity plays out differently depending on the intended application. If the desired application is a screening tool, choosing a cut-off score with a high sensitivity and NPV but 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 cut-off. As opposed to predicting empirical use of antibiotic therapy directed at ESBL-EKP, a threshold score with a higher specificity and PPV, with lower sensitivity, should be used [7,8].

However, from this review, we noticed a few predictors that were present in most (at least two) of the models. These are previous antibiotic use, previous hospitalization, transfer from another healthcare facility, and previous procedures (urinary catheterization and invasive procedures) (Table III). This similarity would perhaps be useful for those intending to validate these scores or develop their own. Validation in local settings is important, as suggested by the primary authors, as they developed a tool for their local use and made no claims that their score should be generalized elsewhere. Having said that, the authors did give suggestions on who could use the score, on whom, and in what circumstances (Table III).

Table IV
Appraisal of included studies

Study	Clear CPR	Appropriate sampling	External validation	Blinding	Exclusions were described	Description of statistical methods	Calculation of performance	Rule refined	Local applicability	Reasonable and easy to use	Impact on clinical management
Tumbarello *et al.* [9]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Unclear	Yes	Unclear
Johnson *et al.* [8]	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Unclear	Yes	Unclear
Kengkla *et al.* [7]	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Unclear	Yes	Unclear
Lee *et al.* [10]	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Unclear	Yes	Unclear

CPR, clinical prediction rule.

To our knowledge this is the first review of predictive models for ESBL-EKP infection or colonization. A comprehensive literature search from multiple databases using broad search terms was performed. We also performed a citation track to identify recently published studies. Furthermore, extraction and double checking of data was done by four researchers. Members of our author team came from different backgrounds, allowing each author to express different perspectives on model evaluation. We attempted to contact corresponding authors of each study for missing information. A major limitation of this review is that only four heterogeneous studies were identified for inclusion into the systematic review. Due to the differences in the methodology and study endpoints, a meta-analysis was not performed.

In conclusion, this study has identified predictive risk models of ESBL-EKP infection or colonization. However, their usefulness remains ambiguous due to the various differences in the study settings. Further external validation studies to confirm their utility in supporting decision-making are needed. Caution is required when deciding to use these scores in a local clinical setting. Nevertheless the existing models have much potential. Those wishing to develop a score for infection or colonization with ESBL-EKP are advised to build on previous works, and to update and adapt existing models to local contexts. The newly developed model should then be validated in a different dataset to test its true performance.

Conflict of interest statement
None declared.

Funding sources
None.

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