

# Pathogen Distribution, Drug Resistance Risk Factors, and Construction of Risk Prediction Model for Drug-Resistant Bacterial Infection in Hospitalized Patients at the Respiratory Department During the COVID-19 Pandemic

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**Objective:** To investigate the distribution and drug resistance of pathogens among hospitalized patients in the respiratory unit during the COVID-19 pandemic, analyze the risk factors of drug resistance, construct a risk prediction model.

**Methods:** This study isolated 791 strains from 489 patients admitted to the Affiliated Hospital of Chengdu University, who were retrospectively enrolled between December 2019 and June 2021. The patients were divided into training and validation sets based on a random number table method (8:2). The baseline information, clinical characteristics, and culture results were collected using an electronic database and WHONET 5.6 software and compared between the two groups. A risk prediction model for drug-resistant bacteria was constructed using multi-factor logistic regression.

**Results:** *K. pneumoniae* (24.78%), *P. aeruginosa* (17.19%), *A. baumannii* (10.37%), and *E. coli* (10.37%) were the most abundant bacterial isolates. 174 isolates of drug-resistant bacteria were collected, ie, Carbapenem-resistant organism-strains, ESBL-producing strains, methicillin-resistant *S. aureus*, multi-drug resistance constituting 38.51%, 50.57%, 6.32%, 4.60%, respectively. The nosocomial infection prediction model of drug-resistant bacteria was developed based on the combined use of antimicrobials, pharmacological immunosuppression, PCT>0.5 ng/mL, CKD stage 4–5, indwelling catheter, and age > 60 years. The AUC under the ROC curve of the training and validation sets were 0.768 (95% CI: 0.624–0.817) and 0.753 (95% CI: 0.657–0.785), respectively. Our model revealed an acceptable prediction demonstrated by a non-significant Hosmer-Lemeshow test (training set,  $p=0.54$ ; validation set,  $p=0.88$ ).

**Conclusion:** *K. pneumoniae*, *P. aeruginosa*, *A. baumannii*, and *E. coli* were the most abundant bacterial isolates. Antimicrobial resistance among the common isolates was high for most routinely used antimicrobials and carbapenems. COVID-19 did not increase the drug resistance pressure of the main strains. The risk prediction model of drug-resistant bacterial infection is expected to improve the prevention and control of antibacterial-resistant bacterial infection in hospital settings.

**Keywords:** COVID-19, respiratory and critical care medicine, drug-resistant bacteria, risk factors, line chart

## Introduction

Antimicrobial resistance (AMR) has become more prevalent in recent years due to the widespread use of antibiotics in clinical practice. Drug-resistant bacterial infection significantly increases the mortality rate, hospitalization time, and treatment cost, which increases with age.<sup>1</sup> By 2050, the number of bacterial infections is expected to rise to 10 million, indicating that bacterial resistance is a serious threat to global health.<sup>2</sup> Among these, nosocomial infections caused by Gram-negative bacilli (GNB) are the most challenging issue for dealing with AMR.<sup>3</sup>

Lower respiratory tract infections (LRTIs) are common infections across the globe and a major cause of illness and death targeting people of all ages.<sup>4</sup> Antimicrobials are commonly used to treat LRTIs and drug-resistant bacteria are commonly detected in respiratory departments. In line with the standard construction of the national respiratory and critical medicine department in China, large tertiary hospitals are equipped with respiratory and critical medicine departments and independent respiratory intensive care unit (RICU) wards. Patients in RICU usually have severe infections that necessitate the use of high-grade antimicrobials; as a result, the diagnostic and treatment environment for patients has improved due to increased detection of drug-resistant bacteria.<sup>5</sup>

The Coronavirus Disease 2019 (COVID-19) infection has affected people globally, and the number of cases continues to increase. Studies indicate that the probability of bacterial and fungal infections occurring in patients with COVID-19 infection is extremely low.<sup>6–8</sup> Patients hospitalized with COVID-19 typically present with pneumonia with fever, cough, and dyspnoea, similar to atypical bacterial pneumonia.<sup>8</sup> Since it is difficult to distinguish them from hospital-acquired pneumonia and ventilator-associated pneumonia, several COVID-19 patients are often administered antimicrobials, which increases the burden of AMR.<sup>6,7,9,10</sup> Several studies have shown that the COVID-19 pandemic has further complicated the era of AMR.<sup>11,12</sup> During the pandemic, several variants of SARS-CoV-2 with varying transmissibility and severity have emerged. Among these variants, omicron is currently the most prevalent lineage globally, with lower pathogenicity.<sup>13</sup> At present, the spread of COVID-19 has peaked in China, and many patients with severe and critical COVID-19 infections are visiting the respiratory general wards or RICU.<sup>14</sup> Noteworthy, it is important to appropriately use antimicrobials to prevent aggravating the already unpromising forms of AMR.

This study aims to provide clinical evidence for the management of antibacterial-resistant bacterial infection by analyzing the clinical risk factors of drug-resistant bacteria infection in hospitalized respiratory patients during the COVID-19 pandemic. We will also construct and validate the risk prediction model for drug-resistant bacteria infection.

## Materials and Methods

### Study Design and Source of Strains

This is a retrospective study conducted between December 2019 and June 2021, at the Affiliated Hospital of Chengdu University in the southwest, China. The hospital is one of the large tertiary general teaching hospitals in southwest China with over 1000 bed capacity. The respiratory medical unit is equipped with over 120 beds. Data on all culture samples were collected from the respiratory and critical care medicine department of the hospital. The samples included valid sputum or tracheal aspirate, urine, blood, pleural fluids, pus swabs, ascitic fluid, feces, and central vein catheter specimens. We implemented the standard operating procedures of sample collection, storage, and transport. Moreover, hospitalized patients above 18 years with complete data were included. Negative and non-bacterial as well as positive cultures but with colonization were excluded. We also excluded patients with hospitalization time < 48 hours and incomplete information. Only the first infection was included if the patient had repetitive infections. Eventually, 791 strains from 489 patients were included. General patient information and data on clinical parameters including age, gender, blood count, biochemistry, inflammatory indicators, disease history, types of samples collected, culture results, and antimicrobial sensitivity were collected using the electronic medical record system and WHONET 5.6 software. Subsequently, we analyzed strain susceptibility to antimicrobial agents. The patients were divided into training and validation sets using the random number table method (8:2). A risk prediction model of drug-resistant bacterial infection was constructed using the training set and validated in a validation set. Age, gender, admission to RICU, invasive operation, combined use of antimicrobials, underlying diseases, and outcomes of each group were analyzed. Quality control strains included *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853, and *Staphylococcus aureus* ATCC 25923. Specimen collection and inspection followed the Clinical Microbiological Specimen Collection and Inspection Guidelines.<sup>15</sup>

This study was approved by the institutional ethics committee of the Affiliated Hospital of Chengdu University. We confirm that all methods were performed in line with the relevant guidelines and regulations. Since this was a retrospective data review, the need for informed consent from patients (Ethics Committee of Affiliated Hospital of Chengdu University, PJ2020-021-03) was waived.

## Sample Processing, Bacterial Identification, and Antimicrobial Susceptibility Testing

The sputum and sterile samples were placed on chocolate, blood, and MacConkey agar plates and incubated in the culture media, in a 5% CO<sub>2</sub> at 35°C for 48–72 hours, depending on the specimens. The growth of the medium was manually checked daily. Blood samples were inoculated into blood culture bottles and were incubated in the BD BACTEC FX system (Becton, Dickinson, and Company) at 37°C for 5 days. MicroScan WalkAway 40 automatic microbial identification instrument and drug susceptibility system (Beckman Coulter, Brea, California, USA) were used for simultaneous strain identification and drug susceptibility testing via negative Combo Panel Type 61 and positive Combo Panel Type 11. A microdilution method was used to evaluate the drug sensitivity and establish the minimum inhibitory concentration (MIC). This method uses a small volume of broth to disperse into a round or pointed bottom sterile plastic micro-dilution plate, called micro-dilution. Each hole should contain 0.1mL broth. The bacterial solution was diluted to 0.5 mc, before diluting 1000 times. After sealing, the bacterial solution was placed into a 35 °C ordinary air incubator and incubated for 16–20h, before reading the results. *Haemophilus* and *Streptococcus* were detected via incubation for 20–24 hours. Drug sensitivity of *Staphylococcus* and *Enterococcus* to oxacillin and vancomycin was evaluated by incubation for 24 hours. The MIC is the minimum drug concentration that can completely suppress bacterial growth in the small hole. It is only meaningful when the bacterial growth test is significant in the positive control hole (without antimicrobial). The maximum drug concentration that inhibits bacterial growth should be recorded when a single hole jumping occurs. The outcomes should not be reported and the test should be repeated in case of multiple hole jumps. The positive and negative drug-sensitive composite plates contain 16 and 20 antibacterial drugs respectively (Reach Surgical (Beijing), Inc.). Results were reported consistent with the Clinical Laboratory Standards Institute Criteria (CLSI) 2021.<sup>16</sup>

## Definitions

Valid sputum and bronchoalveolar lavage fluid: squamous cells < 10/LP and leukocytes > 25/LP were observed microscopically. Extended-Spectrum  $\beta$ -Lactamases (ESBLs), mediated by plasmids, can cause resistance to many  $\beta$ -lactamide antimicrobials. It is an important mechanism of antibiotic resistance in Gram-negative bacteria. ESBL-producing bacteria can develop resistance to various antimicrobials such as penicillins, penicillins, broad spectrum-cephalosporins, and monobactams. The isolates of carbapenem-resistant *Enterobacteriaceae* (CREs), *P. aeruginosa*, and *A. baumannii* were defined as gram-negative bacteria resistant or non-susceptible to one or more carbapenems based on CLSI current breakpoint. Multidrug resistance (MDR) was defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories (carbapenems,  $\beta$ -lactamase inhibitor combinations, cephalosporins, aminoglycosides, and fluoroquinolones).<sup>17</sup> All these mono-microbial infections and polymicrobial infections were included.

## Statistical Analysis

Continuous and categorical variables were presented as median (interquartile range (IQR)) and absolute number (percentage), respectively. The risk prediction model of drug-resistant bacterial infection was constructed using a multi-factor logistic regression. A line diagram was determined using the regression coefficient of the model. The model was repeated for 1000 bootstrap self-sampling. Receiver operating characteristic (ROC), area under the curve (AUC), and calibration curve were used to evaluate the discrimination and calibration performance of the model in the training and validation sets. The significance level was set at  $P < 0.05$ . The differences between patients with drug-resistant bacteria infections and those without infections were compared using  $\chi^2$ . All statistical analyses were performed using SPSS 24.0. WHONET 5.6 was used to analyze basic information about the strains. The prediction model was constructed and confirmed by R 3.6.3.

## Results

### Distribution and Constituent Ratio of Pathogens

A total of 5445 specimens were collected, out of which 9 samples were excluded due to incomplete information. The final samples analyzed were 5436; nearly 70% of the patient samples included were male. More than two-thirds (75.26%) of patients aged above 60 years. We excluded negative cultures, non-bacterial cultures, and repeated strains from the same sample of the same patient. Finally, only 791 strains from 489 patients were included in the analysis. The isolation rates of

gram-positive and gram-negative bacteria were 12.5% (99/791) and 87.5% (692/791), respectively. *K. pneumoniae* > *P. aeruginosa* > *A. baumannii* = *E. coli* were the top four isolated strains (isolation rates; 24.78%, 17.19%, 10.37%, and 10.37%, respectively) (Table 1).

## Detection of Drug-Resistant Bacteria

A total of 174 isolates of drug-resistant bacteria (174/791, 22.00%) were collected from sputum or tracheal aspirate (n = 136, 78%), urine (n = 25, 14.37%), blood (n = 6, 3.45%), pleural fluids (n = 3, 1.72%), and other specimens (n = 4, 2.30%). The detection rates of carbapenem-resistant *A. baumannii*, *P. aeruginosa*, and *K. pneumoniae* were 43.90%, 16.91%, and 3.57%, respectively. Carbapenem-resistant organism (CRO)-strains, ESBL-producing strains, methicillin-resistant *Staphylococcus aureus* (MRSA), *P. aeruginosa* (MDR), *A. baumannii* (MDR) were 67 (38.51%), 88 (50.57%), 11 (6.32%), 6 (3.45%), and 2 (1.15%) cases, respectively (Table 2). Furthermore, ESBL-producing *E. coli* (53/174, 30.46%) and *K. pneumoniae* (28/174, 16.09%), carbapenem-resistant *A. baumannii* (CR-Ab) (34/179, 19.54%), carbapenem-resistant *P. aeruginosa* (CR-Pa) (17/174, 9.77%), *K. pneumoniae* (CR-Kp) (7/174, 4.02%), and MRSA (11/174, 6.32%) were the major isolated drug-resistant bacteria.

**Table 1** Distribution of Pathogens

Name of Bacteria	Number of Strains	Proportion
Klebsiella pneumoniae	196	24.78%
Pseudomonas aeruginosa	136	17.19%
Acinetobacter baumannii	82	10.37%
Escherichia coli	82	10.37%
Enterococcus faecium	35	4.42%
Enterobacter cloacae	34	4.30%
Staphylococcus aureus	31	3.92%
Stenotrophomonas maltophilia	25	3.16%
Enterobacter aerogenes	24	3.03%
Serratia marcescens	22	2.78%
Proteus mirabilis	11	1.39%
Haemophilus influenzae	11	1.39%
Klebsiella Oxytoca	9	1.14%
Others	93	11.76%
Total	791	100%

**Table 2** Detection of Drug Resistant Bacteria

Bacterial Species	Number of Strains	Proportion
Acinetobacter baumannii-CR-Ab	34	19.54%
Pseudomonas aeruginosa-CR-Pa	17	9.77%
Klebsiella pneumoniae-CR-Kp	7	4.02%
Enterobacter aerogenes-CRE	4	2.30%
Enterobacter cloacae-CRE	2	1.15%
E. coli-CRE	2	1.15%
Citrobacter freundii-CRE	1	0.57%
Pseudomonas aeruginosa-MDR	6	3.45%
Acinetobacter baumannii-MDR	2	1.15%
Escherichia coli-ESBL	53	30.46%
Klebsiella pneumoniae-ESBL	28	16.09%
Proteus mirabilis-ESBL	7	4.02%
Staphylococcus aureus-MRSA	11	6.33%
Total	174	100%

## Analysis of Drug Resistance of Major Gram-Negative Bacteria

The resistance rates of drug-resistant gram-negative bacteria to tigecycline, ceftazidime, amikacin, ertapenem, meropenem, imipenem, cefepime, ceftazidime, and aztreonam were 0, 23.0%, 39.7%, 24.7%, 54.4%, 41.5%, 87.0%, 88.5%, and 81.6%, respectively. Furthermore, the resistance rate to ampicillin, ceftriaxone, cefotaxime, cefazolin, and cefuroxime was approximately 100%. Major gram-negative bacteria resistant to common major antimicrobials (without removing duplicate strains from similar specimens from the same patients) are shown in [Supplementary Material 1](#).

## MRSA Drug Resistance Profile

Although the resistance rate of MRSA to linezolid, vancomycin, daptomycin, quinupristin/dalfopristin, trimethoprim-Sulfa methoxazole, and furantoin was 0, its resistance rate to ampicillin, ceftriaxone, ampicillin-sulbactam, amoxicillin clavulanate potassium was 100%. In contrast, its resistance rate to levofloxacin, moxifloxacin, and ciprofloxacin was more than 50%, and its resistance rate to rifampin was less than 20%.

## Patient Profile Analysis

The general information, RICU admission, invasive operations, combined antimicrobial use, underlying disease, albumin level, WBC, and PCT were not significantly different between the two groups ( $P > 0.05$ ) except for active cancer ( $P < 0.05$ , validation set > training set), indicating the suitability of data for training and validation analysis. The training set was divided into drug-resistant and non-drug-resistant groups based on their susceptibility to antimicrobials. Univariate analysis showed that age, admission to RICU, invasive operations (indwelling urinary catheter, tracheal intubation/incision, PICC/CVC), combined antimicrobial use (combined respiratory quinolones, amikacin, antifungal drugs), use of carbapenem antimicrobials, combined chronic underlying diseases (chronic respiratory disease, CKD stage 4–5, chronic cardiac insufficiency, and pharmacological immunosuppression), albumin <30 g/L, leukocytes >10,000/ul, NLR, CRP, and PCT >0.5 ng/mL were significantly different between the two groups ( $P < 0.05$ ) ([Table 3](#)). Notably, admission to RICU was defined as admission to the RICU > within 24 hours.

**Table 3** Clinical Data Analysis of Training Set and Validation Set

Variant	Training Set, N = 391	Validation Set, N = 98	P	Training Set		P
				Sensitive, N = 287	Drug-Resistance, N = 104	
Gender			0.248			0.232
Male	261 (66.8)	72 (73.5)		197 (68.6)	64 (61.5)	
Female	130 (33.2)	26 (26.5)		90 (31.4)	40 (38.5)	
Age			0.556			0.001
≤60	94 (24.0)	27 (27.6)		82 (28.6)	12 (11.5)	
>60	297 (76.0)	71 (72.4)		205 (71.4)	92 (88.5)	
RICU admission			0.791			<0.001
0	312 (79.8)	76 (77.6)		246 (85.7)	66 (63.5)	
Within a week	18 (4.6)	4 (4.1)		12 (4.2)	6 (5.8)	
>1 week	61 (15.6)	18 (18.4)		29 (10.1)	32 (30.8)	

(Continued)

**Table 3** (Continued).

Variant	Training Set, N = 391	Validation Set, N = 98	P	Training Set		P
				Sensitive, N = 287	Drug-Resistance, N = 104	
Invasive operations			0.623			<0.001
No	279 (71.4)	73 (74.5)		225 (78.4)	54 (51.9)	
Yes	112 (28.6)	25 (25.5)		62 (21.6)	50 (48.1)	
Retained urinary catheter			0.627			<0.001
No	308 (78.8)	80 (81.6)		247 (86.1)	61 (58.7)	
Yes	83 (21.2)	18 (18.4)		40 (13.9)	43 (41.3)	
Indwelling drainage tube			0.809			0.387
No	366 (93.6)	93 (94.9)		271 (94.4)	95 (91.3)	
Yes	25 (6.4)	5 (5.1)		16 (5.6)	9 (8.7)	
Tracheal intubation/incision			1			0.001
No	354 (90.5)	89 (90.8)		269 (93.7)	85 (81.7)	
Yes	37 (9.5)	9 (9.2)		18 (6.3)	19 (18.3)	
PICC/CVC			0.603			<0.001
No	354 (90.5)	91 (92.9)		271 (94.4)	83 (79.8)	
Yes	37 (9.5)	7 (7.1)		16 (5.6)	21 (20.2)	
Undergoing surgery			1			0.495
No	382 (97.7)	96 (98.0)		279 (97.2)	103 (99.0)	
Yes	9 (2.3)	2 (2.0)		8 (2.8)	1 (1.0)	
Antibiotic co-administration			0.324			<0.001
No	274 (70.1)	63 (64.3)		222 (77.4)	52 (50.0)	
Yes	117 (29.9)	35 (35.7)		65 (22.6)	52 (50.0)	
Amikacin			0.79			0.049
No	349 (89.3)	89 (90.8)		262 (91.3)	87 (83.7)	
Yes	42 (10.7)	9 (9.2)		25 (8.7)	17 (16.3)	
Respiratory quinolones			0.532			<0.001
No	357 (91.3)	92 (93.9)		273 (95.1)	84 (80.8)	
Yes	34 (8.7)	6 (6.1)		14 (4.9)	20 (19.2)	
Combined antifungal			0.62			<0.001
No	356 (91.0)	87 (88.8)		272 (94.8)	84 (80.8)	
Yes	35 (9.0)	11 (11.2)		15 (5.2)	20 (19.2)	

(Continued)

Table 3 (Continued).

Variant	Training Set, N = 391	Validation Set, N = 98	P	Training Set		P
				Sensitive, N = 287	Drug-Resistance, N = 104	
Tigecycline			0.945			<0.001
No	382 (97.7)	95 (96.9)		287 (100.0)	95 (91.3)	
Yes	9 (2.3)	3 (3.1)		0 (0.0)	9 (8.7)	
Carbapenems			0.789			<0.001
No	330 (84.4)	81 (82.7)		258 (89.9)	72 (69.2)	
Yes	61 (15.6)	17 (17.3)		29 (10.1)	32 (30.8)	
Underlying Diseases			0.243			0.013
No	80 (20.5)	26 (26.5)		68 (23.7)	12 (11.5)	
Yes	311 (79.5)	72 (73.5)		219 (76.3)	92 (88.5)	
Chronic respiratory diseases			0.124			0.97
No	183 (46.8)	55 (56.1)		135 (47.0)	48 (46.2)	
Yes	208 (53.2)	43 (43.9)		152 (53.0)	56 (53.8)	
Dementia			0.622			0.102
No	333 (85.2)	86 (87.8)		250 (87.1)	83 (79.8)	
Yes	58 (14.8)	12 (12.2)		37 (12.9)	21 (20.2)	
Pharmacological immunosuppression			0.137			0.002
No	344 (88.0)	80 (81.6)		262 (91.3)	82 (78.8)	
Yes	47 (12.0)	18 (18.4)		25 (8.7)	22 (21.2)	
Active cancer			0.022			0.731
No	322 (82.4)	70 (71.4)		238 (82.9)	84 (80.8)	
Yes	69 (17.6)	28 (28.6)		49 (17.1)	20 (19.2)	
Chronic cardiac insufficiency			0.376			<0.001
No	309 (79.0)	82 (83.7)		248 (86.4)	61 (58.7)	
Yes	82 (21.0)	16 (16.3)		39 (13.6)	43 (41.3)	
CKD stage 4–5			0.693			<0.001
No	373 (95.4)	95 (96.9)		283 (98.6)	90 (86.5)	
Yes	18 (4.6)	3 (3.1)		4 (1.4)	14 (13.5)	
Diabetes			0.859			0.653
No	305 (78.0)	75 (76.5)		226 (78.7)	79 (76.0)	
Yes	86 (22.0)	23 (23.5)		61 (21.3)	25 (24.0)	
WBC	9.13 ± 5.55	9.56 ± 6.25	0.509	8.72 ± 5.16	10.27 ± 6.39	0.015

(Continued)



**Table 3** (Continued).

Variant	Training Set, N = 391	Validation Set, N = 98	P	Training Set		P
				Sensitive, N = 287	Drug-Resistance, N = 104	
WBC<4000/ul			I			0.764
No	368 (94.1)	92 (93.9)		269 (93.7)	99 (95.2)	
Yes	23 (5.9)	6 (6.1)		18 (6.3)	5 (4.8)	
WBC>10000/ul			0.345			0.001
No	277 (70.8)	64 (65.3)		217 (75.6)	60 (57.7)	
Yes	114 (29.2)	34 (34.7)		70 (24.4)	44 (42.3)	
N	7.13 ± 5.44	7.56 ± 6.16	0.5	6.68 ± 5.07	8.39 ± 6.23	0.006
L	1.27 ± 0.99	1.21 ± 0.74	0.565	1.31 ± 1.05	1.17 ± 0.78	0.194
NLR	10.09 ± 14.77	9.28 ± 10.93	0.614	8.87 ± 13.12	13.43 ± 18.25	0.007
CRP	54.14 ± 69.15	66.50 ± 74.52	0.12	47.79 ± 65.89	71.66 ± 75.00	0.002
PCT	2.46 ± 8.42	4.06 ± 15.71	0.17	2.07 ± 7.79	3.55 ± 9.93	0.124
PCT>0.5 ng/mL			I			0.002
No	243 (62.1)	61 (62.2)		192 (66.9)	51 (49.0)	
Yes	148 (37.9)	37 (37.8)		95 (33.1)	53 (51.0)	
Serum albumin	34.32 ± 5.66	33.61 ± 5.70	0.266	35.23 ± 5.57	31.81 ± 5.16	<0.001
Serum albumin<30g/L			0.659			<0.001
No	302 (77.2)	73 (74.5)		237 (82.6)	65 (62.5)	
Yes	89 (22.8)	25 (25.5)		50 (17.4)	39 (37.5)	
Die			I			<0.001
No	337 (86.2)	85 (86.7)		260 (90.6)	77 (74.0)	
Yes	54 (13.8)	13 (13.3)		27 (9.4)	27 (26.0)	

## Construction of Predictive Models

A logistic regression model was constructed based on a drug-resistant organism as the dependent variable (assignment method: no=0, yes=1), the combination of antifungal drugs or a fluoroquinolone, pharmacological immunosuppression, PCT>0.5 ng/mL, CKD stage 4–5, indwelling urinary catheter, and age>60 years as independent variables (assignment method: no=0, yes=1) (Logit (P) =  $-2.634 + \text{antifungal drugs} \times 0.850 + \text{fluoroquinolone} \times 0.982 + \text{pharmacological immunosuppression} \times 0.746 + \text{PCT} > 0.5 \text{ ng/mL} \times 0.719 + \text{CKD stage 4–5} \times 1.647 + \text{indwelling urinary catheter} \times 0.729 + \text{age} > 60 \text{ years} \times 0.905$ ). The use of combination antifungal drugs or a fluoroquinolone, pharmacological immunosuppression, PCT>0.5 ng/mL, CKD stage 4–5, indwelling urinary catheter, and age>60 years were independent risk factors for hospital-resistant bacterial infections (Table 4). The variance inflation factor (VIF) was less than 2, and no multicollinearity existed among the factors (Table 5). The corresponding predicted probability was defined as the predicted probability of patients with drug-resistant bacteria hospital infection (Figure 1).



**Table 4** Logistic Regression Analysis of Risk of Drug-Resistant Bacterial Infection

Risk Factors	$\beta$	OR	95% CI	P
Combination of antifungal drugs	0.850	2.340	1.020–5.366	0.043
Combination of respiratory quinolones	0.982	2.670	1.191–6.043	0.017
Pharmacological immunosuppression	0.746	2.109	1.034–4.245	0.038
PCT>0.5 ng/mL	0.719	2.052	1.233–3.427	0.006
CKD stage 4–5	1.647	5.191	1.624–20.026	0.009
Indwelling urinary catheter	0.729	2.073	1.132–3.763	0.017
Age>60 years	0.905	2.472	1.253–5.259	0.013

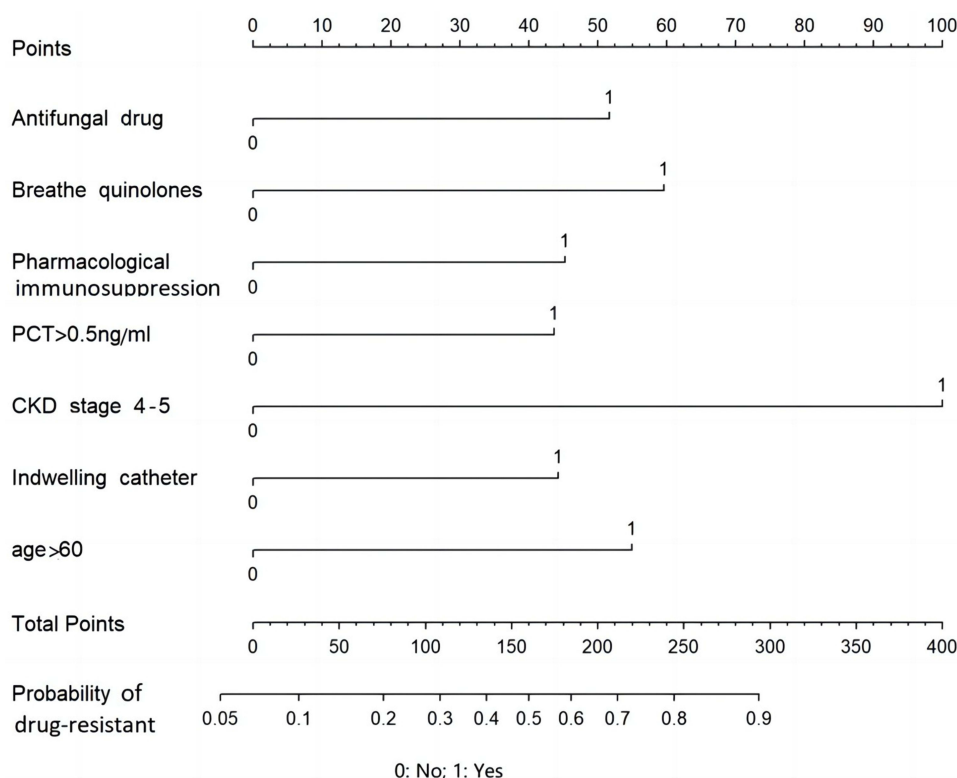
**Table 5** Multicollinearity Test Result

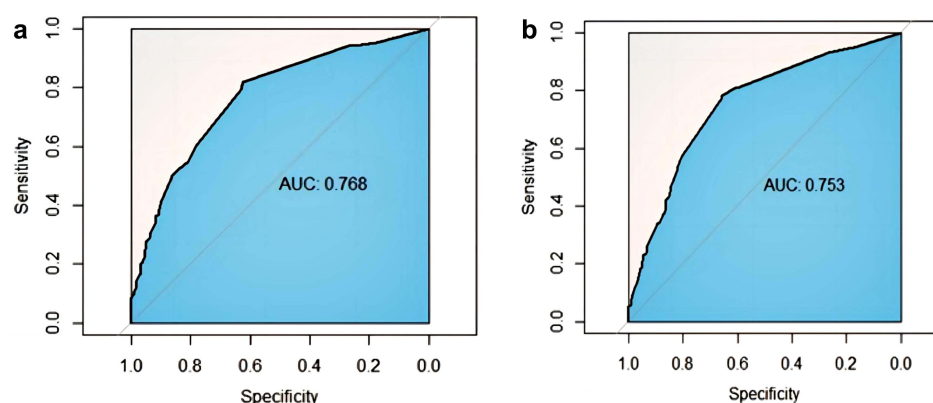
	Antifungal	Quinolones	Pharmacological Immunosuppression	PCT>0.5 ng/mL	CKD Stage 4–5	Indwelling Urinary Catheter	Age>60 Years
VIF	1.086	1.102	1.047	1.037	1.025	1.168	1.020

**Abbreviation:** VIF, variance inflation factor.

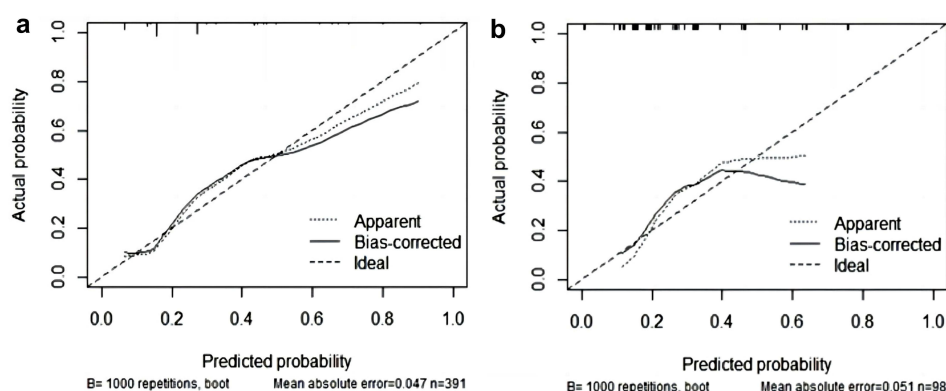
## Verification of Prediction Model

The model was internally and externally verified using the training and validation sets, respectively. All verifications were bootstrap self-sampled 1000 times. The area under the ROC curve of training and validation sets were 0.768 (95% CI: 0.624–0.817) and 0.753 (95% CI: 0.657–0.785), respectively (Figure 2). The predictive performance of the model was evaluated using a calibration curve. The prediction and observation of the model in the training and validation sets showed good consistency. Our model showed acceptable prediction, demonstrated by a non-significant Hosmer-Lemeshow test (training set,  $p=0.54$ ; validation set,  $p=0.88$ ) (Figures 2 and 3). In summary, the model displayed good discrimination and consistency.

**Figure 1** The nomogram for the assessment of the risk of drug-resistant bacteria infection.



**Figure 2** ROC curve of the nomogram in the training and validating sets. (a) Training set; (b) Validation set.



**Figure 3** Calibration curve of the nomogram in the training and validating sets. (a) Training set; (b) Validation set.

## Discussion

This study found that more than two-thirds (75.26%) of patients were above the age of 60 years, with men accounting for 68.1%. Sputum or tracheal aspirate (78%), urine (14.37%), and blood (3.45%) were the most commonly collected samples. Moreover, the proportion of main sample types was comparable to previous findings reported by China Antimicrobial Surveillance Network (CHINET) 2020 and 2021.<sup>18</sup> The proportion of respiratory tract samples was significantly higher than that from CHINET 2020<sup>19</sup> (38.8%) and 2021 (38.7%), respectively. Out of 5436 specimens during the study period, bacterial growth was only documented in 791 (14.66%) culture samples. The isolation rates of gram-positive and gram-negative bacteria were 12.5% and 87.5%, respectively. This was different from CHINET 2021,<sup>18</sup> with gram-negative bacteria accounting for 71.4% and gram-positive bacteria accounting for 28.6%. Here, *K. pneumoniae* (24.78%), *P. aeruginosa* (17.19%), *A. baumannii* (10.37%), and *E. coli* (10.37%) were the most abundant bacterial isolates from inpatients, and *S. aureus* (3.92%) ranked 7th. However, our finding was lower than that from CHINET 2021<sup>18</sup> except *E. coli* (18.96%). *K. pneumoniae* (14.12%), *P. aeruginosa* (7.96%), and *A. baumannii* (7.28%) were the major clinical isolates in the study hospital. Furthermore, ESBL-producing *E. coli* (30.46%) and *K. pneumoniae* (16.09%), CR-Ab (19.54%), CR-Pa (9.77%), CR-Kp (4.02%), and MRSA (6.32%) were the major isolated drug-resistant bacteria. Specifically, (43.90%) of *A. baumannii* and (16.91%) of *P. aeruginosa* isolates were carbapenem-resistant, whereas only (3.57%) of *K. pneumoniae* and (2.43%) of *E. coli* were carbapenem-resistant. This was different from CHINET 2021. The detection rates of carbapenem-resistant *A. baumannii*, *K. pneumoniae*, and *P. aeruginosa* in Sichuan were 65.40%, 26.70%, and 18.90%, respectively, lower than the detection rates reported in 2019<sup>18,20</sup> (72.4%, 34%, and 22.4%, respectively) and higher than the detection rates of this study. This suggests that drug resistance rates vary in different regions and years. Similarly, studies in the United States and

Japan revealed that carbapenem resistance rates are significantly higher for non-fermenters (>60%) than for fermenters (<10%),<sup>21</sup> with ESBL prevalence of 64.6% in *E. coli* and 14.3% in *K. pneumoniae*. These findings show that gram-negative drug-resistant bacteria, particularly *K. pneumoniae*, *P. aeruginosa*, *E. coli*, and *A. baumannii* are the major pathogens among hospital-acquired drug-resistant infections. Several resistance mechanisms exist, including the production of ultra-broad-spectrum  $\beta$ -lactamases, carbapenemases, increased efflux pump activity, alteration of drug binding sites, and alteration of cell membrane permeability.<sup>22,23</sup> ESBL production is the primary cause of drug resistance in *E. coli* and *K. pneumoniae*. The high proportion of carbapenem-resistant gram-negative bacteria indicates that it is difficult to reduce carbapenem-resistant gram-negative bacterial infections. The bacterial isolation rate was different from hospital-acquired infections (HAI) in hospitalized COVID-19 patients.<sup>11,24–26</sup> A study of 989 adult hospitalized patients with COVID-19 infections revealed that the most common isolates in COVID-19 patients were *S. pneumoniae* (16.21%), *S. aureus* (16.21%), *P. aeruginosa* (13.51%), *E. coli* (9.46%), and *K. pneumoniae* (8.11%).<sup>24</sup> In a retrospective study in China, the prevalence of carbapenem-resistant *Enterobacteriaceae* colonization increased from 6.7% in 2019 to 50% in March–April 2020.<sup>25</sup> Li et al also discovered *A. baumannii* (35.8%) and *K. pneumoniae* (30.8%) as the most common pathogens isolated from COVID-19 inpatients (Wuhan, China), with carbapenem resistance rates of 91.2% and 75.5%, respectively.<sup>26</sup> As demonstrated from the above studies, the overall bacterial isolation rate of patients with COVID-19 infections was low.<sup>6–8</sup> During the irrational use of antibiotics, the drug resistance rate increased, particularly for carbapenem.<sup>6,7,9,10,25,26</sup> The drug resistance rates in our study were generally lower than that in the above studies. Additionally, CHINET 2021 showed that the resistance rates of major strains were lower than that of 2019.<sup>18,20</sup> These findings may indicate that COVID-19 did not increase the pressure of drug resistance of key strains in this region.

In this work, the resistance rates of drug-resistant gram-negative bacteria to tigecycline, ertapenem, and ceftazidime were 0, 24.7%, and 23.0%, respectively. Moreover, its resistance rate to carbapenems remained high, however, the resistance rate of ertapenem (24.7%) was lower than that of meropenem (54.4%) and imipenem (41.5%), possibly due to the lower rate of ertapenem use in the hospital. The resistance rates of drug-resistant gram-negative bacteria to ampicillin, ceftriaxone, cefotaxime, cefazolin, and cefuroxime were approximately 100%. Its resistance rate to aztreonam, ceftazidime, piperacillin sodium tazobactam, and amikacin was 81.6%, 87.0%, 88.5%, 43.6%, and 39.7%, respectively. This finding might suggest that the combination of amikacin can effectively treat resistant gram-negative bacteria, whereas tigecycline can treat carbapenem-resistant gram-negative bacteria. This finding was also consistent with the other studies.<sup>27–29</sup> The current treatments for drug-resistant gram-negative bacteria, particularly CRO and MDR have limitations in clinical settings. Of note, polymyxin, tigecycline, and ceftazidime-avibactam have advantages and disadvantages.<sup>30</sup> Therefore, it is important to develop an individualized treatment based on the distribution characteristics of drug-resistant bacteria in the region and the actual situation of patients.<sup>3,18,20</sup> Drug resistance varies across countries and regions. As a consequence, an early understanding of the distribution characteristics and drug resistance of pathogenic bacteria in the region, integrated with standardized diagnosis and treatment plan for nosocomial infections, as well as adjusting the type and dose of antibacterial drugs based on the drug sensitivity results are effective strategies for reducing the production of drug-resistant bacteria, while also promoting disease treatment and control.<sup>30</sup>

Univariate analysis revealed that more than 10 factors, including admission to the RICU, tracheal intubation/incision, PICC/CVC, combined use of fluoroquinolone or antifungal drugs or aminoglycosides, use of carbapenem antimicrobials, combined chronic respiratory disease, chronic cardiac insufficiency, pharmacological immunosuppression, CKD stage 4–5, and albumin <30 g/L were associated with drug-resistant bacterial infections. Similarly, other studies indicate that current or pre-existing RICU admission, invasive operations, use of fluoroquinolone, and use of carbapenems are important risk factors for hospital-acquired drug-resistant bacterial infections.<sup>31–34</sup> Moreover, the constructed predictive model had good discrimination, calibration, and clinical utility. Previous studies indicate that elderly patients, specifically those with pharmacological immunosuppression are at a higher risk of opportunistic hospital infections, specifically multi-drug resistant bacterial infections.<sup>35</sup> Indwelling urinary catheters also contribute to drug resistance, increasing the risk of bacterial colonization or opportunistic infections, especially in patients in the immunosuppressed state, which was consistent with previous research.<sup>36–38</sup> Urinary tract infections (mainly caused by *K. pneumoniae*) are among the most common hospital-acquired infections (HAI), causing severe bloodstream infections.<sup>38,39</sup> The above-mentioned studies are consistent with our findings.<sup>31–33,35,39</sup> Most patients in the general respiratory ward, particularly those admitted to the

RICU, are often characterized by advanced age, need for mechanical ventilation support, immunocompromised, and combined structural lung disease, and are prone to co-infection with fungal infections.<sup>40,41</sup> Excessive antifungal drug exposure may alter the composition of the flora, whereas the combination of antimicrobial drugs may promote resistance gene mutations, thereby causing bacterial resistance.<sup>42</sup> Ghannoum et al also supported our research.<sup>43</sup> Nonetheless, the specific mechanisms remain unknown and additional studies are necessary for clarification. This study also revealed that combined fluoroquinolone or antifungal drugs are independent risk factors for hospital-acquired drug-resistance infections, consistent with a meta-analysis of HAI in CRKP.<sup>44</sup> Another meta-analysis for *P. aeruginosa* also showed that antimicrobial overuse, particularly quinolones, can significantly cause *P. aeruginosa* resistance.<sup>45</sup> Patients with chronic renal failure often have immune system deficiencies.<sup>46</sup> Moreover, patient dialysis often requires frequent infusions, injections, and indwelling catheters, which can easily cause HAI.<sup>47</sup> The absorption, distribution, metabolism, and elimination processes of drugs in these patients change.<sup>48</sup> Therefore, antimicrobial doses and usage should be adjusted based on the concentration-time curve of drugs because irrational use can result in drug-resistant bacteria.<sup>49</sup> PCT has been used as a reference for antimicrobial use in clinical settings.<sup>50</sup> Antimicrobials are highly recommended for patients with PCT>0.5 ng/mL.<sup>51</sup> Our study revealed that PCT>0.5ng/mL is also an independent risk factor for drug-resistant bacterial infection. This finding was consistent with research conducted in Italy.<sup>52</sup>

The COVID-19 pandemic presents new challenges in the operation and management of healthcare systems across the globe. For instance, respiratory clinicians cannot precisely identify viral and bacterial infections, provide timely and adequate empirical treatment for patients at high risk of drug resistance, and safely prevent overuse of antimicrobial overuse in patients without identifiable risk factors.

However, this study has limitations: First, the data were obtained from the Department of Respiratory and Critical Care Medicine of the same tertiary care teaching hospital. Therefore, the clinical applicability of the model should be further verified using data from different multiple centers. Secondly, this is a single retrospective study with limited sample size, potentially resulting in bias.

## Conclusion

In conclusion, we analyzed the distribution of bacteria and drug resistance in respiratory inpatients during the COVID-19 pandemic and established a risk prediction model for HAI with drug-resistant bacteria in hospitalized patients. Consequently, we found that *K. pneumoniae*, *P. aeruginosa*, *A. baumannii*, and *E. coli* were the most abundant bacterial isolates in nosocomial infection. Besides, antimicrobial resistance among common isolates was high for most routinely used antimicrobials and carbapenems. COVID-19 did not increase the drug resistance pressure of the major strains. The combined use of antifungal, fluoroquinolone, indwelling catheter, chronic renal failure, and age > 60 years were the independent risk factors of drug-resistant bacterial infection. The model showed discrimination, consistency, and clinical utility and could be used for hospital-associated infection prevention and control.

## Abbreviations

RICU, Respiratory intensive care unit; PICC, peripheral inserted central catheter; CVC, Central venous catheter; CKD, Chronic Kidney Disease; WBC, White Blood Cells; N, Neutrophil granulocyte; L, Lymphocyte; NLR, Neutrophil To Lymphocyte Ratio; CRP, C-reactive protein; PCT, Procalcitonin.

## Data Sharing Statement

All data generated or analyzed during this study are included in this published article.

## Ethics Approval and Consent to Participate

This study has been approved by the ethical committee of Affiliated Hospital of Chengdu University. This clinical study will follow the relevant provisions of the Helsinki Declaration of the World Medical Congress and the Measures for Ethical Review of Biomedical Research Involving Human Beings issued by the National Health and Family Planning Commission of the People's Republic of China. The research only uses the previous medical record information and has removed the relevant personal information of the subject, which will not cause risks to the subject and will not have

adverse effects on the rights and health of the subject, so the application for exemption of informed consent is made. We will make every effort to protect the privacy and personal information of the subject's personal medical data within the scope permitted by law.

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## 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.

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## Disclosure

The authors declare that they have no competing interest.

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