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ORIGINAL ARTICLE

# Development of a Clinical Prediction Tool for Detecting Hospital-acquired Extended-spectrum β-lactamase-Producing Gram-Negative Bacteria in Pediatric Patients

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## ABSTRACT

**Objectives:** Extended-spectrum β-lactamase (ESBL)-producing bacteria are important causes of hospital-acquired infections. While prediction tools exist for adults, limited data are available in children. This study aimed to develop a simple tool to identify pediatric patients at risk for ESBL-producing bacteria.

**Methodology:** A retrospective study was conducted in a tertiary government hospital involving pediatric inpatients. Risk factors were analyzed using logistic regression to derive a scoring system based on independent predictors. Model performance was evaluated using the area under the curve, the Hosmer–Lemeshow test and internal validation.

**Results:** Among 389 pediatric patients, three risk factors were independently associated with ESBL production: prior cephalosporin use within 3 months, mechanical ventilation, and indwelling urinary catheterization. These were incorporated into a 4-point scoring system. The model demonstrated moderate discrimination (AUC 0.70, Hosmer-Lemeshow p=0.0805) and correctly classified 74.8% cases as low (0-1) and high risk (2-4). Bootstrapped validation accuracy was 63.2%, showing good internal stability.

**Conclusion:** This practical tool, based on readily available clinical data, may aid early risk stratification for ESBL production and guide antibiotic therapy in children, supporting antimicrobial stewardship. Prospective validation in diverse pediatric populations is recommended.

**KEYWORDS:** Extended-spectrum β-lactamase (ESBL), clinical prediction tool, hospital-acquired infection, antimicrobial stewardship

## INTRODUCTION

One of the emerging threats to health systems globally is the emergence of antimicrobial resistance, particularly among extended-spectrum β-lactamase (ESBL)-producing gram-negative bacteria. These enzymes confer resistance to β-lactam antibiotics, which include penicillins and cephalosporins, thereby limiting our effective treatment options and increasing the length of hospital stay, healthcare costs, and risk for mortality when empiric antibiotics are inadequate or delayed.[1,2] Literature primarily focuses on adult patients, but over the past years, pediatric patients have been increasingly affected, particularly those with repeated healthcare exposure, prolonged hospitalization, or immunocompromising conditions.[3] In low- to middle-income countries, where the capacity to perform diagnostic tests is oftentimes limited, empiric antibiotic selection is often based on clinical judgment, which can complicate resistance patterns and treatment outcomes.[4]

Worldwide, the incidence of ESBL-producing gram-negative bacteria in children is rising. A 2019

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meta-analysis reported a pooled prevalence of 9% among pediatric bloodstream infections, with higher rates in neonates.[5] Risk factors commonly present in the pediatric population include recent use of antibiotics, admissions to the intensive care unit, and underlying chronic medical conditions.[3,6] Existing adult-based prediction models have shown utility in identifying patients at risk for ESBL-producing bacteria. In the study by Augustine et al. (2017) conducted in the United States, independent predictors included male sex, age > 55 years, sepsis, prolonged hospitalization, history of ESBL infection within the previous year, and prior use of cephalosporins and other antibiotics.[7] Similarly, Kengkla et al. (2015) in Thailand identified outpatient procedures within 1 month, prior infection with ESBL within the previous year, and prior courses of β-lactams and/or cephalosporins within three months as significant predictors.[8] These models, however, have limited applicability to the pediatric population due to clinical and physiological differences,[7] highlighting the growing need for pediatric-specific risk stratification tools.

Given these challenges, this study aimed to develop a simple, evidence-based clinical prediction tool to guide empiric therapy decisions in pediatric patients with gram-negative infections. By identifying independent risk factors and translating them into a practical scoring tool, this study seeks to support a more targeted and judicious use of antibiotics, thereby optimizing treatment outcomes and addressing the challenge of antibiotic resistance, particularly in resource-limited settings.

## MATERIALS AND METHODS

### *Study Design*

This study employed a retrospective cohort design, selected due to feasibility, the availability of clinical and microbiologic data, and the intention of developing an initial prediction model prior to prospective validation.

### *Study Participants*

This study was conducted at the Philippine General Hospital, a tertiary-level pediatric center. Medical records of patients aged 0 to 18 years old admitted from January 1, 2022 to December 31, 2024 with hospital-acquired (infection which occurred >48 hours after admission), laboratory-confirmed ESBL-producing and non-ESBL-producing gram-negative bacterial infection were reviewed. Patients included in this study were those with clinically significant infections based on physician assessment and documentation; who had culture-proven, hospital-acquired ESBL-producing or non-ESBL-producing gram-negative bacteria from the blood, endotracheal aspirate, urine or cerebrospinal fluid as determined by routine antimicrobial susceptibility testing using VITEK® 2, disk diffusion, or Clinical and Laboratory Standards Institute (CLSI) guidelines; and had complete clinical and microbiological documentation.

Patients with incomplete medical records and those discharged before antibiotic susceptibility results became available were excluded from the study.

A formal sample size calculation was not performed due to the manner of sampling, wherein all eligible patients meeting the inclusion criteria within the predetermined study period were included in the analysis. However, the sample size adequacy for developing a logistic regression-based model was assessed.

### *Data Collection*

Relevant clinical and microbiological data were extracted from patient records using a standardized data collection form. The following variables were included: age and sex; location of the patient at the time of organism isolation (general ward, intensive care unit, surgical ward); duration of hospitalization (prolonged hospitalization defined as > 7 days); history of ESBL infection within 1 year; intervention history (recent surgery <3 months, indwelling central venous catheter, indwelling urinary catheterization maintained for a minimum of 48 hours prior to collection of a positive culture, irrespective of culture site, and mechanical ventilation following a minimum hospital stay of 48 hours); comorbid conditions (chronic kidney disease, cardiovascular disease, neurological disease, gastrointestinal disease, autoimmune disease, malignancy, current immunosuppressive therapy); prior antibiotic use within 3 months (penicillins, cephalosporins, beta-lactamase inhibitors, carbapenems, fluoroquinolones, aminoglycosides); and microbiologic data, including ESBL production status. Records with incomplete variables were excluded.

### *Data Analysis*

Raw data were encoded in Microsoft Excel by the primary investigator. Data analysis was done using IBM SPSS Statistics (Version 29.0; IBM Corp., Armonk, NY), and bootstrapping was performed using standard SPSS procedures.

*Descriptive Analysis*

Categorical variables were summarized using frequencies and percentages**.** Continuous variables were described using means and standard deviations or medians and interquartile ranges, depending on data distribution.

*Univariate and Multivariable Analysis*

The association between each clinical variable and the presence of ESBL-producing organisms was initially assessed using Chi-square or Fisher's exact test for categorical variables, and Independent t-test or Mann–Whitney U test for continuous variables. Variables with a p-value < 0.05 were considered candidates for inclusion in the multivariable analysis. A multiple logistic regression model was developed to identify independent predictors of ESBL-producing gram-negative infections. Adjusted odds ratios (aORs), 95% confidence intervals (CIs), and p-values were reported.

*Post-hoc Subgroup Analysis*

The study population included a heterogeneous mix of pediatric patients, from premature neonates in the neonatal intensive care unit to adolescents in the general ward. This approach was adopted to strengthen the clinical applicability of the prediction tool across a varied pediatric hospital setting, reflecting actual patient diversity. However, the inclusion of a broad patient group may introduce differences in baseline risk profiles and pathogen distributions that a single model may not fully account for. This heterogeneity may then affect the precision of risk estimation in specific subgroups and is considered a limitation of the study.

Subgroup analysis was done to determine the consistency of identified risk factors across more clinically homogeneous groups, including age-based subgroups, neonatal intensive care unit patients, and patients with *Klebsiella pneumoniae* infection. These analyses were not pre-specified in the original study design and were conducted post hoc; thus, they were considered exploratory in nature. The findings from these subgroup analyses are intended to provide supportive insights instead of definitive conclusions. Further prospective studies with pre-specified subgroups are warranted to validate these observations.

*Risk Estimation of the Clinical Prediction Tool*

Each predictor retained in the final logistic regression model was assigned a weighted score based on its corresponding β coefficient. Coefficients were standardized by dividing each by the smallest absolute β value and rounding to the nearest whole number. The total score for each patient was calculated by summing the points assigned to each risk factor present.

*Model Performance Assessment*

Discrimination of the clinical score was assessed using the area under the receiver operating characteristic (ROC) curve (AUC). Calibration was assessed using the Hosmer–Lemeshow goodness-of-fit test.

Internal validation was performed through bootstrap analysis. A total of 200 bootstrap samples were generated from the original dataset (n = 389) using sampling with replacement so each bootstrap sample was equal in size to the original dataset.

For each dataset that was resampled, the full modeling process was repeated and performance metrics (accuracy, sensitivity, specificity, positive predictive value, and negative predictive value) were calculated. The average of these estimates across all samples was used to derive the internally validated model performance. The bootstrap-derived performance estimates were consistent with the apparent performance, which suggests generalizability of the prediction tool.

*Ethical Considerations*

Ethical approval was obtained from the University of the Philippines Manila Research Ethics Board (UPMREB) prior to data collection. A request was submitted to the UPMREB panel for a waiver of informed consent. Patient data was anonymized before analysis. All identifiers were removed and replaced with a study code number to ensure confidentiality. The dataset was encrypted, password-protected, and stored in an external hard drive accessible only to the primary investigator and shared with the statistician for data analysis. These steps were in accordance with the Data Privacy Act of 2012.

Raw electronic data will be deleted 5 years from study completion. All paper files are stored in a designated drawer with lock and key and will be shredded 2 years from study completion. The primary investigator has no financial or professional conflicts of interest.

## RESULTS

*Demographics and Clinical Characteristics*

Of the 403 patients with gram-negative isolates (*Escherichia coli, Klebsiella pneumoniae, Klebsiella oxytoca,* and *Aeromonas* species), 389 were included in the final study. Fourteen were excluded due to incomplete

medical records, including no data on antibiotic exposure and device use. The majority were isolates of *Klebsiella pneumoniae,* seen in 297 patients (76.35%). A total of 279 patients belonged to the ESBL cohort, while 110 patients belonged to the non-ESBL cohort. Since there were 279 ESBL-positive cases (events) and three predictor variables retained in the final multivariable model, approximately 93 events per variable were yielded. This exceeded the recommended threshold of at least 10 to 20 events per predictor variable and supports adequacy of the sample size for reliable model development.

For both the ESBL and non-ESBL cohorts, the majority of patients were male (56.56% overall), with a median age of less than 1 year old, and were in the intensive care unit (52% overall) at the time of isolation of the gram-negative bacteria.

The risk factors of patients with ESBL-producing gram-negative bacteria are summarized by univariate logistic regression in Table 1. Among the risk factors, the significant variables (p<0.05) determined to be associated with ESBL production were prolonged hospitalization of more than 7 days (OR 1.76, 95% CI [1.01, 3.07], p=0.048), indwelling central venous catheter (OR 1.82, 95% CI: [1.16,2.84], p=0.009), indwelling urinary catheterization (OR 2.38, 95% CI [1.23,4.62], p=0.010), mechanical ventilation (OR 1.81, 95% CI [1.16, 2.83], p=0.009), chronic kidney disease as a comorbidity (OR 3.43, 95% CI [1.18,9.95], p=0.023), neurological disease as a comorbidity (OR 2.08, 95% CI [1.23,3.38], p=0.003), prior cephalosporin use within the past 3 months (OR 3.39, 95% CI [2.14., 5.37], p <0.001) and prior fluoroquinolone use within the past 3 months (OR 2.04, 95% CI [1.09,3.82], p=0.026).

After adjusting for confounding factors using multivariable logistic regression with backward stepwise selection, three variables were independently associated with ESBL-producing infections as highlighted in Table 2: (1) prior cephalosporin use within the past 3 months, (2) indwelling urinary catheterization, and (3) mechanical ventilation. Some of the risk factors that showed an association in the univariable analysis were no longer significant after adjusting for the other risk factors, suggesting that their association was shared or can be explained by the other associated variables.

*Clinical Predictors*

All the independent variables (prior cephalosporin use within 3 months, indwelling urinary catheterization and mechanical ventilation) were incorporated in the logistic regression model to compute the coefficient weights, which represent the relationship between the predictor variables and whether they are associated with ESBL production or not. As highlighted in Table 2, the ESBL prediction score was then developed by dividing these coefficients by the smallest coefficient (0.61) to derive the scores which will be part of the final risk score, ranging from 0 to 4.

**Table 1.** Crude odds ratios from univariate logistic regression of risk factors of infection due to ESBL-producing gram-negative bacteria

| Risk Factors | | Crude OR | 95% CI | p-value |
|---|---|---|---|---|
| Age, median (IQR) | | 1.02 | 0.98, 1.06 | 0.378 |
| Female sex | | 1.22 | 0.78, 1.91 | 0.390 |
| Location at the time of isolation | General ward | Reference | | |
| | Intensive care unit | 1.07 | 0.68, 1.69 | 0.772 |
| | Surgical ward | 0.50 | 0.21, 1.43 | 0.218 |
| Prolonged hospitalization (>7 days) | | 1.76 | 1.01, 3.07 | 0.048 |
| History of ESBL infection within 1 year | | 1.32 | 0.69, 2.51 | 0.401 |
| Intervention history | Recent surgery (<3 months) | 1.47 | 0.93, 2.33 | 0.103 |
| | Indwelling central venous catheter | 1.82 | 1.16, 2.84 | 0.009 |
| | Indwelling urinary catheterization | 2.38 | 1.23, 4.62 | 0.010 |
| | Mechanical ventilation | 1.81 | 1.16, 2.83 | 0.009 |
| Comorbid conditions | Chronic kidney disease | 3.43 | 1.18, 9.95 | 0.023 |
| | Cardiovascular disease | 1.07 | 0.65, 1.76 | 0.782 |
| | Neurological disease | 2.08 | 1.28, 3.38 | 0.003 |
| | Gastrointestinal disease | 0.65 | 0.41, 1.01 | 0.056 |
| | Autoimmune disease | 5.33 | 0.69,41.22 | 0.109 |
| | Malignancy | 0.83 | 0.46, 1.50 | 0.527 |
| | Current immunosuppressive therapy | 1.01 | 0.54, 1.89 | 0.970 |
| Prior antibiotic use within 3 months | Penicillins | 1.07 | 0.69, 1.68 | 0.754 |
| | Cephalosporins | 3.39 | 2.14, 5.37 | <0.001 |
| | β -Lactamase inhibitors | 1.05 | 0.64, 1.73 | 0.837 |
| | Carbapenems | 1.31 | 0.83, 2.08 | 0.241 |
| | Fluoroquinolones | 2.04 | 1.09, 3.82 | 0.026 |
| | Aminoglycosides | 1.21 | 0.77, 1.89 | 0.408 |

**Table 2.** Significant predictors of ESBL-producing gram-negative bacteria and point allocation in the ESBL prediction score

| | Adjusted OR | 95% CI | p-value | Coefficient | Score |
|---|---|---|---|---|---|
| Prior cephalosporin use within 3 months | 3.04 | 1.89, 4.87 | <0.001 | 1.11 | 2 |
| Indwelling urinary catheterization | 2.01 | 1.01, 4.01 | 0.047 | 0.70 | 1 |
| Mechanical ventilation | 1.84 | 1.15, 2.95 | 0.011 | 0.61 | 1 |

*Scoring System*

The developed ESBL prediction scoring system was then used to predict the risk of ESBL production by determining the cut-off according to the discrimination plot and performance of diagnostic parameters.

Since the dataset had an uneven distribution of ESBL cases, additional performance metrics apart from accuracy—sensitivity, specificity, positive and negative predictive values (PPV and NPV), and the AUC were also assessed.

Two possible scores were analyzed:

**Score of 2 to 4**: This threshold showed good sensitivity (76%) and high PPV (81%), meaning it correctly identified most ESBL cases and was reliable when predicting a positive result. However, specificity (54%) and NPV (47%) were moderate. Overall, accuracy was 65%, which was acceptable.

**Score of 3 to 4**: At this higher threshold, specificity improved to 70% and PPV increased to 83%, making it better at ruling out false positives. However, sensitivity dropped to 57%, and NPV was lower at 39%. The overall accuracy was 64%.

Therefore, if the goal is to **screen for the likelihood of an ESBL-producing infection**, 2 points and above is preferred for its higher sensitivity. If the aim is to **avoid unnecessary use of carbapenems**, adopting a more conservative score of 3 points and above may be more appropriate due to its higher specificity and PPV.

Ultimately, a score of 2 and above showed the strongest overall performance with an accuracy of 64.8%, and was chosen to identify patients at high risk for ESBL infection. Risk scores were then classified into 2 risk levels: low risk and high risk. As shown in Table 3, a low risk level was defined as an overall score of 0 to 1 point (N = 52, 13.37%), and a high risk level was defined as a score of 2 to 4 points (N = 337, 86.63%).

**Table 3.** Classification of cases and controls into low- and high-risk, and the corresponding risk estimation

| Category | Score range | ESBL cohort (n=279, 71.72%) | Non-ESBL cohort (n=110, 28.28%) | Risk estimation | | |
|---|---|---|---|---|---|---|
| | | | | Overestimated | Correct | Underestimated |
| Low (n=52, 13.37%) | 0 – 1 | 20 | 32 | - | 32 (8.23%) | 20 (5.14%) |
| High (n=337, 86.63%) | 2 – 4 | 259 | 78 | 78 (20.05%) | 259 (66.58%) | - |
| **Total** | | **279** | **110** | **78 (20.05%)** | **291 (74.81%)** | **20 (5.14%)** |

With this scoring system and cut-off, 8.23% (n=32) of cases were correctly classified as low risk (score of 0-1), with 5.14% (n=20) misclassified as underestimated risk. On the other hand, at high risk levels (score of 2-4), the scoring system correctly classified 66.58% (n=259) of the 389 cases, with 20.05% (n=78) misclassified as overestimated risk.

*Post-hoc Subgroup Analysis*

Due to the heterogeneity of the study population, which ranged from otherwise healthy adolescent patients in the general ward to critically ill, long-staying preterm neonates in the NICU, a post-hoc subgroup exploratory analysis was conducted to refine the dataset and examine if the associations were consistent across more homogenous groups. The subgroups analyzed were the following: 1) patients admitted to the NICU 2) age groups: neonates (<1 month old) versus older infants and children (≥1 month); and 3) patients with *Klebsiella pneumoniae* as the isolated pathogen. Similar key risk factors—prior cephalosporin use, indwelling urinary catheterization, and mechanical ventilation— emerged as independent predictors of ESBL infection across multiple subgroups. Hence, these three variables were retained in the final prediction model. This analysis was exploratory and not pre-specified.

Overall, the scoring system demonstrated risk estimation accuracy of 74.81% (n=291), successfully differentiating between patients who were at risk and those who were not at risk for ESBL production. Table 4 shows the clinical interpretation for the risk scores.

**Table 4.** Interpretation of risk scores

| Total Score | Estimated Risk of ESBL Infection | Clinical Interpretation |
|---|---|---|
| **0 - 1** | Low risk | Standard empiric antibiotics likely sufficient |
| **2 - 4** | High risk | Empiric treatment should include ESBL-active agents (e.g., carbapenems) |

*Model Performance Assessment*

The computed AUC for the final logistic regression model as shown in Figure 1 was at 0.6811 (95% CI 0.6213, 0.7409) and 0.70 to the simplified scoring system, both indicating a moderate discriminative ability in a well-calibrated predictive model (Hosmer-Lemeshow $x^2$ = 8.3205, p = 0.0805). In interpreting the Hosmer-Lemeshow test, a p > 0.05 is considered a good fit (opposite of other tests), indicating that the model's predictions are close to actual outcomes.

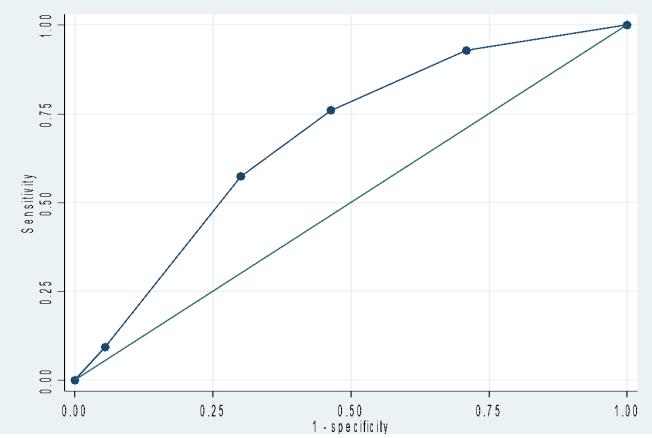


**Figure 1.** Area under the ROC curve of the performance of the developed clinical prediction tool for ESBL infection

Internal validation through bootstrapping was then done. As shown in Table 5, model performance was assessed in the training set (n = 389) and internally validated using bootstrap resampling (n = 200). Each bootstrap sample was derived by applying the same model to the validation set.

A score of 2 and above provided the best balance between sensitivity and specificity and maintained this balance across both the training and validation sets. At the optimal threshold, the model demonstrated a sensitivity of 76.0% and a specificity of 53.6% in the training set. Internal validation using bootstrapping showed a slight decrease in accuracy from 64.8% (training) to 63.2% (validation), indicating moderate discriminative stability. This suggests the prediction model is not overfitted and has reasonable internal generalizability. Before wider clinical application, the prediction model requires external validation in independent datasets—ideally from other centers or regions—to confirm its generalizability and accuracy in different populations.

**Table 5.** Comparison of the diagnostic performance of the model derived from training set (n=389) against the validation set (n=200) taken by bootstrap resampling

| Cut-off score | TP | FP | TN | FN | Sensitivity | Specificity | PPV | NPV | Accuracy |
|---|---|---|---|---|---|---|---|---|---|
| **Training set (n=389)** | | | | | | | | | |
| ≥ 1 | 259 | 78 | 32 | 20 | 92.8% [89.1, 95.6] | 29.1% [20.8, 38.5] | 76.9% [72.0, 81.3] | 61.5% [47.0, 74.7] | 61% [56.4, 65.5] |
| ≥ 2 | 212 | 51 | 59 | 67 | 76.0% [70.5, 80.9] | 53.6% [43.9, 63.2] | 80.6% [75.3, 85.2] | 46.8% [37.9, 55.9] | 64.8% [59.5, 70.1] |
| ≥ 3 | 160 | 33 | 77 | 119 | 57.3% [51.3, 63.2] | 70.0% [60.5, 78.4] | 82.9% [76.8, 87.9] | 39.3% [32.4, 46.5] | 63.7% [58.5, 68.9] |
| 4 | 26 | 6 | 104 | 253 | 9.3% [6.2, 13.4] | 94.5% [88.5, 98.0] | 81.3% [63.6, 92.8] | 29.1% [24.5, 34.1] | 51.9% [49.2, 54.7] |
| **Validation set* (n=200)** | | | | | | | | | |
| ≥ 1 | 131 | 34 | 18 | 17 | 88.5% [82.2, 93.2] | 34.6% [22.0, 49.1] | 79.4% [72.4, 85.3] | 51.4% [34.0, 68.6] | 61.6% [54.5, 68.6] |
| ≥ 2 | 104 | 26 | 26 | 44 | 70.3% [62.2, 77.5] | 50.0% [35.8, 64.2] | 80.0% [72.1, 86.5] | 37.1% [25.9, 49.5] | 63.2% [56.0, 70.4] |
| ≥ 3 | 76 | 13 | 39 | 72 | 51.4% [43.0, 59.6] | 75.0% [61.1, 86.0] | 85.4% [76.3, 92.0] | 35.1% [26.3, 44.8] | 60.1% [52.3, 67.9] |
| 4 | 17 | 6 | 46 | 131 | 11.5% [6.84, 17.8] | 88.5% [76.6, 95.6] | 73.9% [51.6, 89.8] | 26.0% [19.7, 33.1] | 50.0% [44.9, 55.1] |

*By bootstrap re-sampling

TP - true positive; FP - false positive; TN - true negative; FN - false negative; PPV - positive predictive value; NPV - negative predictive value

## DISCUSSION

This study identified prior cephalosporin use, mechanical ventilation, and indwelling urinary catheterization as independent predictors of hospital-acquired ESBL-producing gram-negative infections in pediatric patients and developed a corresponding clinical prediction tool with moderate discriminative ability. While similar prediction tools have been created for the adult population, data on pediatric risk factors remain scarce. The findings may offer initial insights into whether risk factors reported in the adult age group also apply in diverse pediatric settings.

The clinical prediction model showed moderate discriminative ability with an AUC of 0.70 in a well-calibrated predictive model (Hosmer-Lemeshow $x^2$ = 8.3205, p = 0.0805), which indicates that this tool has a reasonable ability to distinguish whether the isolates are ESBL-producing or not. Internal validation done showed that the accuracy was maintained at 64.8% (training set) and 63.2% (validation set), both exhibiting the highest among all the cut-off scores. These findings suggest moderate discriminative ability and stable performance, not solely attributable to random variation in the dataset.

*Independent Risk Factors for ESBL Production*

For the multivariable analysis, 3 independent predictors were associated with ESBL-producing infection which were similar to the predictors generated after subgroup analysis: prior cephalosporin use within 3 months, indwelling urinary catheterization, and mechanical ventilation. Among these, prior cephalosporin use was consistent with the 2 previous studies done in adult populations.[7,8]

The findings also align with existing pediatric literature identifying previous antibiotic exposure and invasive device use as key risk factors for ESBL-producing infections. Prior exposure to broad-spectrum antibiotics, especially cephalosporins, had the strongest risk factor with a point allocation of 2 points. It has also been consistently implicated in the emergence of ESBL-producing bacteria due to selective antibacterial pressure as observed in pediatric and mixed-population studies.[3,6] However, antibiotic exposure often correlates with the severity of the underlying illness, which leads to increased healthcare contact. As a result, increased healthcare contact cannot be entirely ruled out as a possible confounding factor.

Similarly, the association between device use (indwelling urinary catheterization and mechanical ventilation) and risk for ESBL infection represents not

only a direct entry point for pathogens, but also a surrogate marker for critical illness and prolonged hospitalization.[3,6] These factors may differ across pediatric populations which may also affect the applicability of individual predictors. Therefore, the predictive value should be interpreted within a broader clinical context, recognizing that the inclusion of these factors into a simplified scoring system may involve compromises between precision and generalizability.

*Applications of the ESBL Clinical Prediction Tool*

The clinical prediction tool is simple and feasible to implement in hospital settings. All the required variables are documented in electronic medical records or obtainable through clinical interviews with the patient or guardian. This allows the tool to be readily available in real-time clinical decision-making at the point of care.

In this study, the clinical prediction tool correctly classified 74.8% of cases (291 of 389) using a score-based risk categorization (0–1 as low risk, 2–4 as high risk). This level of performance suggests potential utility in guiding empiric antibiotic selection (standard empiric antibiotics are likely sufficient for low risk, while ESBL-active agents are suggested for high risk).

On the other hand, its use may raise concerns for potential overuse of carbapenems, given the specificity at 54% at the preferred cut-off. A proportion of patients may be classified as high risk despite not having ESBL infection, which has implications for antimicrobial stewardship. The tool should therefore be used to support, and not replace, clinical judgment and should be utilized alongside patient assessment and resistance patterns. In critically ill patients, however, prioritizing higher sensitivity may be justified to avoid delays in appropriate therapy.

In addition, the observed 20.05% overestimation rate highlights the potential for false positives, which may lead to unnecessary use of carbapenems. This has necessary implications for antimicrobial stewardship, especially in resource-limited settings where judicious antibiotic use is critical.

Finally, the predominance of *Klebsiella pneumoniae* (76.35%) in the study population may also have implications in the generalizability of the findings to settings where other gram-negative organisms are more common.

*Limitations and Implications for Future Research*

While the model shows potential clinical utility, several limitations must be acknowledged. The study was conducted based on retrospective data from a single tertiary institution, hence results may not be generalizable to the entire pediatric population. A comparison of included versus excluded cases was not feasible due to limited data, which is acknowledged as a potential source of selection bias. Prospective validation is also needed to confirm applicability across broader clinical settings.

Despite these limitations, this study provides a practical framework for early identification of at-risk pediatric patients. By integrating readily available clinical variables, the prediction tool may assist clinicians in making timely empiric antibiotic decisions, potentially improving outcomes while still promoting antimicrobial stewardship. Future research should focus on prospective validation, integration into electronic medical records, and assessment of clinical impact. Additionally, expanding the model to include microbiome data and/or laboratory parameters may further improve predictive performance.

## CONCLUSION AND RECOMMENDATIONS

This study developed a clinical prediction tool to estimate the risk of hospital-acquired ESBL-producing gram-negative infections in pediatric patients. Using three independent predictors -- prior cephalosporin use within the past three months, mechanical ventilation, and indwelling urinary catheterization, the model had moderate discriminative ability, with an AUC of 0.70. These findings support the feasibility of a simple scoring tool using readily available clinical variables, which may aid in early risk stratification and guide empiric antibiotic therapy in pediatric settings.

Performance of the tool should be interpreted with caution due to the imbalanced dataset and modest specificity at the selected cut-off. Emphasis is therefore placed on AUC and diagnostic trade-offs. The tool may be especially useful in resource-limited settings, but is intended to support, not replace, clinical judgment. Further external and prospective validation is needed to confirm its clinical utility and generalizability.

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## Conflicts of Interest

None declared.

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