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ORIGINAL RESEARCH

Risk Stratification for ESBL-Producing Enterobacterales in Elderly Diabetic Patients with Urinary Tract Infections: A Multicenter Model to Support Empirical Antibiotic Decision-Making

Tingting Huang[1], Jibao Qin[2], Xi Jiang[1], Ming Hu[1], Jiaping Wang[1], Kaiyong Chen[3], Fumeng Yang[4], Jin Gu[5], Huiyi Wu[1], Xinkuan Chen[6]

[1]Department of Laboratory Medicine, Donghai Hospital Affiliated to Kangda College of Nanjing Medical University / Donghai County People's Hospital, Lianyungang, Jiangsu, People's Republic of China; [2]Department of Laboratory Medicine, Dongfang Hospital Affiliated to Kangda College of Nanjing Medical University, Lianyungang, Jiangsu, People's Republic of China; [3]Department of Laboratory Medicine, Guanyun County People's Hospital, Lianyungang, Jiangsu, People's Republic of China; [4]Department of Laboratory Medicine, Lianyungang Second People's Hospital Affiliated to Kangda College of Nanjing Medical University, Lianyungang, Jiangsu, People's Republic of China; [5]Department of Laboratory Medicine, Lianyungang Hospital Affiliated to Nanjing University of Traditional Chinese Medicine, Lianyungang, Jiangsu, People's Republic of China; [6]Department of Laboratory Medicine, First Hospital Affiliated to Kangda College of Nanjing Medical University / The First People's Hospital of Lianyungang, Lianyungang, Jiangsu, People's Republic of China

Correspondence: Xinkuan Chen, Email 18961328118@189.cn

Objective: Antimicrobial resistance among elderly diabetic patients with urinary tract infections (UTIs) poses a significant challenge for empirical antibiotic therapy. Delayed availability of microbiological susceptibility results often leads to treatment mismatch and inappropriate broad-spectrum antibiotic use. This study aimed to develop and validate a clinically interpretable risk stratification model to estimate the probability of extended-spectrum β-lactamase (ESBL)-producing Enterobacterales isolation prior to microbiological confirmation, thereby supporting early empirical antibiotic decision-making.

Methods: We conducted a multicenter retrospective cohort study including elderly (≥60 years) patients with type 2 diabetes and positive urine cultures. Multivariable logistic regression was used to construct a prediction model for ESBL-positive isolation. Model discrimination and calibration were evaluated using the area under the receiver operating characteristic curve (AUC), Brier score, calibration plots, and bootstrap internal validation. Internal–external cross-validation and independent external validation were performed to assess model transportability. Decision curve analysis (DCA) was applied to evaluate clinical net benefit across threshold probabilities.

Results: A total of 612 patients were included, of whom 364 (58.6%) had ESBL-positive isolates. Independent predictors included diabetes duration ≥10 years, HbA1c ≥8.5%, recent antibiotic exposure, urinary tract device use, and low-level pyuria (<5 WBC/HPF). The model demonstrated stable discrimination (AUC 0.81 in the training set; 0.79 in internal validation; 0.81 in external validation) and good calibration (Brier score 0.18–0.19). Decision curve analysis showed meaningful clinical net benefit across a wide range of threshold probabilities (10%–65%). Exploratory analysis indicated that empirical therapy mismatch was associated with prolonged hospitalization and increased sepsis incidence, underscoring the potential clinical relevance of early resistance risk identification.

Conclusion: This multicenter risk stratification model provides a practical tool for early estimation of ESBL-producing Enterobacterales risk in elderly diabetic patients with UTIs. By integrating routinely available clinical and laboratory variables, the model may support antimicrobial stewardship efforts and improve empirical antibiotic decision-making before susceptibility results become available. Prospective validation in diverse healthcare settings is warranted to confirm its clinical impact.

Keywords: diabetes, bacteriuria, positive urine culture, ESBL, enterobacterales, nomogram, risk prediction

Introduction

Urinary tract infection (UTI) is a prevalent and complex issue in diabetic patients, often resulting in recurrent infections and complications.[1–3] A major challenge in managing UTIs is the increasing antimicrobial resistance, particularly the

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high prevalence of extended-spectrum beta-lactamase (ESBL)-producing Enterobacterales, which complicates empirical antimicrobial therapy in diabetic individuals.[4] Previous studies have demonstrated a significant association between diabetes and the risk of ESBL-positive isolates, particularly in elderly patients, even after adjusting for factors such as antibiotic use and urinary tract devices.[5] Delayed availability of microbiological susceptibility results often leads to empirical antibiotic therapy decisions under uncertainty, contributing to treatment mismatch and inappropriate broad-spectrum antibiotic use.

In elderly patients, infections frequently present with atypical features, such as muted inflammatory responses, non-specific symptoms, and complex clinical manifestations due to multiple comorbidities. Immunosenescence and chronic metabolic disorders can alter the host's inflammatory response, reducing the clinical value of traditional inflammatory markers like pyuria.[6,7] In elderly diabetic patients, this reduced inflammatory response during infection does not necessarily correlate with a lower risk of infection. In fact, the "inflammatory signal paradox" suggests that diminished inflammation may be associated with a higher likelihood of resistant pathogen isolation. This highlights the need for a reevaluation of the reliance on inflammation as the primary indicator of infection risk in this group.[6]

Currently, there is no rapid risk stratification tool for ESBL-positive isolation in elderly diabetic patients with positive urine cultures, leading to a therapeutic dilemma. Insufficient or mismatched antimicrobial therapy may result in reduced clinical cure rates and increased treatment failure, while overuse of broad-spectrum antibiotics exacerbates resistance.[4] Studies have shown that mismatched empirical therapy is significantly linked to prolonged hospitalization and poor outcomes, particularly in elderly patients with multiple underlying conditions.[4]

From a pathophysiological perspective, chronic hyperglycemia impairs innate immunity and alters inflammatory signaling, which may lead to atypical infection presentations. In this context, resistant pathogens are more likely to colonize or proliferate in a host with compromised defense mechanisms, increasing the risk of ESBL-positive isolation.[8–10] However, these mechanisms remain largely theoretical, and practical tools to quantify this risk using readily available clinical data are lacking.

Nomograms, regression-based visual prediction tools, integrate multiple risk factors to provide personalized risk assessments with strong interpretability and clinical applicability. They have been widely used in disease prediction and decision support.[11–13] However, predictive models for ESBL-positive isolation risk in elderly diabetic patients with positive urine cultures remain scarce. In this study, we utilized multi-center real-world data to analyze independent risk factors for ESBL-positive isolation in this patient population. We developed and validated a nomogram model with strong discrimination and calibration. This model provides a risk stratification strategy based on laboratory indicators for elderly patients with atypical inflammatory phenotypes, helping clinical decision-making before microbiological results are available, while complementing—not replacing—clinician judgment.

Although previous studies have examined risk factors for ESBL-producing organisms, few have addressed the paradoxical relationship between inflammatory response intensity and antimicrobial resistance in elderly diabetic populations. As immunosenescence and metabolic dysregulation increasingly affect host–pathogen interactions, there is a growing need for clinically interpretable tools that integrate host immune phenotype and resistance risk. This study aims to develop a prediction model and explore a clinically relevant association between atypical inflammatory presentation and antimicrobial resistance risk.[14]

Materials and Methods

Study Design and Participants

This multi-center retrospective cohort study analyzed data from the urinary tract infection (UTI) database of four hospitals, spanning from January 2022 to December 2024 (initial sample size, n=1,950). The study included type 2 diabetic patients aged ≥60 years with positive urine cultures. The study followed TRIPOD reporting guidelines.

Inclusion Criteria

Aged ≥60 years; Diagnosed with type 2 diabetes; Positive urine culture; Complete clinical data.

Exclusion Criteria

Non-Enterobacterales isolates or indeterminate ESBL phenotype; multiple positive cultures within the same hospitalization (only the first culture retained to avoid duplication); missing key variables that could not be supplemented; and severe immunosuppression, defined as any of the following: (1) ongoing immunosuppressive therapy (eg., systemic corticosteroids equivalent to ≥20 mg/day of prednisone for ≥14 days, chemotherapy, or biologic agents); (2) hematologic malignancy; (3) solid organ or hematopoietic stem cell transplantation; or (4) significantly impaired immune function, such as a CD4+ T-cell count <200 cells/μL.

Given the Retrospective Design, the Study Focuses on Risk Association, Not Causal Inference.

Sampling and Laboratory Assays

Urine samples were collected using midstream clean-catch procedures according to standard clinical protocols. Complete blood count (CBC) parameters, especially neutrophil counts, were obtained at admission. Random blood glucose levels and urine dipstick parameters, including leukocyte esterase and nitrite, were recorded. ESBL production was confirmed using phenotypic methods based on antimicrobial susceptibility testing according to CLSI guidelines. All laboratory procedures were performed following standard protocols to ensure accuracy and reproducibility.

Definition of Predictors

Candidate predictors were pre-defined based on existing literature and clinical knowledge, to minimize selection bias. The predictors included:

Demographic factors (age, gender)

Diabetes-related indicators (duration, HbA1c)

Clinical manifestations (fever, urinary symptoms, asymptomatic bacteriuria)

Comorbidities (chronic kidney disease, hypertension)

Exposure history (antibiotic exposure, urinary tract devices)

Laboratory indicators (pyuria level, leukocyte esterase, nitrites)

Low pyuria was defined as <5 WBC/HPF, reflecting reduced inflammatory response.[14] Continuous variables were dichotomized based on pre-set clinical thresholds to improve interpretability and reduce overfitting risk.[15]

Definition of Outcome

The primary outcome was whether the isolate was ESBL-positive Enterobacterales (yes/no). ESBL determination followed CLSI standards, with phenotypic confirmation.[6] This is a microbiological endpoint, not equivalent to clinical infection diagnosis.

UTI and asymptomatic bacteriuria (ASB) definitions followed established guidelines.[6,14]

UTI was defined as the presence of urinary symptoms (eg., dysuria, frequency, urgency, or fever) together with a positive urine culture. ASB was defined as significant bacteriuria in the absence of urinary symptoms.

Statistical Analysis

Statistical analyses were performed using R software (version 4.2.1). Continuous variables were compared using the Mann–Whitney *U*-test, and categorical variables with the χ^2 or Fisher's exact test.

A complete case analysis yielded a final sample of 612, which was randomly split into training and validation sets (7:3).

Multivariable logistic regression was used for model construction. Univariate selection was set to P<0.10 for preliminary variable selection. Final candidate variables were based on clinical judgment to reduce model instability. Stepwise regression was applied for model simplification (parsimony), not for exploring new predictors. Pyuria was analyzed as a binary variable (<5 vs ≥5 WBC/HPF), with <5 WBC/HPF defined as the risk category.

Model performance was evaluated using:

AUC (discrimination)

Calibration curve and Brier score (calibration)
Decision curve analysis (DCA) (clinical net benefit).[16]

Internal Validation and Overfitting Control

Bootstrap resampling (1,000 iterations) assessed optimistic bias and adjusted AUC.[17,18] Sensitivity analysis was conducted by constructing both the full model and a continuous variable model to verify robustness.

Center Effect and Generalizability

To control for center variability, a mixed-effects logistic model (hospital as random intercept) was used for sensitivity analysis.[18] Further internal-external cross-validation (IECV) was performed using a leave-one-center-out strategy to assess model portability.

The final model had an events per variable (EPV) of approximately 72, well above the recommended threshold (≥10), indicating a low risk of overfitting.[13,19]

This study followed clinically informed principles and parsimony in model development. All candidate variables were pre-defined based on literature and clinical relevance, not purely data-driven exploration, minimizing overfitting and selection bias. The model's stability and generalizability were assessed through internal validation, sensitivity analysis, and IECV to ensure robust and conservative performance evaluation.

To avoid loss of information and reduced statistical power caused by dichotomization of continuous variables, restricted cubic spline (RCS) functions were used to explore potential nonlinear relationships between continuous variables (eg., HbA1c and disease duration) and the outcome. Knots were placed at the 5th, 35th, 65th, and 95th percentiles. Nonlinearity was assessed using a likelihood ratio test comparing the model with only the linear term to the model including spline terms.

Results

Baseline Characteristics of Patients

A total of 612 diabetic patients with positive urine cultures were included in this study, selected from an initial cohort of 1,950. Among them, 364 (58.6%) were in the ESBL-positive group, and 258 (41.4%) were in the ESBL-negative group. The baseline characteristics of both groups are detailed in Table 1. Univariate analysis revealed that the ESBL-positive group had significantly higher proportions of patients with longer diabetes duration, higher HbA1c levels, recent

Table 1 Baseline Characteristics of Elderly Diabetic Patients with Positive Urine Cultures Stratified by ESBL Status

Variable	Overall (n=612)	ESBL-Positive (n=364)	ESBL-Negative (n=258)	Statistic (U/χ^2)	P value
Age, median (IQR), years	72.3 (66.5–78.9)	72.8 (67.1–79.5)	71.7 (65.8–78.1)	44,218	0.215
Sex, n (%)				0.079	0.779
Male	285 (45.8)	169 (46.4)	116 (45.0)		
Female	327 (53.4)	195 (53.6)	142 (55.0)		
Diabetes duration ≥10 years, n (%)	287 (46.1)	198 (54.4)	89 (34.5)	24.837	<0.001
HbA1c ≥8.5%, n (%)	254 (40.8)	173 (47.5)	81 (31.4)	17.289	<0.001
Recent antibiotic exposure, n (%)	198 (31.8)	148 (40.7)	50 (19.4)	32.115	<0.001
Urinary tract device use, n (%)	134 (21.9)	105 (28.8)	29 (11.2)	28.904	<0.001
Pyuria <5 WBC/HPF, n (%)	149 (23.9)	118 (32.4)	31 (12.0)	35.627	<0.001
Chronic kidney disease, n (%)	85 (13.9)	55 (15.1)	30 (11.6)	1.556	0.212

antibiotic exposure, use of urinary tract devices, and low-level pyuria (<5 WBC/HPF), compared to the ESBL-negative group (all P<0.001).

Prediction Model Construction and Validation

The study population (n=612) was randomly divided into a training cohort (n=408, 66.7%) and a validation cohort (n=204, 33.3%). Model development was performed in the training cohort, and performance was evaluated in the validation cohort.

In the training set, univariate logistic regression was first performed on the candidate variables, and those with P < 0.10 were included in the multivariable model. The multivariable logistic regression results showed that low-level pyuria (<5 WBC/HPF) was independently associated with a significantly increased risk of ESBL-positive isolation. This association remained stable after adjusting for potential confounders, including diabetes duration, blood glucose control, recent antibiotic exposure, and use of urinary tract devices.

To further explore potential nonlinear relationships between continuous variables and the outcome, restricted cubic spline (RCS) analysis was performed. The results suggested a potential nonlinear association between HbA1c and the risk of ESBL-positive isolation, supporting the use of flexible modeling strategies beyond simple dichotomization. The corresponding RCS curves are shown in Figure 1.

The regression coefficients, odds ratios (OR), and 95% confidence intervals for each predictor in the final model are shown in Table 2.

Based on the main model, we further compared the alignment between initial empirical antimicrobial treatment and final antimicrobial susceptibility results. The results indicated that patients with mismatched treatment had longer hospital stays (median: 9 days vs. 6 days) and a higher incidence of sepsis (9.7% vs. 5.9%) compared to those whose treatment matched the susceptibility results. This analysis is exploratory and aims to highlight the potential clinical impact of treatment mismatch related to resistance, rather than assessing the model's performance or establishing causality.

To evaluate the robustness of the model construction strategy, we constructed a full model and performed internal validation using bootstrap resampling. The results confirmed that the effect directions and relative strengths of the main predictors were consistent with those in the main model. When diabetes duration and HbA1c were treated as continuous

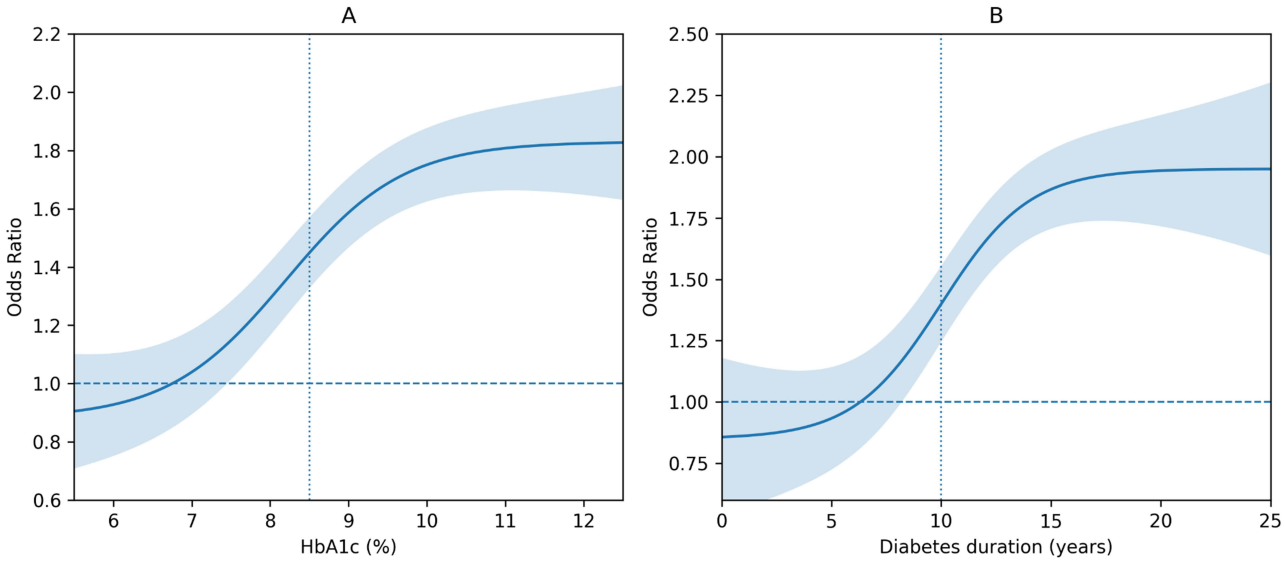

Figure 1 Restricted cubic spline analysis of the association between continuous predictors and the risk of ESBL-positive isolation. (**A**) Restricted cubic spline (RCS) curve illustrating the association between HbA1c and the risk of ESBL-positive isolation. (**B**) RCS curve illustrating the association between diabetes duration and the risk of ESBL-positive isolation. The solid lines represent estimated odds ratios (ORs), and the shaded areas indicate 95% confidence intervals. The horizontal dashed line represents OR = 1.0 (reference level). Vertical dotted lines indicate clinically relevant cutoff values (HbA1c = 8.5% and diabetes duration = 10 years). The curves suggest nonlinear relationships, with risk increasing at lower to moderate levels and tending to plateau at higher levels.

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Table 2 Multivariable Logistic Regression Analysis of Risk Factors for ESBL-Producing Enterobacterales Isolation in Elderly Diabetic Patients

Variable	β Coefficient	Standard Error	Wald χ^2	OR (95% CI)	P value
Diabetes duration ≥10 years	0.77	0.15	25.31	2.15 (1.62–2.85)	<0.001
HbA1c ≥8.5%	0.64	0.14	19.84	1.89 (1.42–2.52)	<0.001
Recent antibiotic exposure	1.04	0.15	46.52	2.82 (2.10–3.78)	<0.001
Urinary tract device use	1.17	0.16	54.57	3.21 (2.35–4.39)	<0.001
Pyuria <5 WBC/HPF	0.87	0.16	28.98	2.38 (1.75–3.25)	<0.001

variables in the multivariable model, both remained positively correlated with the risk of ESBL-positive isolation, with consistent regression direction and statistical significance compared to the main model based on pre-set cutoffs. The discrimination ability of the continuous variable model (AUC 0.79–0.82) was similar to that of the main model (AUC 0.81), demonstrating the model's robustness across different variable treatments.

Although "presence of UTI symptoms" was initially included as a candidate variable, it was excluded from the final model due to its overlap with the UTI/ASB classification and minimal improvement in model discrimination after including other clinical variables. Notably, higher pyuria levels were associated with a reduced risk of ESBL-positive isolation, supporting the observation that patients with weaker inflammatory responses are more likely to harbor resistant pathogens.

Nomogram Construction

Based on the five independent predictors and their regression coefficients (β values) identified, a nomogram model was constructed to predict the risk of ESBL-positive isolation (Figure 2). In this nomogram, each predictor corresponds to a specific score, and the total score is the sum of individual scores, which is then related to the predicted probability of ESBL-positive isolation. A higher total score indicates a higher risk of ESBL-positive isolation.

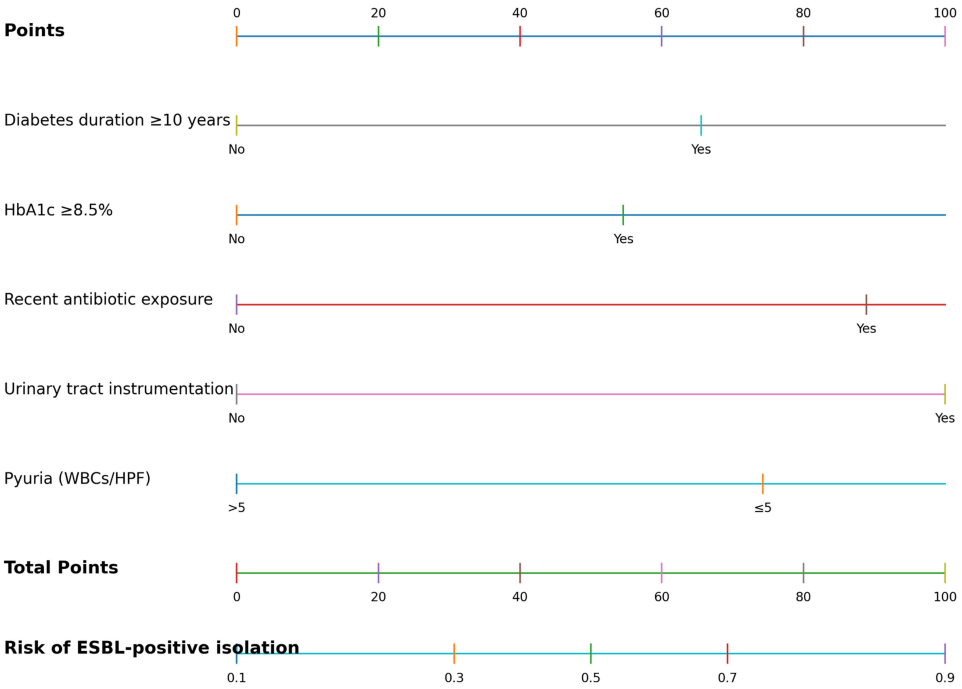

Figure 2 Nomogram for predicting the risk of ESBL-positive Enterobacterales isolation among diabetic patients with positive urine culture or bacteriuria.

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Due to the varying weights of different predictors in the model, the total score may exceed 100 in practical application. The relationship between the total score and the predicted probability has been calibrated in the risk axis of the nomogram, with the predicted probability ranging from 0.1 to 0.9. Unlike prediction models that rely on complex biomarkers, this study aims to integrate commonly available laboratory indicators and clinical variables to construct a risk assessment tool with interpretability and applicability, particularly from the perspective of geriatric medicine, to address the challenge of early recognition of infections in elderly patients with atypical presentations.

Risk Stratification Based on Nomogram Score

To enhance clinical interpretability, the total nomogram score was further categorized into three risk strata based on predicted ESBL probability. Patients with a total score <40 were classified as low risk (estimated probability <20%), scores between 40 and 80 as intermediate risk (20–50%), and scores >80 as high risk (>50%). This categorization facilitates rapid bedside risk assessment and may support empirical decision-making before microbiological results become available.Table 3.

Interaction and Stratification Analysis

No significant interaction was observed between low-level pyuria (<5 WBC/HPF) and chronic kidney disease after including interaction terms in the multivariable logistic regression model. The direction and statistical significance of the regression coefficients for the main predictors remained consistent with the main model, indicating good model stability.

Clinical Application Example

To demonstrate the practical use of the nomogram, consider the following example: A 74-year-old female with type 2 diabetes for 12 years (≥10 years), an HbA1c of 9.2% (≥8.5%), a history of systemic antibiotic exposure within the last 3 months, an indwelling catheter during hospitalization, and pyuria of 3 WBC/HPF (<5 WBC/HPF).

When these variables are input into the nomogram, the scores for diabetes duration, HbA1c, recent antibiotic exposure, urinary device use, and low-level pyuria are 18, 15, 27, 30, and 20, respectively, totaling 110 points. This corresponds to a predicted probability of 72% for ESBL-positive isolation, indicating a high risk for antimicrobial resistance.

It is important to note that this model supports early risk stratification and clinical vigilance, rather than directly guiding specific antibiotic selection. Clinical decisions should be based on the patient's overall condition, infection severity, and local resistance patterns, with adjustments made once microbiological results are available.

Model Validation and Performance Evaluation

ROC curve analysis showed that the nomogram model demonstrated strong discriminatory ability in both the training and internal validation sets (Figure 3A). The AUC values for both sets were comparable, suggesting stable performance across different subsets without significant decline. Bootstrap internal validation and internal-external cross-validation (IECV) further confirmed consistent discrimination and calibration, indicating robust stability and generalizability.

Calibration analysis showed good alignment between predicted probabilities and observed risks, with the calibration curve closely following the 45° reference line (Figure 3C). The Hosmer–Lemeshow test yielded $\chi^2 = 7.32$, P = 0.502, and

Table 3 Clinically Interpretable Risk Stratification Derived from the Nomogram Model for Estimating ESBL-Producing Enterobacterales Risk

Total Score	Risk Level	Estimated ESBL Probability
<40	Low risk	<20%
40–80	Intermediate risk	20–50%
>80	High risk	>50%

Note: Risk categories were defined based on predicted probability thresholds to facilitate clinical interpretation.
Abbreviation: ESBL, extended-spectrum beta-lactamase.

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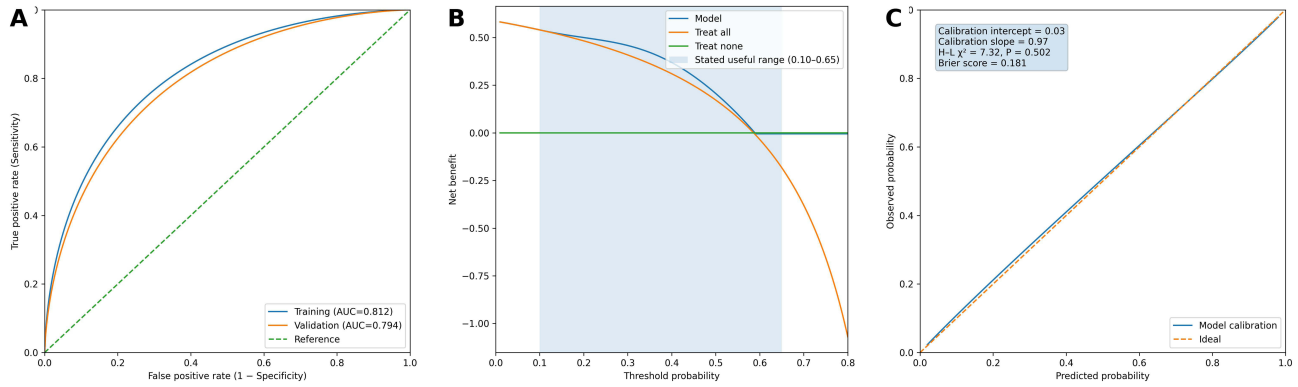

Figure 3 Performance evaluation of the Model for Predicting the Risk of ESBL-Positive Isolation in Diabetic Elderly Patients with Positive Urine Cultures. (**A**) ROC curve; (**B**) Decision curve analysis; (**C**) Calibration curve.

the Brier score was 0.181. The calibration intercept was 0.03, with a slope of 0.97, and after bootstrap correction (1,000 iterations), the intercept remained at 0.01 and slope at 0.95, indicating no significant bias or overfitting.

Further bootstrap validation showed an apparent AUC of 0.812 in the training set, with an average optimistic bias of 0.014. After correction, the AUC was 0.798, which was close to the AUC of 0.794 in the internal validation set, confirming the model's stable performance.

Decision curve analysis demonstrated that, for threshold probabilities between 10% and 65%, the model's risk stratification offered significant clinical net benefit (Figure 3B). Within this range, the model-assisted risk identification was more beneficial than the "treat-all" or "treat-none" strategies.

In conclusion, the nomogram model showed strong discriminatory ability, good calibration, and clinical utility in internal validation, making it a valuable tool for antimicrobial resistance risk stratification before microbiological results are available.

Cross-Center External Validation Results

In the internal–external cross-validation (IECV) analysis, the prediction model demonstrated stable discriminatory ability across external validation sets from four hospitals. The AUC values of the external validation sets from different centers ranged from 0.76 to 0.82, indicating that the model maintained good reproducibility in distinguishing risk across different medical institutions.

Calibration assessment showed that the calibration intercepts across centers were generally close to 0, and the calibration slopes were near 1 (intercept range: −0.10 to 0.12; slope range: 0.88 to 1.05). No systematic overestimation or underestimation of risk was observed in the consistency. In centers with varying baseline ESBL prevalence levels, slight shifts in the calibration intercept were noted, suggesting that recalibration-in-the-large could further improve the absolute consistency of predicted probabilities.

Decision curve analysis revealed that within the clinically relevant threshold probability range (approximately 10%–65%), the external validation sets from most centers showed high net clinical benefit. This provided a potential advantage over the "treat-all" or "treat-none" strategies, supporting the model's clinical value in different healthcare settings.

External Validation Results

To assess the generalizability of the nomogram model, we performed external validation using a dataset from the Second People's Hospital of Lianyungang, affiliated with Nanjing Medical University, for the period from January 2025 to December 2025. The validation results were as follows:

AUC

The AUC of the external dataset was 0.81, which is similar to the AUC of the training set (0.83), indicating good discriminatory ability.

Calibration Curve

The calibration intercept was 0.02, and the slope was 0.98, showing good calibration between the predicted probabilities and actual observed risks.

Brier Score

The Brier score for the external dataset was 0.188, which is comparable to the training set Brier score (0.185), indicating high prediction accuracy in the external validation dataset.

Decision Curve Analysis (DCA)

In the external validation dataset, the model demonstrated high clinical net benefit within the threshold probability range of 10%–65%, highlighting the model's clinical value at different decision thresholds.

Here is the revised and professionally refined version of your Discussion section, with improved grammar, conciseness, and a more polished academic tone:

Discussion

This study developed and validated a risk prediction model for the isolation of extended-spectrum beta-lactamase (ESBL)-producing Enterobacterales in elderly diabetic patients with positive urine cultures. The model, constructed using multivariable regression analysis, identified key predictors such as diabetes duration, recent antibiotic use, urinary device use, and inflammation-related markers. Its robustness and good calibration performance were validated through multi-center data, demonstrating its potential as a clinical tool, particularly for early antibiotic management.[2,4]

Low Inflammation-High Resistance (LIHR) Model: Abnormal Inflammatory Phenotype and Resistance Risk

We found a significant association between low-level pyuria (<5 WBC/HPF) and ESBL-positive isolation. This suggests that the relationship between inflammation intensity and resistance risk is not linear. In diabetic patients, prolonged hyperglycemia may impair neutrophil function and disrupt inflammatory signaling, leading to a reduced inflammatory response during infection.[8–10] Furthermore, immunosenescence in elderly patients may decrease the sensitivity of inflammatory markers, thus underestimating the infection risk.[6] This seemingly counter-intuitive finding may reflect complex host–pathogen interactions rather than a simple inflammatory response pattern. In older adults, immunosenescence may impair neutrophil recruitment and activation, leading to attenuated inflammatory responses despite active infection. This blunted immune response may allow more adaptable or resistant pathogens to persist and proliferate.

In addition, antimicrobial-resistant organisms may exhibit altered virulence and host interaction profiles, potentially eliciting weaker inflammatory signaling. A low-inflammatory urinary microenvironment may further facilitate the colonization and persistence of resistant strains, particularly in patients with multiple comorbidities or prior antibiotic exposure. These mechanisms may partially explain the observed association between low pyuria and increased antimicrobial resistance.

This phenomenon prompted us to propose the "Low Inflammation-High Resistance (LIHR)" framework, which highlights the non-linear relationship between inflammation and resistance risk in elderly diabetic patients. This model integrates laboratory markers with host factors, moving beyond the traditional reliance on inflammation intensity, and offers clinical applicability. Future research should further explore the biological mechanisms underlying this phenomenon, potentially incorporating immune phenotyping or inflammatory pathway markers.[8–10]

Model Objective: Risk Stratification, Not Treatment Guidance

The primary purpose of this model is to assist clinicians in early risk stratification rather than directly guiding antibiotic selection. Its clinical value lies in identifying high-risk patients before microbiological results are available, enabling timely clinical decision-making.[16] To enhance clinical interpretability, we dichotomized certain continuous variables based on predefined clinical thresholds. To mitigate the limitations associated with dichotomization, we further applied restricted cubic spline (RCS) analysis to explore potential nonlinear relationships between continuous variables and the

outcome, allowing a more flexible and informative assessment of risk patterns. Although this may result in some loss of information, sensitivity analysis showed that the model's performance was not significantly impacted, further confirming its practical applicability.[13,19]

Given the regional variations in antimicrobial resistance patterns and usage, we recommend recalibrating the model when applying it to new patient populations, particularly by adjusting the intercept to optimize prediction accuracy.[20] By adhering to TRIPOD guidelines, we ensured transparency and reproducibility in variable selection, model construction, and validation.

Inclusion of ASB: Clinical Relevance Discussion

We included asymptomatic bacteriuria (ASB) in this study due to its high prevalence and clinical significance in elderly diabetic patients. ASB may represent colonization by resistant pathogens or selective pressure from prolonged antibiotic use.[14] While ASB does not always lead to symptomatic infection, its presence may indicate a higher risk of resistance, particularly in the context of empirical antibiotic therapy. Sensitivity analysis confirmed that including ASB did not significantly alter the model's performance, further enhancing its robustness.[6]

The inclusion of ASB underscores the need for early identification of resistance risk, even in the absence of overt symptoms. Future studies could explore whether early identification and management of ASB could improve clinical outcomes in these high-risk populations.

External Validation and Model Applicability

External validation results showed that the nomogram model performed consistently across different datasets, with AUC values comparable to those of the training set, confirming its stability and predictive accuracy across multiple healthcare institutions. These findings support the model's robustness and potential clinical utility for early risk stratification of ESBL-producing Enterobacterales.

However, although external validation was performed, all datasets were derived from the same regional healthcare network, and thus may not fully represent geographically independent validation. Therefore, further validation in independent and geographically diverse populations is warranted to enhance the generalizability of the model.

Methodological Robustness and Future Applications

The robustness of this model was rigorously evaluated using stepwise regression, full model analysis, bootstrap internal validation, and internal-external cross-validation (IECV).[21] The key predictors remained consistent across different methodologies, further validating the model's stability. By using multi-center real-world data, we enhanced the model's general applicability. However, recalibration may be necessary when applying the model to different populations to improve prediction accuracy.[20]

In the future, this model could be integrated into clinical workflows to support real-time risk stratification in urgent care settings, further improving the management of elderly diabetic patients with urinary tract infections.

Clinical Implications for Elderly Patients

This study demonstrates that in elderly diabetic patients, low inflammation does not necessarily indicate a low risk of infection. Immune aging and metabolic disorders can lead to atypical infection presentations, diminishing the effectiveness of traditional inflammatory markers for risk assessment. Our risk model, which combines clinical and laboratory factors, provides an effective tool for early identification of high-risk patients, helping clinicians make more informed decisions and improving patient outcomes.

Study Limitations

Several limitations of this study should be acknowledged. The retrospective design may introduce selection bias and limit causal inference. Although we adjusted for multiple confounders, residual confounding cannot be entirely excluded.

All participating centers were derived from the same regional healthcare network, which may limit the geographic generalizability of the findings. Therefore, further validation in independent and geographically diverse populations is warranted to confirm the robustness and transportability of the model.

Some clinically relevant variables, such as detailed antibiotic exposure patterns, pathogen-specific resistance mechanisms, and direct measures of host immune function, were not fully captured, which may have influenced the observed associations.

A non-diabetic control group was not included in this study. As a result, the findings are specific to elderly diabetic patients with bacteriuria and should not be directly extrapolated to non-diabetic populations.

Clinical Summary

In elderly diabetic patients, low inflammation does not necessarily indicate low infection risk. By integrating laboratory markers, metabolic background, and antibiotic use history, our model helps identify resistance risks early, supporting clinical decisions before microbiological results are available. This model is especially effective in the early management of high-risk patients, helping optimize antimicrobial stewardship and reduce the inappropriate use of broad-spectrum antibiotics.

Data Sharing Statement

The data used in this study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Ethical approval was obtained from the Ethics Committee of Donghai Hospital Affiliated to Nanjing Medical University (Approval No.: LJYY2023-11). Given the retrospective nature of the study, the Ethics Committee waived the need for individual informed consent. All patient data were anonymized to ensure confidentiality and protect participant privacy.

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Author Contributions

Tingting Huang and Jibao Qin are co-first authors. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no potential conflicts of interest in this work.

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