

# Increased Incidence and Risk Factors of Infections by Extended-Spectrum $\beta$ -Lactamase-Producing Enterobacterales During the COVID-19 Pandemic: A Retrospective Case-Control Study

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**Purpose:** To investigate changes in the incidence of infections by extended-spectrum  $\beta$ -lactamase-producing *Enterobacterales* (ESBL-E) and analyzed whether there was an association between endogenous changes in the organism due to COVID-19 infection and the infections by ESBL-E.

**Patients and Methods:** The study was a single-center retrospective case-control design. A total of 107 patients infected by ESBL-E during the COVID-19 pandemic were selected as the case group, while 214 uninfected patients selected by 1:2 propensity score matching (PSM) acted as the control group. Univariate analysis, LASSO logistic regression, and multivariate logistic regression were used to determine the risk factors for ESBL-E infection. An interrupted time series was used to analyze the changes in the incidence of ESBL-E infections in hospitalized patients during the COVID-19 pandemic.

**Results:** The incidence of infection with ESBL-E showed a significant increase during COVID-19 (3.42 vs 4.92 per 1000 patients,  $p = 0.003$ ). The incidence of ESBL-E infections increased at an average rate of 0.45 per 1000 patients per week compared to the pre-pandemic period ( $p = 0.022$ ). Multivariate logistic regression analysis showed that a length of hospitalization  $\geq 15$  days (OR: 2.98 (1.07–8.28), chronic kidney disease (OR: 4.25 (1.32–13.70), white blood cell (WBC)  $> 9.5 \times 10^9/L$  (OR: 3.04 (1.54–6.01), use of hormonal drugs (OR: 2.38 (1.04–5.43), antibacterial drug use 1 type (OR: 5.38 (2.04–14.21), antibacterial drug use 2 types (OR: 23.05 (6.71–79.25) and antibacterial drug use  $\geq 3$  types (OR: 88.35 (8.55–912.63) were independent risk factors for infection with ESBL-E, while chronic obstructive pulmonary disease (COPD) was a protective factor (OR: 0.14 (0.03–0.66). COVID-19 was not an independent risk factor for infection by ESBL-E.

**Conclusion:** During the COVID-19 pandemic, the incidence of infections by ESBL-E increased significantly. Increased exposure to traditional risk factors were the main reasons, however, COVID-19 was not an independent risk factor for ESBL-E infection.

**Keywords:**  $\beta$ -lactamases, COVID-19, risk factor, antibacterial drugs, case-control study, LASSO

## Introduction

Extended-spectrum  $\beta$ -lactamases (ESBLs) are enzymes produced by certain bacteria that hydrolyze penicillins, cephalosporins, and monocyclic amides antibiotics, and are usually strongly inhibited by clavulanic acid.<sup>1,2</sup> They are mainly found in gram-negative bacilli, of which *Escherichia coli* and *Klebsiella pneumoniae* are the most common.<sup>3,4</sup> The prevalence of extended-spectrum  $\beta$ -lactamase producing *Enterobacterales* (ESBL-E) is increasing worldwide and has

become one of the public health issues of global concern.<sup>5</sup> A case-control study in Canada found that ESBL-E infection was associated with longer hospital stays, increased hospital costs, and higher mortality.<sup>6</sup>

Since December 2019, cases of coronavirus disease 2019 (COVID-19) have emerged worldwide and rapidly formed a worldwide pandemic in a short period of time, posing a serious threat to public safety.<sup>7,8</sup> During the pandemic when hospitals experienced personal protective equipment (PPE) supply challenges, staffing shortages, and extended patient stays, there may have been a shift in clinical focus of infection control to prevent respiratory transmission and a decrease in antimicrobial surveillance and stewardship.<sup>9,10</sup> A multi-center, retrospective cohort analysis in 271 healthcare facilities in the United States showed that antibiotic multidrug resistance rates were significantly higher during the COVID-19 pandemic than before the pandemic.<sup>11</sup> The authors also emphasized that the results of this study were limited to the United States and that further investigations were needed to determine whether or not antibiotic multidrug resistance rates had also increased in hospitalized patients in other countries during the COVID-19 pandemic. COVID-19 caused a reduction in the immunity of patients making them prone to combined or secondary bacterial and fungal infections, with some patients needing to use catheters and ventilators more frequently and for longer periods of time.<sup>12–14</sup> These conditions also increased the risk of multidrug resistance. Therefore, it is vital to prevent, identify and monitor infections by ESBL-E, especially during the COVID-19 epidemic. There are many studies on the risk factors for ESBL-E infection. According to a published systematic review, the most commonly reported risk factors for ESBL-E colonization and infection were previous exposure to antimicrobial drugs and recent hospitalization or surgical treatment.<sup>15</sup> However, there are few studies on risk factors for ESBL-E infection during the COVID-19 pandemic.

The purpose of this study was to investigate the changes in the incidence of ESBL-E infections and the risk factors during the COVID-19 pandemic. The study also evaluated whether endogenous changes in the organism due to COVID-19 infection are potential independent risk factors for ESBL-E infection.

## Patients and Methods

### Patient Selection and Data Collection

The study was a retrospective, case-control design that included patients admitted to a tertiary care general hospital in Ningxia between December 8, 2022, to February 1, 2023. Patients identified as positive for an ESBL-E infection determined by a drug sensitivity test were selected as the case group ( $n = 107$ ). Non-infection patients were included as the control group ( $n = 214$ ) and were selected using age and sex as matching variables with a caliper value of 0.02 and propensity score matching (PSM) according to the 1:2 nearest neighbor matching method. Inclusion criteria for all the patients were: (1) length of hospitalization  $> 24$  h; (2) the case group included patients with positive ESBL-E confirmed by strain identification and a drug sensitivity test. Exclusion criteria: (1) presence of duplicate strains in the same patient; (2) patient previously included in the study.

Patients with a positive drug sensitivity test for ESBL-E were identified through the hospital LIS testing system, and their clinical information then extracted from the electronic medical record system according to case number. The following study indicators were identified based on previous relevant studies: general characteristics (sex, age, length of hospitalization, previous hospitalization, intensive care unit [ICU] admission, COVID-19, and nutritional status); underlying diseases (hypertension, diabetes mellitus, chronic kidney disease, chronic obstructive pulmonary disease [COPD]); comorbidities (hypoproteinemia, respiratory failure, and sepsis); invasive operations (mechanical ventilation, central venous placement, retained urinary catheter, and tracheal intubation); treatment and drug use (surgery, blood transfusion, whether antibacterial drugs were used and the length of use and type of antibacterial drugs administered, combination of antibacterial drugs, and whether hormonal drugs were used and length of use); laboratory tests (serum albumin and lactate levels, and white blood cell [WBC] count).

### Antimicrobial Susceptibility Testing and Phenotypic Detection of ESBL-E

The strains were cultured and identified with reference to the National Clinical Laboratory Practice (4th edition), with the drug susceptibility test performed by the Kirby-Bauer disk diffusion method. The criteria for an ESBL-E infection included: (1) Primary screening test: Drug-sensitive disks containing cefpodoxime (10  $\mu$ g) and ceftazidime (30  $\mu$ g) were

selected. Muller-Hinton (MHA) agar and standard disk diffusion method were used to test the diameter of the inhibition ring. A ring diameter for cefpodoxime of  $\leq 17$  mm and  $\leq 22$  mm for ceftazidime was highly suspected as indicating the presence of an ESBLs strain, with further tests needed to confirm the diagnosis. (2) Phenotype confirmation test: Ceftazidime (30  $\mu$ g) and ceftazidime plus clavulanic acid (30  $\mu$ g and 10  $\mu$ g), and cefotaxime (30  $\mu$ g) and cefotaxime plus clavulanic acid (30  $\mu$ g and 10  $\mu$ g) were used to measure the diameter of the inhibition rings of the two disks either alone or with clavulanic acid. Any group with clavulanic acid was considered to be infected with ESBL-E if the increase in inhibition diameter was  $\geq 5$  mm compared to that measured without clavulanic acid.

## COVID-19 Definition

According to the diagnostic criteria of the Novel Coronavirus Pneumonia Treatment Protocol (Trial Version 9)<sup>16</sup> developed by the National Health Commission, a suspected case with one of the following pathogenic or serological findings can be diagnosed as a confirmed case of COVID-19: (1) Positive nucleic acid test for a novel coronavirus; (2) Novel coronavirus-specific IgM and IgG antibodies positivity in patients who had not received the novel coronavirus vaccine.

## Statistical Analysis

The raw data were entered and collated using Microsoft Excel (Office 2021) software. The continuous variables were expressed as median (M) and quartile interval (P25, P75), while the categorical variables were expressed as frequency (n) and percentage (%). Univariate and multivariate logistic regression analyses were performed using SPSS 26.0. The Mann–Whitney *U*-test was used to test for differences between continuous variables, while the chi-square test was used for comparison of categorical variables. Significant independent variables were screened using the LASSO logistic regression model, with the screened independent variables then included in a multivariate logistic regression model for analysis. An interrupted time series was used to analyze the changes in the incidence of ESBL-E infections in hospitalized patients during the COVID-19 pandemic. R software version 4.2.2 and the “glint” package were used for the LASSO regression analysis. Interrupted time series analysis was performed using stataMP17 analysis. A *p* value < 0.05 was considered statistically significant.

## Results

### Sociodemographic and Clinical Characteristics of Study Participants

A total of 321 hospitalized patients during the COVID-19 pandemic (December 8, 2022 to February 1, 2023) were included as subjects in this study. The case group included 52 males (48.6%) and 55 females (51.4%) and the control group included 103 males (48.13%) and 111 females (51.87%). There was no significant difference in the sex ratio between the two groups (*p* = 0.937). The median age of both the case and control groups was 67 years, and the difference was not statistically significant (*p* = 0.983) (Table 1). During the COVID-19 pandemic, ESBL-E infections were mainly *Escherichia coli* and *Klebsiella pneumoniae*, with a detection rate of 53.13% (85/160) and 11.40% (20/194), respectively.

### Incidence of Infections by ESBL-E Before and During COVID-19

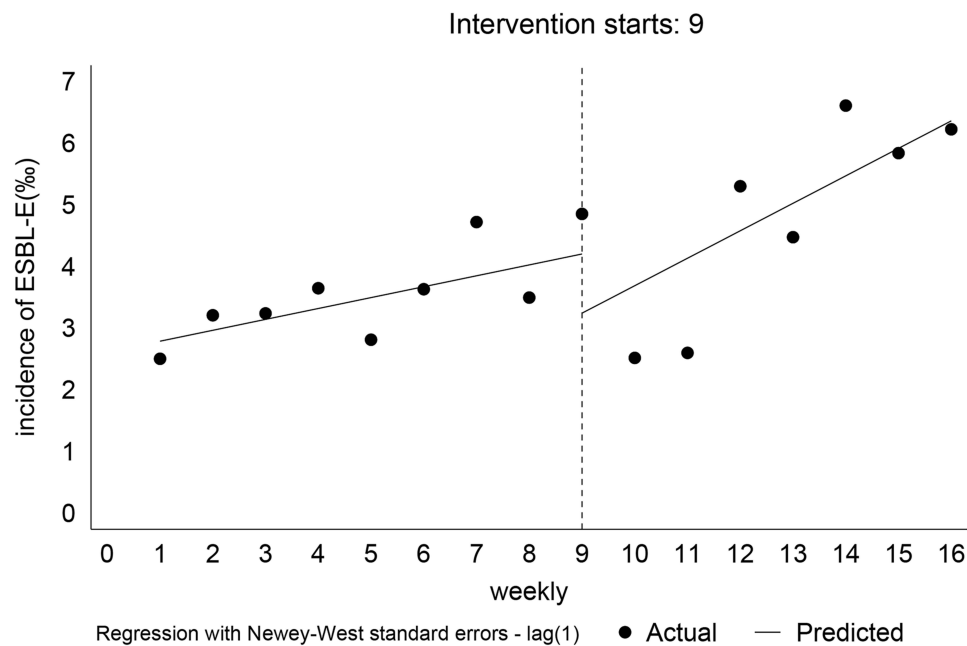
A total of 38,325 patients were hospitalized before the pandemic (December 8, 2021 to February 1, 2022), of which 131 patients with ESBL-E infection were detected. During the COVID-19 pandemic (December 8, 2022 to February 1, 2023) 27,865 patients were hospitalized, of which 137 patients with ESBL-E infection were detected. Although the number of hospitalized patients decreased during the pandemic, the incidence of ESBL-E infections increased significantly (3.42 vs 4.92 per 1000 patients, *p* = 0.003). Interrupted time series analysis showed that the incidence of ESBL-E infection increased at an average rate of 0.18 per 1000 patients per week before the pandemic (*p* = 0.015). The incidence of ESBL-E infection showed a decrease immediately after the start of the pandemic (0.96 per 1000 patients, *p* = 0.936) and then increased at a rate of 0.45 per 1000 patients weekly (*p* = 0.022) (Figure 1).

**Table I** Univariate Analysis of Risk Factors for Extended-Spectrum  $\beta$ -Lactamase Producing *Enterobacteriales* (ESBL-E), n (%)

Variables	Case group (n=107)	Control group (n=214)	p value
<b>General Characteristics</b>			
Male	52 (48.6%)	103 (48.1%)	0.937
Age, M (P <sub>25</sub> , P <sub>75</sub> ), (years)	67 (52, 81)	67 (52, 81)	0.983
Length of hospitalization, days			<b>&lt; 0.001</b>
<15	63 (58.9%)	203 (94.9%)	
≥15	44 (41.1%)	11 (5.1%)	
Previous hospitalization	48 (44.9%)	98 (45.8%)	0.874
ICU admission	21 (19.6%)	14 (6.5%)	<b>&lt; 0.001</b>
COVID-19	61 (57.0%)	88 (41.1%)	<b>0.007</b>
Nutritional status (≥3 points)	28 (26.2%)	26 (12.1%)	<b>0.002</b>
<b>Underlying diseases</b>			
Hypertension	48 (44.9%)	83 (38.8%)	0.297
Diabetes mellitus	30 (28.0%)	37 (17.3%)	<b>0.026</b>
COPD	4 (3.7%)	18 (8.4%)	0.118
Chronic kidney disease	13 (12.1%)	8 (3.7%)	<b>0.004</b>
<b>Comorbidities</b>			
Sepsis	11 (10.3%)	4 (1.9%)	<b>0.001</b>
Respiratory failure	25 (23.4%)	17 (7.9%)	<b>&lt; 0.001</b>
Hypoproteinemia	49 (45.8%)	38 (17.8%)	<b>&lt; 0.001</b>
<b>Laboratory tests</b>			
Albumin (< 40 g/L)	95 (88.8%)	170 (79.4%)	<b>0.038</b>
WBC (> 9.5×10 <sup>9</sup> /L)	51 (47.7%)	47 (22.0%)	<b>&lt; 0.001</b>
Serum lactate level (> 2.2 mmol/L)	34 (31.8%)	51 (23.8%)	0.128
<b>Invasive operations</b>			
Mechanical Ventilation	22 (20.6%)	7 (3.3%)	<b>&lt; 0.001</b>
Central venous placement	30 (28.0%)	17 (7.9%)	<b>&lt; 0.001</b>
Retained urinary catheter	37 (34.6%)	26 (12.1%)	<b>&lt; 0.001</b>
Tracheal intubation	22 (20.6%)	5 (2.3%)	<b>&lt; 0.001</b>
<b>Treatment and drug use</b>			
Blood transfusion	20 (18.7%)	15 (7.0%)	<b>0.002</b>
Surgery	28 (26.2%)	73 (34.1%)	0.149
Use of antimicrobial drugs	101 (94.4%)	100 (46.7%)	<b>&lt; 0.001</b>
Length of antimicrobial drug use, days			<b>&lt; 0.001</b>
<7	40 (37.4%)	191 (89.3%)	
≥7	67 (62.6%)	23 (10.7%)	
Antibacterial drug combination			<b>&lt; 0.001</b>
Not used	6 (5.6%)	114 (53.3%)	
Single use	67 (62.6%)	88 (41.1%)	
Two or more	34 (31.8%)	12 (5.6%)	
Types of antibacterial drugs			<b>&lt; 0.001</b>
Not used	6 (5.6%)	114 (53.3%)	
1 type	43 (40.2%)	85 (39.7%)	
2 types	32 (29.9%)	14 (6.5%)	
≥3 types	26 (24.3%)	1 (0.5%)	
Use of hormonal drugs	43 (40.2%)	23 (10.7%)	<b>&lt; 0.001</b>
Length of hormonal drug use, days			<b>0.001</b>
<7	95 (88.8%)	209 (97.7%)	
≥7	12 (11.2%)	5 (2.3%)	

**Notes:** The nutritional status was obtained from the nutritional risk screening scale. A score of less than 3 indicates that the patient's nutritional status is re-evaluated weekly if he or she will undergo major surgery; A score greater than or equal to 3 indicates that the patient is at risk of malnutrition and requires nutritional support therapy. P values in bold are statistically significant (P < 0.05).

**Abbreviations:** M, median; ICU, intensive care unit; COPD, chronic obstructive pulmonary disease; WBC, white blood cell.



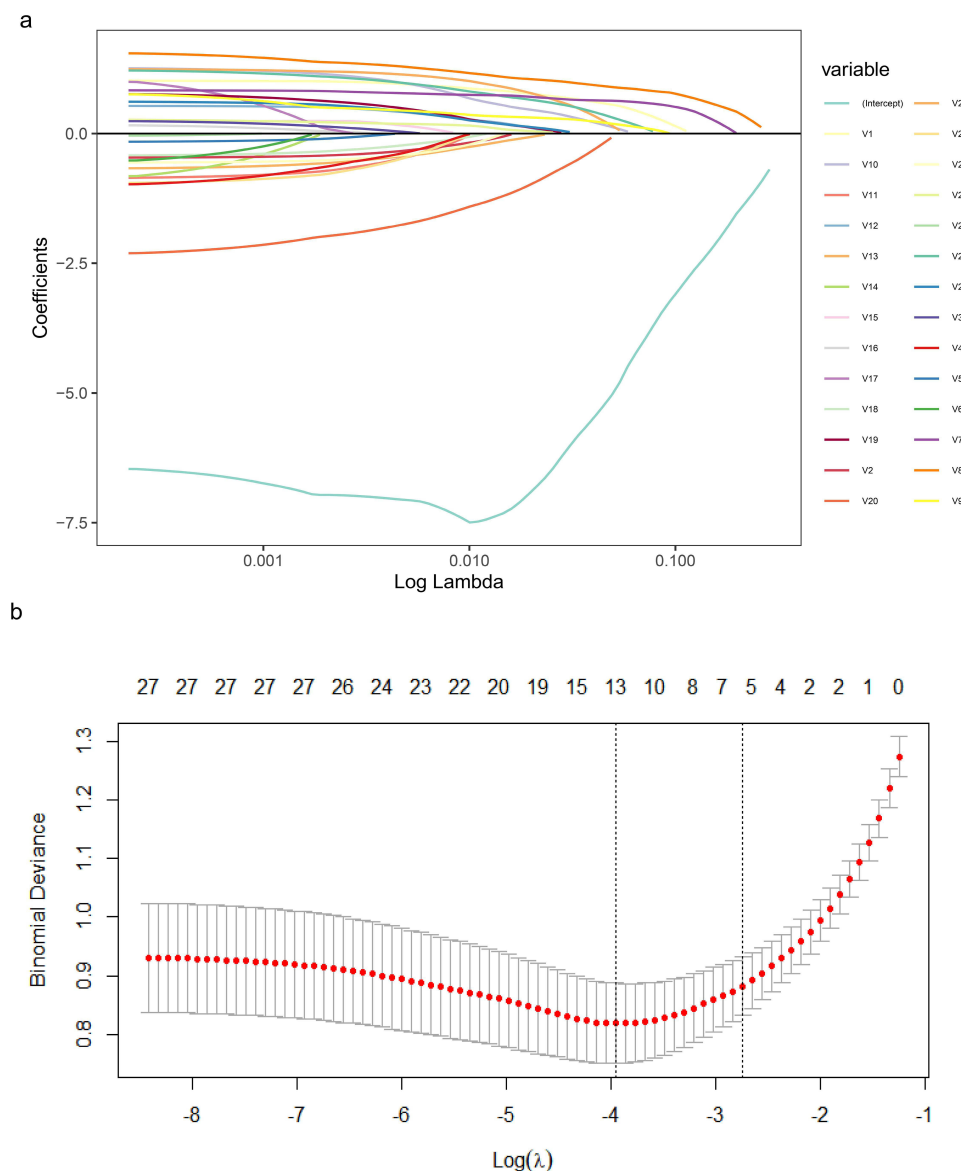
**Figure 1** Interrupted time series analysis of the incidence of infections by ESBL-E. Baseline: weeks 1–8 are the weekly incidence of infections by ESBL-E before COVID-19 (December 8, 2021 to February 1, 2022); Intervention stage: weeks 9–16 are the weekly incidence of infections by ESBL-E during the COVID-19 pandemic (December 8, 2022 to February 1, 2023). The black dots indicate the actual weekly incidence of infection by ESBL-E; The dotted line indicates the start of the intervention, which is the beginning of the COVID-19 pandemic; The solid line indicates the incidence of infection by ESBL-E as predicted by the ITSA model.

## Factors Associated with Infections by ESBL-E

In [Table 1](#), possible risk factors associated with ESBL-E infection are listed, including general characteristics, underlying diseases, comorbidities, laboratory indicators, invasive operations, and treatment and drug use. The results of univariate analysis showed that the age and sex of the case group and the control group were balanced and comparable ( $p > 0.05$ ). Differences between the two groups were observed for the length of hospitalization (41.1% vs 5.1%,  $p < 0.001$ ), ICU admission (19.6% vs 6.5%,  $p < 0.001$ ), COVID-19 (57.0% vs 41.1%,  $p = 0.007$ ), nutritional status (26.2% vs 12.1%,  $p = 0.002$ ), diabetes mellitus (28.0% vs 17.3%,  $p = 0.026$ ), chronic kidney disease (12.1% vs 3.7%,  $p = 0.004$ ), sepsis (10.3% vs 1.9%,  $p = 0.001$ ), respiratory failure (23.4% vs 7.9%,  $p < 0.001$ ), hypoproteinemia (45.8% vs 17.8%,  $p < 0.001$ ), albumin  $< 40$  g/L (88.8% vs 79.4%,  $p = 0.038$ ), and WBC  $> 9.5 \times 10^9/L$  (47.7% vs 22.0%,  $p < 0.001$ ). Some patients received invasive operations such as mechanical ventilation and central venous line placement, and the differences between the two groups compared were statistically significant ( $p < 0.001$ ). In addition, differences between two groups were reported for blood transfusion (18.7% vs 7.0%,  $p = 0.002$ ), use of antimicrobial drugs (94.4% vs 46.7%,  $p < 0.001$ ), length of antimicrobial drug use  $\geq 7$  days (62.6% vs 10.7%,  $p < 0.001$ ), antibacterial drug combination  $\geq 2$  (31.8% vs 5.6%,  $p < 0.001$ ),  $\geq 3$  types of antibacterial drugs (24.3% vs 0.5%,  $p < 0.001$ ), use of hormonal drugs (40.2% vs 10.7%,  $p < 0.001$ ), and length of hormonal drug use  $\geq 7$  days (11.2% vs 2.3%,  $p = 0.001$ ) ([Table 1](#)).

We used a LASSO logistic regression model to construct the risk factor selector ([Figure 2a](#)). The number of corresponding variables screened out by the model is shown in [Figure 2b](#). After the LASSO regression model analysis, 13 variables with non-zero coefficients were screened at a lambda.min of 0.021, including length of hospitalization, diabetes mellitus, COPD, chronic kidney disease, hypoproteinemia, serum lactate level  $> 2.2$  mmol/L, WBC  $> 9.5 \times 10^9/L$ , blood transfusion, surgery, length of antimicrobial drug use, antibacterial drug combination, types of antibacterial drugs, and use of hormonal drugs ([Figure 2b](#)).

Multivariate logistic regression analysis was performed with the infection status of ESBL-E as the dependent variable, COVID-19 as the reference variable, and the variables screened by LASSO regression as the independent variables. The independent variables were included step-wise in the multivariate logistic regression model to determine whether COVID-19 was an independent risk factor for ESBL-E infections. The results showed that the difference caused



**Figure 2** LASSO Logistic regression. (a) LASSO coefficient profiles of the 27 variables. As the value of  $\lambda$  decreases, the function of the model to select important variables is enhanced; (b) The cross-validation results. The left dashed line corresponds to the parameter  $\lambda_{\min}$ , and the right dashed line corresponds to the parameter  $\lambda_{1se}$ . The left solid line was chosen as the best  $\lambda$  value. 13 variables were selected when  $\lambda = 0.021$ .

by COVID-19 in the model was not statistically significant ( $p > 0.05$ ). Multi-variate analysis showed that a length of hospitalization  $\geq 15$  days (OR: 2.98; 95% CI: 1.07–8.28), COPD (OR: 0.14; 95% CI: 0.03–0.66), chronic kidney disease (OR: 4.25; 95% CI: 1.32–13.70), WBC  $> 9.5 \times 10^9/L$  (OR: 3.04; 95% CI: 1.54–6.01), use of hormonal drugs (OR: 2.38; 95% CI: 1.04–5.43), use of one type of antibacterial drug (OR: 5.38; 95% CI: 2.04–14.21), use of two types of antibacterial drugs (OR: 23.05; 95% CI: 6.71–79.25) and  $\geq 3$  types of antibacterial drugs (OR: 88.35; 95% CI: 8.55–912.63) were independently associated with the development of an ESBL-E infection (Table 2).

## Discussion

Antimicrobial resistance has become one of the major public health problems and is a global public health crisis.<sup>17,18</sup> ESBL-E is an important pathogen causing nosocomial infections. On the one hand, there is the rapid spread and dissemination of drug-resistant mechanisms, and on the other hand, there is the unwise overuse of antimicrobial agents and inadequate infection control measures, especially in healthcare settings.<sup>19,20</sup>



**Table 2** Multivariate Logistic Regression Analysis of Risk Factors for Extended-Spectrum  $\beta$ -Lactamase Producing *Enterobacterales* (ESBL-E), OR (95% CI)

Variables	Model 1	Model 2	Model 3	Model 4
COVID-19	1.90 (1.19–3.04)**	1.23 (0.69–2.20)	0.81 (0.43–1.52)	0.61 (0.30–1.28)
Length of hospitalization $\geq 15$ days		10.49 (4.83–22.81)***	8.80 (3.92–19.72)***	2.98 (1.07–8.28)*
Diabetes mellitus		1.83 (0.95–3.54)	2.09 (1.07–4.11)*	1.58 (0.66–3.80)
COPD		0.27 (0.07–0.99)*	0.25 (0.07–0.95)*	0.14 (0.03–0.66)*
Chronic kidney disease		3.41 (1.17–9.92)*	3.35 (1.12–10.00)*	4.25 (1.32–13.70)*
Hypoproteinemia		2.68 (1.44–5.02)**	2.23 (1.17–4.25)*	1.25 (0.57–2.76)
Serum lactate level ( $> 2.2$ mmol/L)		0.89 (0.47–1.72)	0.94 (0.48–1.84)	1.73 (0.80–3.76)
WBC ( $> 9.5 \times 10^9/L$ )		2.96 (1.65–5.34)***	3.25 (1.76–5.97)***	3.04 (1.54–6.01)**
Blood transfusion			1.88 (0.74–4.74)	1.67 (0.64–4.40)
Surgery			0.66 (0.33–1.33)	0.59 (0.26–1.33)
Use of hormonal drugs			4.06 (1.99–8.29)***	2.38 (1.04–5.43)*
Length of antimicrobial drug use $\geq 7$ days				2.14 (0.97–4.72)
Antibacterial drug combination				0.66 (0.25–1.77)
Antibacterial drug use 1 type				5.38 (2.04–14.21)**
Antibacterial drug use 2 types				23.05 (6.71–79.25)***
Antibacterial drug use $\geq 3$ types				88.35 (8.55–912.63)***

**Notes:** In model 1, only the COVID-19 variable was included; Eight variables were included in model 2, including COVID-19, length of hospitalization days  $\geq 15$  days, diabetes mellitus, COPD, chronic kidney disease, hypoproteinemia, serum lactate level, WBC; In model 3, three variables were added, including blood transfusion, surgery, and use of hormonal drugs; In Model 4, three variables were added, including length of antimicrobial drug use, antibacterial drug combination, and the type of antimicrobial drug used. The COVID-19 variable is the reference variable. \* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$ .

**Abbreviations:** COPD, chronic obstructive pulmonary disease; WBC, white blood cell; OR, odds ratio; CI, confidence interval.

This study showed that the incidence of ESBL-E infection during the COVID-19 pandemic showed a significant increase compared to that observed in the pre-pandemic period ( $p = 0.003$ ), and a significantly higher rate of increase (0.18 vs 0.45 per 1000 patients weekly). A review by Chih-Cheng Lai et al<sup>21</sup> in 2021 indicated a rapid increase in the incidence of ESBL *Klebsiella pneumoniae* infection during the COVID-19 period, a finding similar to that of our study. A gradual increase in the incidence of ESBL-E infections was reported before the emergence of COVID-19, with the increase during the COVID-19 pandemic possibly being a continuation of the pre-pandemic growth trend.<sup>22,23</sup> Alternatively, this increase may also be attributable to increased exposure to risk factors for ESBL-E infections during the COVID-19 pandemic, such as increased antimicrobial drug use and longer hospital stays.<sup>21</sup> According to previous reports, 62% of COVID-19 patients received antimicrobial therapy, with antimicrobial prescriptions often for broad-spectrum agents.<sup>24</sup> Therefore, inappropriate use of antimicrobial drugs may also have contributed to the increased incidence of ESBL-E infections during the COVID-19 epidemic.<sup>25</sup>

Using multivariate regression analysis, our study showed that a length of hospitalization  $\geq 15$  days, having chronic kidney disease, using hormonal drugs or  $\geq 1$  type of antibacterial drugs, and WBC  $> 9.5 \times 10^9/L$  were independent risk factors for ESBL-E infection, whereas COPD was a protective factor. Our study found that COVID-19 is not an independent risk factor for ESBL-E infection. A systematic review published in 2022 showed that the increase in multi-drug resistant pathogens during the COVID-19 pandemic may have been due to disruptions in infection control measures and high rates of antibiotic use.<sup>26</sup> Therefore, the increase in the incidence of ESBL-E infection during the COVID-19 pandemic may have been caused by increased exposure to traditional risk factors and not by endogenous changes in the organism due to COVID-19 infection.

In our study, the median number of days of hospitalization was 13.00 (8.00, 21.00) days for patients in the case group and 6.00 (3.00, 8.25) days for patients in the control group. The multivariate analysis showed that a length of hospitalization  $\geq 15$  days was a risk factor for ESBL-E infection, a result similar to the findings of Kizilates F et al.<sup>27</sup> On the one hand, hospitals are high-risk places for cross-infection, with longer periods of hospitalization being associated with a higher risk of infection by pathogenic microorganisms. On the other hand, patients who are hospitalized for a long period of time will receive more medical operations, while patients with low immunity are more likely to be infected by

pathogens. Therefore, shortening the hospitalization time of patients, reducing the loss of the body weight, and strictly implementing the requirements for aseptic operations are potentially effective measures for preventing the occurrence of hospital ESBL-E infection.

Antimicrobial drug abuse is considered a major cause of antimicrobial resistance, and limiting its use is essential to reduce the emergence and spread of resistance. During the COVID-19 pandemic, irrational use of antibiotics was also one of the risk factors for hospital-acquired ESBLs infections.<sup>28</sup> Previous studies have reported that during the COVID-19 pandemic, prophylactic and empirical use of antimicrobial drugs was often used by physicians to combat infection.<sup>29</sup> This reduced the incidence of infection and patient mortality, but the administration of antimicrobial drugs increased significantly. Our study showed that the use of more types of antibiotics was associated with a higher risk of ESBL infections. Although the duration of antimicrobial use was not statistically significant in our multivariate logistic regression analysis, the *p* value of 0.06 was very close to the critical value of statistical difference, a result which may have been due to the influence of other uncontrolled confounding factors. The prolonged use of antimicrobial drugs and the use of multiple antimicrobial drugs can lead to dysbiosis in the human body, as well as induce secondary infections by the organism. These changes provide conditions for the colonization and infection of drug-resistant bacteria. As a consequence, the rational use of antimicrobial drugs and improving supervision of antimicrobial drug administration are important measures for reducing the occurrence of multi-drug resistance in hospitals.

Our study also showed that chronic kidney disease was an independent risk factor for ESBL-E infections. Patients with chronic kidney disease were approximately 4.25 folds more likely to be infected with ESBL-E compared to other patients. The finding consistent with the those of Kiddee et al.<sup>30</sup> This association may be due to the low autoimmune function of patients with chronic kidney disease and their frequent visits to hospitals for invasive operations such as hemodialysis. Therefore, patients with chronic kidney disease have an increased chance of being exposed to an environment contaminated with pathogenic bacteria. In addition, previous studies have demonstrated that chronic kidney disease is usually associated with *Enterobacteriaceae* carriage of ESBL-E.<sup>31,32</sup> Our study found that the use of hormonal drugs was an independent risk factor for the development of ESBL-E infection in hospitalized patients. In a systematic review by Welte T et al,<sup>33</sup> it was common for patients with COVID-19 to receive high doses of steroids during the COVID-19 pandemic. Moreover, Xu et al<sup>34</sup> reported that the use of glucocorticoids was a risk factor for infections caused by ESBL-producing *Escherichia coli*, as their application could lead to low immune function and cause intestinal flora translocation. This creates favorable conditions for the development of ESBL-E infections in hospitalized patients.

Our study had some limitations. First, it was a single center study with a relatively small sample size. Second, it was a retrospective, case-control study, and although the effects of some potential confounders were controlled by subject matching and multivariate regression analysis, there is still a possibility that the effects were attributable to unknown confounders. Third, the time period of this study was relatively short and it is possible that the effects of some influencing factors may not yet have emerged, resulting in limitations of our findings. Therefore, a multicenter prospective study is required to further refine our findings.

## Conclusion

In summary, the incidence of ESBL-E infections in hospitalized patients increased significantly during the COVID-19 pandemic. In addition, prolonged hospitalization, having chronic kidney disease, and irrational use of hormones and antimicrobials were independent risk factors for ESBL-E infections. Also, we found that the increased incidence of ESBL-E infection in the period of the COVID-19 pandemic was influenced by increased exposure to traditional risk factors rather than due to endogenous changes in the organism caused by COVID-19. Therefore, the control of ESBL-E infections still needs to be based on the management of risk factors and the development of programs and policies for the rational use of antimicrobial drugs.

## Ethical Approval Statement

The study was performed in compliance with the Declaration of Helsinki and was approved by the Medical Ethics Committee of People's Hospital of Ningxia Hui Autonomous Region (Approval No.:2017-008). Written informed



consent was waived by the Ethics Committee of People's Hospital of Ningxia Hui Autonomous Region as the study exclusively focused on bacteria.

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## Disclosure

The authors report no conflicts of interest in this work.

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