

Predicting Drug Resistance: The Use of Novel Inflammatory Markers in Identifying ESBL-Producing *Klebsiella pneumoniae*

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Purpose: To explore the association of the Systemic Inflammatory Response Index (SIRI) and Systemic Inflammatory Immunity Index (SII) with extended-spectrum β -lactamase (ESBL)-producing *Klebsiella pneumoniae* (*K. pneumoniae*) and its resistance prediction.

Methods: A total of 425 patients with *K. pneumoniae* infections were included in the study. Data on general clinical characteristics and relevant laboratory indicators were collected. The patients were divided into ESBL-producing and non-ESBL-producing groups based on the presence of ESBLs. Logistic regression analysis was used to analyze the risk factors associated with ESBL-producing *K. pneumoniae*. The receiver operating characteristic (ROC) curve was employed to assess the predictive efficacy of SIRI and SII for ESBL-producing *K. pneumoniae* and its resistance to antibiotics.

Results: SIRI and SII levels in the ESBL-producing group were significantly higher than those in the non-ESBL-producing group. Logistic regression analysis showed that the odds ratios for SIRI and SII were 1.092 and 1.158, respectively, with 95% confidence intervals of 1.001–1.115 and 1.015–1.204, respectively. The critical values for predicting ESBL-producing *K. pneumoniae* were 1.067 for SIRI and 579.68 for SII, with area under the curve (AUC) values of 0.725 and 0.723, respectively. The AUC values for predicting resistance of ESBL-producing *K. pneumoniae* to piperacillin (PIP), amoxicillin/clavulanate (AMC), and cefazolin (CZO) were 0.614, 0.657, and 0.648 for SIRI, and 0.675, 0.613, and 0.625 for SII, respectively.

Conclusion: SIRI and SII are significantly associated with the risk of ESBL-producing *K. pneumoniae* and can be used to predict a patient's risk of infection with this organism. Additionally, SIRI and SII accurately predict the resistance of ESBL-producing *K. pneumoniae* to PIP, AMC, and CZO antibiotics.

Keywords: systemic inflammation response index, systemic inflammatory immune index, extended-spectrum β -lactamase, *Klebsiella pneumoniae*, prediction of drug resistance

Introduction

Klebsiella pneumoniae (*K. pneumoniae*) is a Gram-negative bacterium belonging to the Enterobacteriaceae family. It is widely found in nature and can cause various infections, including respiratory tract infections, urinary tract infections, and bloodstream infections.¹ According to the 2023 bacterial resistance monitoring report from the National Bacterial Resistance Monitoring Network, *K. pneumoniae* ranks second in Gram-negative bacterial infections, following *Escherichia coli*, and shows a significant increasing trend. As an important opportunistic pathogen, *K. pneumoniae* is prevalent in both hospital and community settings. In recent years, the global prevalence of *K. pneumoniae* has attracted significant attention due to the increasing problem of drug resistance.² Extended-spectrum β -lactamase (ESBL)-producing bacteria are of great clinical and epidemiological importance due to their resistance to β -lactam antibiotics.

ESBLs have been detected in all Enterobacteriaceae species worldwide.³ The majority of ESBL enzymes in *K. pneumoniae* are derived from two classical types, Temoneira (TEM) and Sulphydryl Variable (SHV), which are encoded by plasmids.⁴ Compared to bacteremia caused by non-ESBL-producing Enterobacteriaceae, infections caused by ESBL-producing isolates are associated with an approximately 57.0% increased risk of death.⁵ The coexistence of the CRISPR/Cas system and β -lactamases in *K. pneumoniae* may contribute to the mortality, prolonged hospitalization, and economic burden associated with infections caused by these drug-resistant strains. Early diagnosis and treatment are crucial to reducing mortality, hospitalization time, and economic costs.⁶

The Systemic Inflammatory Response Index (SIRI) is a novel inflammatory marker based on peripheral blood neutrophil, monocyte, and lymphocyte counts. It serves as an independent predictor of prognosis in multiple diseases.⁷ Similarly, the Systemic Inflammatory Immune Index (SII) is a new biomarker with broad clinical application value. It can assess immune-inflammatory status, predict disease prognosis, assist in diagnosis, guide treatment, and reflect host responses.⁸

Given that regional differences influence the clinical characteristics and drug resistance patterns of *K. pneumoniae* infections, it is essential to accurately understand the local epidemiology of these infections. Therefore, this study analyzes the clinical characteristics of *K. pneumoniae* infections at Urumqi Friendship Hospital. By investigating the role of the Systemic Inflammatory Response Index (SIRI) and Systemic Inflammatory Immune Index (SII) in antimicrobial resistance among ESBL-producing *K. pneumoniae*, this study aims to provide a scientific basis for optimizing antimicrobial use, developing prevention and control strategies for resistant bacteria, promoting early diagnosis, improving treatment outcomes, and curbing the development of drug resistance.

Methods

Ethics Statement

The Ethics Committee of Urumqi Friendship Hospital approved this research on February 20, 2023, with the approval number 2023022001, in accordance with the Declaration of Helsinki. As this study was retrospective, the Ethics Committee waived the requirement for patient consent. Confidentiality of patient information was strictly maintained throughout the study.

Patients and Study Design

This retrospective study included 425 cases of *K. pneumoniae* infections at Urumqi Friendship Hospital from March 1, 2023, to June 30, 2024, based on predefined inclusion and exclusion criteria.

Inclusion Criteria

1. Age was not restricted.
2. Complete clinical data were available.
3. Cases met the diagnostic criteria for various types of infections as defined in the *Diagnosis Criteria for Nosocomial Infections* issued by the former Ministry of Health in 2001.⁹
4. Based on clinical diagnosis, the isolated strain from the specimen was required to be cultured at least twice, with *K. pneumoniae* identified as the sole pathogenic bacterium.
5. Duplicate strains were excluded, and only the first positive culture result was selected for patients with multiple positive cultures of the target bacterium during hospitalization.

Exclusion Criteria

1. *Klebsiella pneumoniae* strains that were clinically isolated fewer than two times.
2. Cases involving more than two pathogens during the infection.
3. False-positive infections (defined as only one positive culture with no clinical symptoms of infection and no recurrence of negative cultures after *K. pneumoniae* treatment).

Identification Method of *K. pneumoniae*

Clinical Presentation

The physician makes an initial diagnosis based on the patient's clinical signs and symptoms. *Klebsiella pneumoniae* infection may present with a variety of symptoms, including but not limited to fever, cough, chest pain, and dyspnea.

Imaging Tests

A chest Computed Tomography (CT) scan can reveal the presence and extent of lung infection but cannot identify the specific pathogen.

Laboratory Tests

Laboratory staff processed and cultured clinical specimens and performed all bacteriological analyses and confirmatory biochemical testing. Selective culture media, including Blood Agar, MacConkey Agar, and Eosin Methylene Blue Agar (Merck Co., Germany), were used to cultivate all specimens, which were incubated at 37°C for 24 to 48 hours. *Klebsiella pneumoniae* isolates were identified based on cultural and morphological characteristics.¹⁰ The Gram-negative nature of *K. pneumoniae* was confirmed by Gram staining, which revealed pink or red rod-shaped bacteria under a microscope. Definitive identification of the bacterium was achieved using VITEK-2 GN ID cards and the VITEK® 2 Compact System (BioMérieux, France).¹¹

Biochemical Tests

The identification of *K. pneumoniae* in clinical laboratories relies on a series of biochemical tests, including the oxidase test, catalase test, indole test, methyl red test, VP test, and urease test. These tests enable accurate differentiation between *K. pneumoniae* and other members of the Enterobacteriaceae family.

Oxidase Test

Principle: To determine whether bacteria produce cytochrome oxidase.

Reagent: Oxidase test paper or reagent (eg, tetramethyl-p-phenylenediamine).

Steps.

1. Collect a small amount of bacterial colony using a sterile cotton swab.
2. Apply the colony to the oxidase test paper.
3. Observe the color change.

Result: *Klebsiella pneumoniae* is oxidase-negative (no color change).

Catalase Test

Principle: To determine whether bacteria produce catalase, an enzyme that breaks down hydrogen peroxide into water and oxygen.

Reagent: 3% hydrogen peroxide solution.

Steps.

1. Transfer a small amount of bacterial colony onto a clean glass slide.
2. Add 1 drop of 3% hydrogen peroxide solution to the colony.
3. Observe the formation of bubbles.

Result: *Klebsiella pneumoniae* is catalase-positive (bubbles are produced).

Indole Test

Principle: To determine whether bacteria can break down tryptophan to produce indole.

Medium: Tryptophan broth.

Reagent: Kovac's reagent.

Steps.

1. Inoculate the bacteria into tryptophan broth and incubate at 37°C for 24 hours.
2. Add a few drops of Kovac's reagent to the broth.
3. Observe the liquid surface for the formation of a red ring.

Result: *Klebsiella pneumoniae* is indole-negative (no red ring forms).

Methyl Red Test (MR Test)

Principle: To determine whether bacteria produce stable acidic end products from glucose fermentation.

Medium: MR-VP broth.

Reagent: Methyl red indicator.

Steps.

1. Inoculate the bacteria into MR-VP broth and incubate at 37°C for 48 hours.
2. Add a few drops of methyl red indicator to the broth.
3. Observe the color change.

Result: *Klebsiella pneumoniae* is methyl red-negative (the broth remains yellow or orange).

Voges-Proskauer Test (VP Test)

Principle: To determine whether bacteria produce acetoin (acetylmethylcarbinol) as a metabolic byproduct of glucose fermentation.

Medium: MR-VP broth.

Reagent: VP reagent (α -naphthol and potassium hydroxide).

Steps.

1. Inoculate the bacteria into MR-VP broth and incubate at 37°C for 48 hours.
2. Add VP reagent to the broth and shake gently to mix.
3. Observe the development of a red color.

Result: *Klebsiella pneumoniae* is VP-positive (a red color develops).

Urease Test

Principle: To determine whether bacteria produce the enzyme urease, which hydrolyzes urea into ammonia and carbon dioxide.

Media: Urea agar or urea broth.

Steps.

1. Inoculate the bacteria into urea medium.
2. Incubate at 37°C for 24 hours.
3. Observe the color change of the medium.

Result: *Klebsiella pneumoniae* is usually urease-negative (no color change), although some strains may exhibit urease-positive activity.

Data Collection

The general clinical characteristics and relevant laboratory indicators of eligible cases were collected, including patient name, sex (male/female), age, and whether invasive procedures were performed prior to infection.

Fasting peripheral venous blood samples were collected from patients, and laboratory analyses were conducted. Patient blood specimen data were obtained via the electronic medical record system before treatment or surgery during hospitalization. The following parameters were recorded: White blood cells (WBC), Neutrophils (NEU), Lymphocytes (LYM), Eosinophils (EOS), Platelets (PLT), Albumin (ALB), Cystatin C (CYS-C), Creatinine (CREA), Cholesterol (CHOL), Low-density lipoprotein (LDL), Glucose (GLU), Fibrinogen (FIB), D-dimer, Interleukin-6 (IL-6), and procalcitonin (PCT).

Laboratory Methods

Routine blood tests were performed using the Mindray Blood Analysis Line CAL 8000.

ALB, CYS-C, CREA, and other biochemical parameters were analyzed using the C8000 automatic biochemical analyzer.

IL-6 and PCT levels were measured using the Mike i1000 luminescence analyzer.

FIB and D-dimer levels were determined using the STA Compact Max coagulation analyzer.

Calculation of SIRI and SII

The systemic inflammation response index (SIRI) and systemic immune-inflammation index (SII) were calculated using the following formulas:

$$\text{SIRI}^7 = (\text{Neutrophils [NEU]} \times \text{Monocytes [MON]}) / \text{Lymphocytes [LYM]}$$

$$\text{SII}^8 = (\text{Neutrophils [NEU]} \times \text{Platelets [PLT]}) / \text{Lymphocytes [LYM]}$$

Drug Resistance Analysis

In this study, *K. pneumoniae* isolates were tested for the presence of extended-spectrum β -lactamases (ESBLs). The detection was performed according to the guidelines recommended by the Clinical and Laboratory Standards Institute (CLSI, 2023). A strain was confirmed as ESBL-positive if the difference in the inhibition zone diameter between cefotaxime/clavulanic acid and cefotaxime alone was ≥ 5 mm. Based on ESBL production, *K. pneumoniae* isolates were categorized into ESBL-producing and non-ESBL-producing groups, and drug resistance patterns were compared between the two groups.

The Kirby-Bauer disk diffusion susceptibility test was used for drug susceptibility testing. Drug susceptibility test strips were purchased from OXOID (UK).

Drug Sensitivity Test of the Bacterial Strains

Antimicrobial susceptibility testing was performed on the isolated *K. pneumoniae* strains using the microbroth dilution method. The minimum inhibitory concentrations (MICs) of 18 antibiotics were determined. The results were interpreted according to the recommendations of the 2019 edition of the Clinical and Laboratory Standards Institute (CLSI).

The Antibiotics Tested Included the Following

Piperacillin (PIP), ampicillin/sulbactam (SAM), meropenem (MEM), imipenem (IMP), cefazolin (CZO), ceftriaxone (CRO), ceftazidime (CAZ), cefepime (FEP), ceftazidime (FOX), aztreonam (ATM), gentamicin (GEN), ciprofloxacin (CIP), levofloxacin (LVX), cefuroxime (CXM), cefoperazone/sulbactam (CSL), bactrim (SXT), amoxicillin/clavulanate (AMC), and piperacillin/tazobactam (TZP).

Quality Control Strains

For drug susceptibility testing, the following quality control strains were used:

Escherichia coli ATCC 25922

Escherichia coli ATCC 35218

Statistical Analysis

Statistical analysis was performed using SPSS 22.0 software. Data that did not follow a normal distribution were expressed as the median (interquartile range). For comparisons between groups:

The Mann–Whitney *U*-test (rank-sum test) was used for continuous variables.

The chi-squared test (χ^2 -test) was used for categorical variables.

The drug resistance rates between ESBL-producing and non-ESBL-producing groups were compared using the χ^2 -test. Univariate and multivariate logistic regression analyses were conducted to evaluate the correlation between SIRI, SII, and ESBL-producing *K. pneumoniae*. Receiver operating characteristic (ROC) curves were generated to calculate the area under curve (AUC) for SIRI and SII levels in ESBL-producing *K. pneumoniae*, assessing their predictive ability for resistance to different antimicrobial drugs. *P*-value < 0.05 was considered statistically significant.

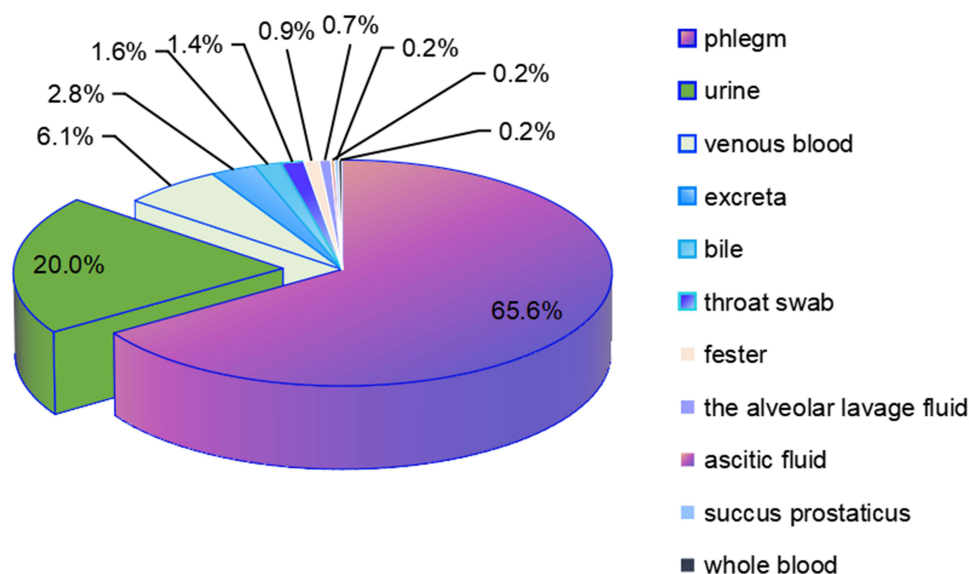


Figure 1 Distribution of specimens with 425 strains of *K. pneumoniae*.

Results

Distribution of Specimens With 425 Strains of *K. pneumoniae*

A total of 425 strains of *K. pneumoniae* (excluding duplicate strains) were selected based on the inclusion and exclusion criteria. The distribution of specimen types was as follows: 279 (65.6%) were sputum, 85 (20.0%) were urine, 26 (6.1%) were blood, 12 (2.8%) were secretions, seven (1.6%) were bile, and six (1.4%) were throat swab samples. Detailed clinical data for all the patients are shown in [Figure 1](#).

Differences in Blood Indices Between the Two Groups

Among the 425 strains of *K. pneumoniae* screened, 62 were ESBL-producing *K. pneumoniae*, and 363 were non-ESBL-producing *K. pneumoniae*. A comparison of clinical data between the two groups revealed significant differences in the following parameters ($P < 0.05$): lymphocyte (LYM), eosinophil (EOS), platelet (PLT), albumin (ALB), cystatin C (CYS-C), systemic inflammatory response index (SIRI), systemic inflammatory immune index (SII), creatinine (CREA), cholesterol (CHOL), low-density lipoprotein (LDL), glucose (GLU), fibrinogen (FIB), and D-dimer. However, no significant differences were observed in the following parameters ($P > 0.05$): white blood cell (WBC), neutrophil (NEU), C-reactive protein (CRP), urea nitrogen (UREA), uric acid (UA), triglyceride (TG), high-density lipoprotein (HDL), and interleukin-6 (IL-6). Detailed clinical data for all patients are presented in [Table 1](#).

SIRI and SII Were Significantly Higher in the ESBLs Group Than Those in the Non ESBLs Group

Further analysis of inflammatory markers in the blood of the two groups revealed the following:

WBC: Statistic = 1024; 95% confidence interval (CI) = -0.38 to 1.16; $P = 0.29$

IL-6: Statistic = 893.5; 95% CI = -5.44 to 7.59; $P = 0.76$

PCT: Statistic = 3284.5; 95% CI = -4.69 to 5.33; $P = 0.48$

CRP: Statistic = 9826; 95% CI = -1.94 to 2.81; $P = 0.83$

No significant differences were observed in WBC, IL-6, PCT, or CRP levels between the two groups ($P > 0.05$).

In contrast, the following markers showed significant differences:

SII: Statistic = 8307; 95% CI = 93.84 to 393.79; $P = 0.0013$

SIRI: Statistic = 8547.5; 95% CI = 0.18 to 1.09; $P = 0.0046$

Table 1 Comparison of General Data Between ESBLs Group and Non ESBLs Group

Variable	ESBLs Group (n=62)	Non ESBLs Group (n=363)	Z	P-value
Gender[n(%)]			0.39	0.53
Male	38(61.3)	207(57)		
Female	24(38.7)	156(43)		
Age[M(P ₂₅ , P ₇₅), years]	71(56, 81)	66(53, 78)	67.96	0.45
WBC[M(P ₂₅ , P ₇₅), ×10 ⁹ /L]	8.63(6.71, 11.46)	9.16(6.32, 13.38)	-1.46	0.144
NEU[M(P ₂₅ , P ₇₅), ×10 ⁹ /L]	6.76(4.68, 9.64)	6.82(4.07, 11.37)	-0.12	0.904
MON[M(P ₂₅ , P ₇₅), ×10 ⁹ /L]	0.47(0.35, 0.60)	0.51(0.36, 0.70)	-3.31	0.001
LYM[M(P ₂₅ , P ₇₅), ×10 ⁹ /L]	1.23(0.98, 1.79)	1.31(0.95, 1.99)	-3.47	0.001
EOS[M(P ₂₅ , P ₇₅), ×10 ⁹ /L]	0.08(0.04, 0.15)	0.06(0.01, 0.15)	-4.55	0.001
PLT[M(P ₂₅ , P ₇₅), ×10 ⁹ /L]	213.0(209.0, 336.0)	199.0(176.0, 235.0)	-5.09	0.001
CRP[M(P ₂₅ , P ₇₈), g/L]	11.73(2.46, 60.37)	11.07(2.66, 68.55)	-0.29	0.77
ALB[M(P ₂₅ , P ₇₅), g/L]	36.5 (32.3, 39.7)	38.8 (34.5, 42.1)	-5.97	0.001
CYS-C[M(P ₂₅ , P ₇₆), mmol/L]	1.08(0.93, 1.31)	1.02(0.85, 1.27)	-2.81	0.005
SIRI[M(P ₂₅ , P ₇₅), ×10 ⁹ /L]	1.89(0.89, 3.79)	1.45(0.76, 3.36)	0.23	0.02
SII[M(P ₂₅ , P ₇₅), ×10 ⁹ /L]	858.47 (513.18, 1819.70)	641.12 (386.47, 1477.80)	-1.56	0.019
UREA[M(P ₂₅ , P ₇₉), mmol/L]	6.10 (4.30, 9.00)	6.05 (4.60, 8.40)	-0.32	0.75
CREA[M(P ₂₅ , P ₈₀), umol/L]	67.00(56.00, 90.00)	72.00(58.00, 89.00)	-2.82	0.005
UA[M(P ₂₅ , P ₈₁), mmol/L]	290.00(225.00, 366.00)	295.00(228.00, 386.00)	-0.75	0.45
CHOL[M(P ₂₅ , P ₇₇), mmol/L]	3.45(2.87, 4.35)	3.90(3.28, 4.69)	-5.68	0.001
TG[M(P ₂₅ , P ₇₈), mmol/L]	1.05(0.86, 1.96)	1.24(0.89, 1.72)	-0.5	0.617
HDL[M(P ₂₅ , P ₇₈), mmol/L]	1.20(1.07, 1.44)	1.00(0.81, 1.23)	-0.97	0.33
LDL[M(P ₂₅ , P ₇₉), mmol/L]	2.32(1.93, 2.82)	2.30(2.05, 2.96)	-3.48	0.001
GLU[M(P ₂₅ , P ₈₀), mmol/L]	5.39(5.11, 8.75)	5.11(4.54, 6.64)	-2.82	0.005
IL-6[M(P ₂₅ , P ₈₁), mmol/L]	22.09(9.96, 50.43)	13.24(5.39, 28.80)	-2.06	0.24
FIB[M(P ₂₅ , P ₈₂), g/L]	4.38(3.33, 5.34)	4.46(3.42, 5.93)	-2.63	0.009
D dimer[M(P ₂₅ , P ₈₃), g/L]	1.23 (0.46, 2.85)	1.02 (0.41, 2.27)	-3.25	0.001

Both SIRI and SII were significantly higher in ESBL-producing *K. pneumoniae* compared to non-ESBL-producing *K. pneumoniae* ($P < 0.05$). See Figure 2 for details.

Linear Analysis of SIRI and SII Versus WBC, IL-6, PCT, and CRP

As shown in Figure 3, the systemic inflammatory response index (SIRI) was positively correlated with C-reactive protein (CRP), and the systemic immune-inflammation index (SII) was positively correlated with white blood cells (WBC), CRP, and interleukin-6 (IL-6) ($P < 0.05$).

SIRI, SII, LYM, and CHOL as Independent Risk Factors in the ESBL-Producing Group

As shown in Table 2, univariate logistic regression analysis revealed that monocytes (MON), lymphocytes (LYM), systemic inflammatory response index (SIRI), systemic immune-inflammation index (SII), and cholesterol (CHOL) were significantly associated with ESBL-producing *K. pneumoniae* ($P < 0.05$). These factors were identified as potential risk factors for ESBL-producing *K. pneumoniae*. Further multivariate logistic regression analysis demonstrated that SIRI, SII, LYM, and CHOL were independent risk factors in the ESBL-producing group, suggesting their potential as important biomarkers for assessing the risk of infection. In contrast, MON was not significant in the multivariate analysis.

SIRI and SII Accurately Predict ESBL-Producing *K. pneumoniae*

Based on ROC curve analysis, the cut-off values for the systemic inflammatory response index (SIRI) and systemic immune-inflammation index (SII) in predicting ESBL-producing *K. pneumoniae* were 1.067 and 579.68, respectively. The area under the curve (AUC) values were 0.725 (95% confidence interval [CI]: 0.668–0.781) for SIRI and 0.723 (95%

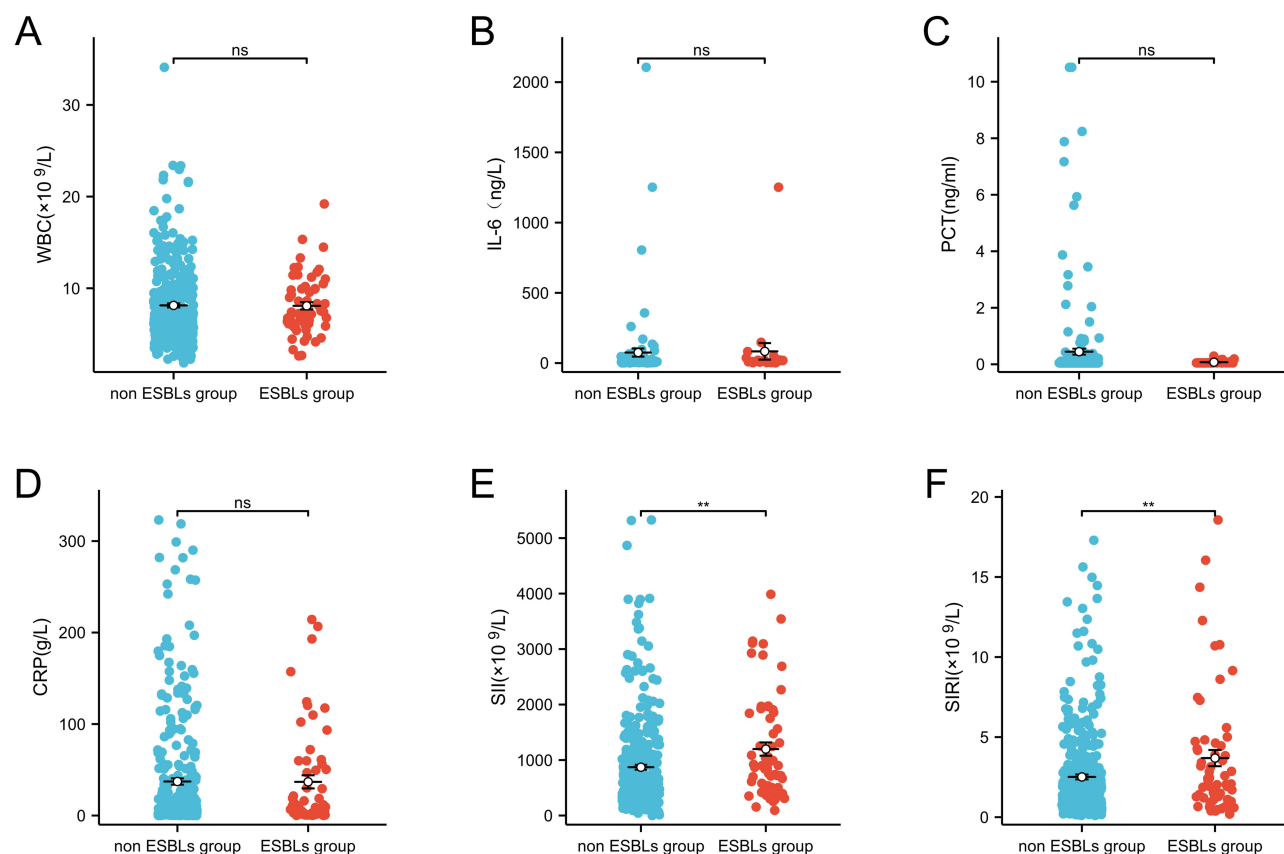


Figure 2 Comparison of different inflammatory indexes in two groups, **(A)** Comparative statistics of WBC in two groups, **(B)** Comparative statistics of IL-6 in two groups, **(C)** Comparative statistics of PCT in two groups, **(D)** Comparative statistics of CRP in two groups, **(E)** Comparative statistics of SII in two groups, **(F)** Comparative statistics of SIRI in two groups.

Note: **: $P < 0.05$.

Abbreviations: WBC, white blood cells; IL-6, interleukin 6; PCT, procalcitonin, CRP, C-reactive protein; SII, systemic inflammatory immune index; SIRI, systemic inflammatory response index.

CI: 0.667–0.779) for SII. Both AUC values exceeded 0.7, indicating a moderate level of predictive accuracy. See Figure 4 for details.

The Resistance Rate to Different Antibiotics Were Significantly Higher in the ESBLs Group Than Those in the Non ESBLs Group

The resistance rates of ESBL-producing *K. pneumoniae* to cefuroxime(CXM) and ceftriaxone(CRO) were 100.00% (62/62). The resistance rates of piperacillin(PIP), ceftazidime(CAZ), ceftazolin(CZO), ciprofloxacin(CIP), aztreonam(ATM), ampicillin/sulbactam (SAM), levofloxacin(LVX), and amoxicillin/clavulanate (AMC) were all higher than 50.00%. The resistance rates of cefepime(FEP), cefoperazone/sulbactam (CSL), gentamicin(GEN), compound sulfamethoxazole, meropenem(MEM), imipenem(IMP), piperacillin/tazobactam (TZP), and ceftioflox(FOX) were less than 50.00%. The resistance rates of the ESBLs group to different antibiotics, except MEM and IMP, were significantly higher than those in the non ESBLs group ($P < 0.05$). As shown in Table 3.

SIRI and SII Accurately Predict Resistance to PIP, AMC, and CZO in ESBL-Producing *K. pneumoniae*

The SIRI and SII cut-off points for PIP resistance in ESBL-producing *K. pneumoniae* were 1.6101 and 1248.60, respectively, with AUC areas of 0.614 and 0.657, respectively. The SIRI and SII cut-off points for AMC resistance in ESBL-producing *K. pneumoniae* were 1.8526 and 1070.50, respectively, with AUC areas of 0.648 and 0.675,

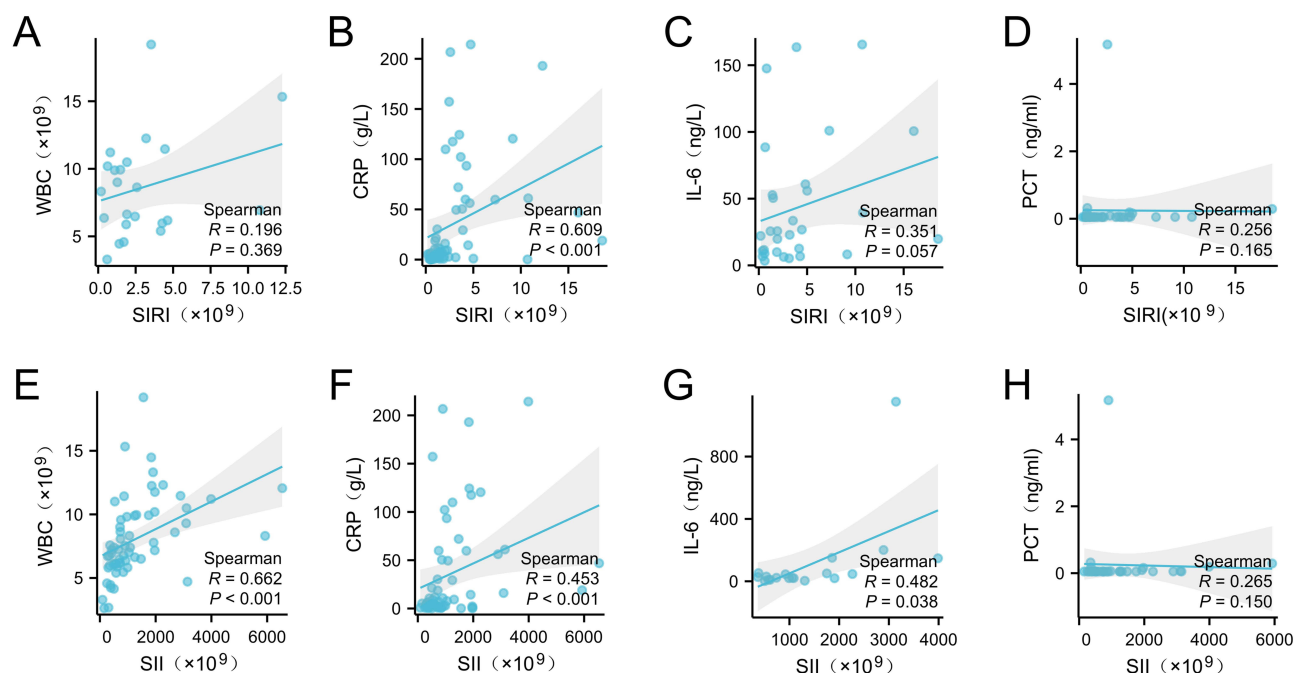


Figure 3 Linear analysis of SIRI and SII versus WBC, IL-6, PCT, and CRP, (A) linear analysis of SIRI versus WBC, (B) linear analysis of SIRI versus CRP, (C) linear analysis of SIRI versus IL-6, (D) linear analysis of SIRI versus PCT, (E) linear analysis of SII versus WBC, (F) linear analysis of SII versus CRP, (G) linear analysis of SII versus IL-6, (H) linear analysis of SII versus PCT.

Abbreviations: WBC, white blood cell; IL-6, interleukin 6; PCT, procalcitonin; CRP, C-reactive protein; SII, systemic inflammatory immunity index; SIRI, systemic inflammatory response index.

respectively. The SIRI and SII cut-off points for resistance to CZO in ESBL-producing *K. pneumoniae* were 1.6106 and 736.72, respectively, with AUC areas of 0.613 and 0.625, respectively. The AUC areas of PIP, AMC, and CZO were all greater than 0.5, with a certain level of accuracy. The SIRI and SII cut-off points for resistance to CAZ, CIP, ATM, SAM, and LVX in ESBL-producing *K. pneumoniae* were less than 0.5, indicating a low accuracy. As shown in Figure 5.

Discussion

Klebsiella pneumoniae (*K. pneumoniae*) is one of the most common Gram-negative pathogens associated with clinical infections, including pneumonia, urinary tract infections, sepsis, wound infections, and meningitis.¹² According to statistical data, *K. pneumoniae* is the third leading cause of hospital-acquired infections in the United States.¹³ The National Bacterial Resistance Monitoring Network reports that *K. pneumoniae* ranks second among Gram-negative bacterial infections, following *Escherichia coli*, and has shown a significant increasing trend.¹⁴ *K. pneumoniae* primarily affects immunocompromised populations, such as the elderly, infants, young children, and individuals with chronic wasting diseases.¹⁵ In recent years, antimicrobial-resistant strains of *K. pneumoniae* have spread globally, highlighting the importance of understanding the clinical characteristics of *K. pneumoniae* infections for early and effective treatment. Since the discovery of extended-

Table 2 Univariate and Multivariate Analysis of ESBLs-Producing *K. Pneumoniae*

Variable	Univariate Analyses			Multivariate Analyses		
	OR	95% CI	P-value	OR	95% CI	P-value
MON[M(P ₂₅ , P ₇₅), ×10 ⁹ /L]	0.502	0.245~1.012	0.05	0.788	0.286~2.172	0.788
LYM[M(P ₂₅ , P ₇₅), ×10 ⁹ /L]	0.637	0.475~0.855	0.003	0.66	0.452~0.964	0.032
SIRI[M(P ₂₅ , P ₇₅), ×10 ⁹ /L]	1.277	1.016~1.141	0.042	1.092	1.001~1.115	0.045
SII[M(P ₂₅ , P ₇₅), ×10 ⁹ /L]	1.326	1.048~1.295	0.038	1.158	1.015~1.204	0.048
CHOL[M(P ₂₅ , P ₇₇), mmol/L]	0.746	0.585~0.952	0.018	0.784	0.616~0.996	0.047

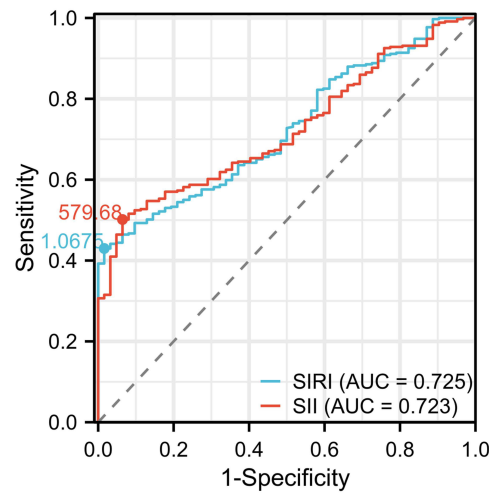


Figure 4 SRI and SII accurately predict ESBL-producing *K. pneumoniae*.
Abbreviations: SII, systemic inflammatory immunity index; SRI, systemic inflammatory response index.

spectrum β -lactamase (ESBL)-producing *K. pneumoniae* in Europe, ESBLs have become a major factor contributing to antibiotic resistance in Enterobacteriaceae, particularly in Klebsiella species.¹⁶

This study revealed that the primary source of isolated *K. pneumoniae* was sputum, followed by urine and blood. Statistical analysis indicated that *K. pneumoniae* predominantly caused respiratory tract, urinary tract, and bloodstream infections, consistent with the findings of Martin.¹⁷ The study further demonstrated that the SRI, SII, IL-6, and D-dimer levels in the ESBL-producing group were significantly higher than those in the non-ESBL-producing group. SRI, calculated based on neutrophil, monocyte, and lymphocyte counts in peripheral blood, is an independent prognostic factor for various malignancies.^{18,19} As a novel inflammatory biomarker, SRI holds broad clinical application prospects due to its simplicity and accessibility. Dynamic monitoring of SRI levels can provide real-time insights into patients' inflammatory status and prognostic risks, enabling more proactive and effective therapeutic interventions to improve

Table 3 Comparative Analysis of *K. Pneumoniae* Resistance Rates Between ESBLs Group and Non ESBLs Group

Antibacterials	ESBLs Group (n=62)		Non ESBLs Group (n=363)		χ^2	P
	Persister(n)	Drug Resistance rate (%)	Persister(n)	Drug Resistance rate (%)		
PIP	57	91.93	21	4.68	262.28	0.001
CXM	62	100	25	6.89	282.02	0.001
CAZ	58	93.55	0	0	202.61	0.001
CRO	62	100	3	0.83	378.21	0.001
FEP	20	32.26	1	0.28	113.14	0.001
CSL	24	38.71	9	2.48	97.06	0.001
CIP	49	79.03	25	6.89	191.67	0.001
ATM	40	64.52	3	0.83	236.21	0.001
GEN	23	37.09	4	1.10	115.32	0.001
SAM	52	83.87	25	6.89	211.55	0.001
LVX	37	59.68	33	9.09	69.29	0.001
SXT	28	45.16	17	4.68	91.65	0.001
MEM	3	4.84	24	6.61	0.76	0.384
IMP	3	4.84	24	6.61	0.35	0.553
AMC	33	53.23	72	19.83	31.91	0.001
TZP	10	16.13	3	0.83	41.82	0.001
CZO	32	51.61	105	28.93	7.81	0.005
FOX	20	32.26	40	11.02	19.70	0.001

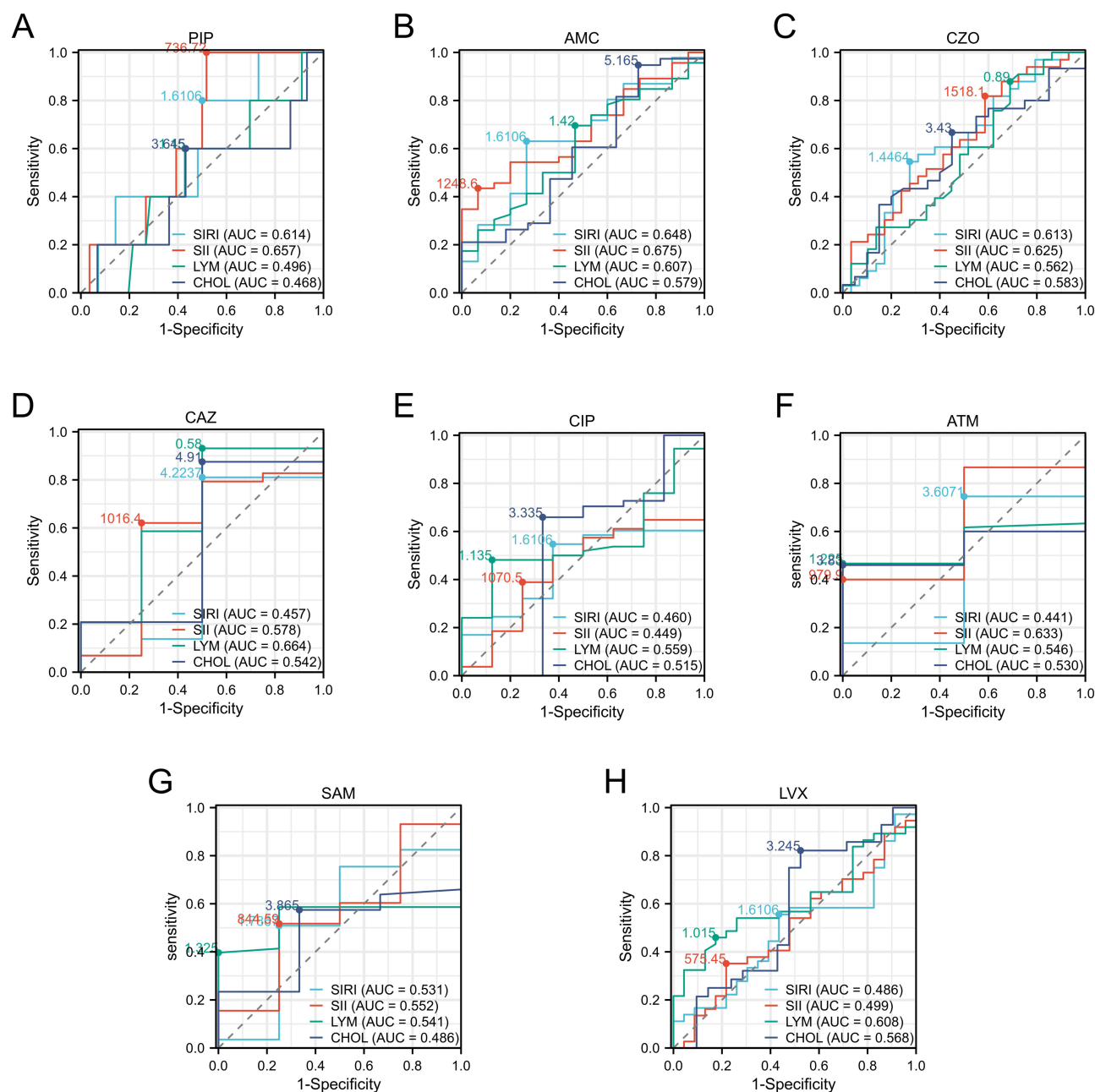


Figure 5 SIRI and SII accurately predict PIP, AMC, and CZO resistance in ESBL-producing *K. pneumoniae*, (A) ROC analysis of resistance of ESBL-producing *K. pneumoniae* to PIP antimicrobials by SIRI, SII, LYM, and CHOL, (B) ROC analysis of resistance of ESBL-producing *K. pneumoniae* to AMC antimicrobials by SIRI, SII, LYM, and CHOL, (C) ROC analysis of resistance of ESBL-producing *K. pneumoniae* to CZO antimicrobials by SIRI, SII, LYM, and CHOL, (D) ROC analysis of resistance of ESBL-producing *K. pneumoniae* to CAZ antimicrobials by SIRI, SII, LYM, and CHOL, (E) ROC analysis of resistance of ESBL-producing *K. pneumoniae* to CIP antimicrobials by SIRI, SII, LYM, and CHOL, (F) ROC analysis of resistance of ESBL-producing *K. pneumoniae* to ATM antimicrobials by SIRI, SII, LYM, and CHOL, (G) ROC analysis of resistance of ESBL-producing *K. pneumoniae* to SAM antimicrobials by SIRI, SII, LYM, and CHOL, (H) ROC analysis of resistance of ESBL-producing *K. pneumoniae* to LVX antimicrobials by SIRI, SII, LYM, and CHOL.

Abbreviations: PIP, piperacillin; AMC, amoxicillin / clavulanate; CZO, ceftazolin; CAZ, ceftazidime; CIP, ciprofloxacin; ATM, aztreonam; SAM, ampicillin / sulbactam; LVX, levofloxacin.

survival rates and quality of life in severe pneumonia patients.²⁰ Similarly, SII, a relatively new inflammatory marker integrating lymphocytes, neutrophils, and platelets, has been proposed. These cell types play critical roles in numerous inflammatory processes.²¹ Previous studies have shown that SII and D-dimer levels are positively correlated with the severity of infection.²² Additionally, *K. pneumoniae* exhibits the highest sensitivity to IL-6 and the lowest sensitivity to WBC.²³ IL-6 has been shown to be more sensitive and specific in predicting bacterial infections, with its elevation being

particularly pronounced in sepsis patients infected with gram-negative bacteria.²⁴ In this study, a positive correlation was observed between SIRI, SII, and IL-6 levels. Notably, while no significant differences were found in WBC, CRP, PCT, or IL-6 levels between the ESBL-producing and non-ESBL-producing groups, SIRI and SII were significantly higher in the ESBL-producing *K. pneumoniae* group. This finding suggests that SIRI and SII could serve as valuable indicators to differentiate ESBL-producing *K. pneumoniae*, enabling clinicians to make timely and accurate diagnoses and provide individualized treatment.

Univariate and multivariate logistic regression analyses revealed that SIRI and SII were significantly associated with the risk of ESBL-producing *K. pneumoniae*. These findings suggest that SIRI and SII could serve as potential biomarkers for predicting ESBL-producing *K. pneumoniae*. In clinical practice, physicians can utilize SIRI and SII levels to assess a patient's risk of infection with drug-resistant organisms, enabling early prevention and targeted treatment to improve patient outcomes. Moreover, studies have demonstrated that SIRI and SII are potentially valuable tools for inflammation scoring in the diagnosis and prognostic assessment of neonatal diarrhea and other inflammation-related diseases, such as colorectal cancer.²⁵ Elevated SIRI and SII levels may indicate a more severe inflammatory response and a higher risk of disease progression.²⁶ As composite inflammatory indexes derived from routine blood test parameters, SIRI and SII offer a more comprehensive reflection of the body's inflammatory response mechanisms across different diseases. Their application prospects lie in providing clinicians with more accurate and holistic information, thereby guiding more precise and effective treatment strategies.

This study found no significant differences in WBC, PCT, CRP, or IL-6 levels between the two groups, whereas SIRI and SII levels showed notable differences. In this study, SIRI and SII demonstrated predictive potential for identifying ESBL-producing *K. pneumoniae*. Furthermore, we found that SIRI was positively correlated with CRP, while SII was positively correlated with WBC, CRP, and IL-6. These findings suggest that SIRI and SII could serve as rapid and effective indicators for evaluating patients' inflammatory status. Sahin et al hypothesized that SIRI and SII might be significantly associated with neutrophils or other inflammatory markers, potentially providing a more comprehensive assessment of patients' inflammatory status and immune response.²⁷ Similarly, Wang et al demonstrated that SII and SIRI could be useful for early screening and risk assessment of symptomatic coronary heart disease in adolescents.²⁸ By monitoring the dynamics of SIRI and SII, clinicians can identify individuals at higher risk of ESBL-producing *K. pneumoniae* infections, enabling the implementation of targeted preventive measures to mitigate disease progression.

The emergence of antibiotic resistance poses an increasingly alarming public health threat, as it significantly undermines the efficacy of antibiotic treatments.²⁹ It is projected that by 2050, antibiotic resistance could become the leading cause of global mortality, potentially surpassing cancer-related deaths.³⁰ ESBL-producing bacteria confer resistance to extended-spectrum cephalosporins and related oxyimino- β -lactams, such as ceftazidime, cefotaxime, and aztreonam, but generally remain sensitive to carbapenems, cephamycins, and β -lactamase inhibitors like clavulanic acid.³¹ In this study, ESBL-producing *K. pneumoniae* exhibited a 100% resistance rate to cefuroxime and ceftriaxone, indicating complete resistance. This is likely attributable to the ability of ESBLs to hydrolyze broad-spectrum β -lactam antibiotics, including third-generation cephalosporins. Additionally, high resistance rates (>50%) were observed for piperacillin, ceftazidime, ciprofloxacin, amikacin, ampicillin/sulbactam, levofloxacin, amoxicillin/clavulanic acid, and cefazolin, suggesting limited efficacy of these drugs in treating ESBL-producing *K. pneumoniae*. Consequently, their use in clinical settings should be approached with caution. In contrast, cefepime, cefoperazone/sulbactam, gentamicin, cotrimoxazole, meropenem, imipenem, piperacillin/tazobactam, and ceftazidime demonstrated resistance rates below 50%, indicating their potential effectiveness against ESBL-producing *K. pneumoniae* infections. Notably, meropenem and imipenem exhibited minimal resistance rates, making them critical therapeutic options for managing such infections. Furthermore, the resistance rates of ESBL-producing *K. pneumoniae* to most antibiotics, except meropenem and imipenem, were significantly higher than those in the non-ESBL-producing group, highlighting the concerning impact of ESBL production on antibiotic resistance. In summary, for ESBL-producing *K. pneumoniae*, antimicrobial drugs with high resistance rates, such as cefuroxime and ceftriaxone, should be avoided in clinical practice. Instead, priority should be given to drugs with low resistance rates, such as meropenem and imipenem. Rational use of antimicrobial agents is essential to prevent further exacerbation of resistance due to misuse or overuse. Specifically, *K. pneumoniae* exhibited the lowest resistance rate to polymyxin B, followed by relatively low resistance rates to tigecycline, amikacin, and carbapenems.

However, high resistance rates were observed for cephalosporins, β -lactams, and quinolone antibiotics.³² These findings align with those reported by Li et al.³³

SIRI and SII demonstrated moderate accuracy in predicting the resistance of ESBL-producing *K. pneumoniae* to specific antimicrobial drugs, although the exact accuracy varied depending on the drug. These indices were particularly useful for forecasting resistance to commonly used antibiotics, such as piperacillin, amoxicillin-clavulanate, and ceftriaxone, in ESBL-producing strains. However, their predictive accuracy for other antibiotics, including SAZ, CIP, ATM, SAM, and LVX, was lower, suggesting limited suitability for predicting resistance to these drugs. Additionally, the predictive efficacy of LYM and CHOL was inferior to that of SIRI and SII. These findings hold significant implications for clinicians and researchers in developing treatment strategies and selecting appropriate antimicrobial therapies. It is important to note that drug resistance patterns of *K. pneumoniae* vary across regions and hospital departments. Nevertheless, the overall resistance rate is increasing, necessitating collaborative efforts among clinicians and hospital administrators to effectively curb its prevalence. This can be achieved through the rational use of antimicrobial drugs, enhanced infection control measures, and robust drug resistance monitoring systems.

In conclusion, SIRI and SII factors significantly associated with the risk of infection with ESBL-producing *K. pneumoniae*. SIRI and SII are accurate in predicting the resistance of ESBL-producing *K. pneumoniae* to antimicrobial drugs such as PIP, AMC, and CZO. The findings of this study can guide clinicians in making precise diagnoses, personalizing medication, effectively preventing and controlling its prevalence through the rational use of antimicrobial drugs, and enhancing infection control and resistance monitoring. SIRI, which integrates neutrophil, monocyte, and lymphocyte counts, offers a comprehensive assessment of the systemic inflammatory response. Similarly, SII combines platelet, neutrophil, and lymphocyte counts to reflect the immune and inflammatory status. Both indices are derived from routine blood tests, eliminating the need for additional invasive procedures, thereby facilitating their application across various clinical settings. Continuous monitoring of SIRI and SII can aid in evaluating changes in a patient's inflammatory and immune status, allowing for timely adjustments to the treatment plan. Research indicates that SIRI and SII are instrumental in predicting the development of antibiotic resistance, particularly in cases of severe and complex infections. However, SIRI and SII have certain limitations. SIRI and SII are comprehensive indicators that cannot distinguish between specific pathogen types, and therefore have limitations in predicting drug resistance to specific pathogens. Both are affected by a variety of factors, such as the patient's underlying disease, immune status, and comorbidities, which may lead to biased prediction results. There are no standardized thresholds and assessment criteria, and results may vary in different studies.

In conclusion, SIRI and SII are significantly associated with the risk of ESBL-producing *K. pneumoniae* infection and demonstrate accuracy in predicting resistance to antimicrobial drugs such as piperacillin (PIP), amoxicillin-clavulanate (AMC), and cefazolin (CZO). These findings can guide clinicians in making precise diagnoses, personalizing treatment strategies, and controlling the prevalence of ESBL-producing *K. pneumoniae* through rational antimicrobial use, enhanced infection control, and robust resistance monitoring. SIRI and SII derived from routine blood tests, they are non-invasive and easily applicable across clinical settings. Continuous monitoring of these indices can help evaluate changes in a patient's condition, enabling timely treatment adjustments.

Our study has several limitations. First, as a single-center, retrospective analysis, it aimed to correlate SIRI and SII with antibiotic resistance outcomes to assess their predictive ability. However, the small sample size may have limited the ability to fully capture the diverse characteristics of patients with *Klebsiella pneumoniae* infections. Future studies should design prospective cohorts to regularly monitor patients' SIRI and SII levels and observe their association with antibiotic resistance development, validating their predictive value and correcting for confounding factors. Additionally, multi-center validation studies across diverse populations and clinical settings are needed to assess the generalizability and stability of these indices. Second, the cutoff values for most inflammation and nutritional indicators were not standardized. In this study, optimal cutoff values for SIRI and SII were determined using ROC curves; however, the lack of standardized thresholds may lead to variability in interpretation. Future large-sample prospective studies are needed to establish universal cutoff values and validate the findings of this research.

Conclusion

This study aimed to evaluate SIRI and SII as potential inflammatory markers for identifying *K. pneumoniae* and to develop a novel model for predicting ESBL-producing *K. pneumoniae* by integrating clinical features. The results demonstrated that SIRI and SII accurately predicted the resistance of ESBL-producing *K. pneumoniae* to piperacillin (PIP), amoxicillin-clavulanate (AMC), and cefazolin (CZO). The proposed model exhibited excellent performance and discriminative ability, providing a theoretical basis for clinical decision-making and treatment planning.

Abbreviations

AUC, Area Under Curve; AMC, Amoxicillin/Clavulanate; ATM, Aztreonam; CAZ, Ceftazidime; CHOL, Cholesterol; CIP, Ciprofloxacin; CI, confidence interval; CREA, Creatinine; CRP, C-reactive Protein; CSL, Cefoperazone/Sulbactam; CT, Computed Tomography; CYS-C, Cystatin C; CZO, Cefazolin; EOS, Eosinophils; ESBL, Extended-Spectrum β -Lactamase; FEP, Cefepime; FIB, Fibrinogen; FOX, Cefoxitin; GEN, Gentamicin; GLU, Glucose; HDL, High-Density Lipoprotein; IL-6, Interleukin-6; IMP, Imipenem; *K. pneumoniae*, *Klebsiella pneumoniae*; LDL, Low-Density Lipoprotein; LYM, Lymphocytes; MEM, Meropenem; MON, Monocytes; NEU, Neutrophils; PCT, Procalcitonin; PIP, Piperacillin; PLT, Platelets; ROC, Receiver Operating Characteristic; SAM, Ampicillin/Sulbactam; SHV, Sulfhydryl Variable; SII, Systemic Immune-Inflammation Index; SIRI, Systemic Inflammatory Response Index; TEM, Temoneira; TZP, Piperacillin/Tazobactam; UREA, Urea Nitrogen; WBC, White Blood Cells.

Data Sharing Statement

This study was approved by the Ethics Committee of Urumqi Friendship Hospital. As a retrospective study, it posed no risks or adverse effects to patients and did not involve the collection of identifiable patient information. All data were anonymized and maintained with strict confidentiality. The authors take full responsibility for all aspects of the study and ensure that any questions related to the accuracy or integrity of the research are thoroughly investigated and resolved. This study was conducted in compliance with the principles of the Declaration of Helsinki.

Acknowledgments

The authors would like to thank the Urumqi Friendship Hospital and the "Sun Hong Famous Doctor's Studio" for their support of this work.

Author Contributions

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.

Funding

This research was supported by the "Tianshan Talents" Medical and Health High-level Personnel Training Plan of the Xinjiang Uygur Autonomous Region (Grant No. TSYC202301B149).

Disclosure

The authors report no conflicts of interest in this work.

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