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ORIGINAL RESEARCH

Exploring the Association of Antimicrobial Use with *Serratia marcescens* Resistance Rates via Multiple Linear Regression

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Purpose: To investigate the macro-level quantitative relationship between *Serratia marcescens* resistance and antimicrobial consumption one quarter in advance, aiming to curb resistance and optimize antimicrobial use.

Patients and Methods: A retrospective analysis was conducted on *S. marcescens* resistance rates and antimicrobial consumption data from our hospital. Multiple linear regression models were employed to identify independent linear correlations between resistance rates and defined daily doses (DDDs) of specific antimicrobials.

Results: Over the past four years, our hospital identified 522 *S. marcescens* strains (3.22% of all bacterial isolates), with 86.59% isolated from respiratory samples. The strains showed sensitivity to cefoperazone-sulbactam, cefepime, ertapenem, imipenem, meropenem, amikacin, trimethoprim-sulfamethoxazole, and tigecycline, with resistance rates <10%. The study showed significant correlations between *S. marcescens* resistance and antibiotic usage. Resistance to cefoperazone-sulbactam and imipenem had independent negative linear relationships with gentamicin DDDs; resistance to cefoxitin correlated negatively with piperacillin-tazobactam DDDs; resistance to cefepime showed a negative association with cefuroxime DDDs. These four relationships were strongly supported by consistent results from Bayesian, Bootstrap, and Winsorized regression. Additionally, amoxicillin-clavulanic resistance positively correlated with meropenem DDDs, and levofloxacin resistance positively correlated with gentamicin DDDs. These positive trends were supported by triple robustness testing. These findings have substantial implications for clinical practice. The negative correlations indicate that the strategic use of specific antimicrobials can effectively suppress the resistance rates to target drugs, while the positive correlations reflect increased co-resistance risks. These findings underscore the necessity for antibiotic rotation and optimized management strategies.

Conclusion: The significant associations between *S. marcescens* resistance rates and prior antimicrobial consumption patterns underscore the critical impact of antibiotic use on resistance development. This highlights the need for better antimicrobial stewardship to delay resistance and guide prescribing.

Keywords: *S. marcescens*, multiple linear regression analysis, correlation

Introduction

Serratia marcescens a facultative anaerobic Gram-negative bacillus belonging to the *Serratia* genus within the *Enterobacteriaceae* family, is a significant opportunistic pathogen in hospitals. Widely distributed in hospital environments, *S. marcescens* is hard to fully eradicate via physical or chemical disinfection. Its high virulence enables it to cause respiratory, urinary tract, bloodstream infections, meningitis, and surgical site infections, especially in patients undergoing invasive procedures, surgeries, with weakened immunity, or experiencing trauma.[1] It spreads rapidly among hospitalized patients and has triggered numerous nosocomial outbreaks.[2,3] According to CHINET data,[4,5] the detection

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rate of *S. marcescens* increased from 0.99% (2483 strains) of all clinically isolated strains in 2019 to 1.15% (5120 strains) in 2023, marking a 16.16% rise. In recent years, the emergence of multidrug-resistant *S. marcescens*, including those resistant to carbapenems,[6,7] has made detecting and controlling its spread a tough challenge.

Currently, international data on the evolution of resistance in *S. marcescens* relative to antimicrobial exposure are limited, and this is also a relatively unexplored area in the research of *S. marcescens*. Antimicrobial selective pressure is a key driver of bacterial resistance. Our research endeavors to innovatively explore the macro-level quantitative relationship between the two. Theoretically, antimicrobial use precedes bacterial resistance.[8,9] This study will explore the correlation between *S. marcescens* resistance rates and antimicrobial Defined Daily Doses (DDDs) from the previous quarter, aiming to inform strategies for curbing *S. marcescens* resistance and optimizing antimicrobial use in clinical practice.

Materials and Methods

Strain Source

S. marcescens strains isolated from patients (2021–2024) were collected under strict aseptic conditions, including sputum, throat swabs, bronchoalveolar lavage fluid, blood, urine, pleural effusion, peritoneal effusion, and drainage fluid, and cultured according to the National Clinical Laboratory Procedures (4th edition).[10] For identical strains isolated multiple times from a single patient sample, only the initial susceptibility result per drug was retained. Colonizing or contaminating strains were excluded to avoid confounding true pathogens, based on at least two of the following clinical-microbiological discordance criteria: (1) Absence of infection-related symptoms (eg, fever, purulent discharge, leukocytosis, or imaging findings); (2) Clinical improvement despite in vitro resistance to empiric antibiotics; (3) Spontaneous resolution without antibiotic therapy. The quality control strains used were *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853, provided by the Clinical Laboratory Center of the National Health and Family Planning Commission. The study was approved by the Hospital Ethics Committee (NO. 2025-L104) (In Q1 2021 and Q3 2023, our hospital did not perform statistical analysis due to insufficient *S. marcescens* detections).

Strain Identification and Antimicrobial Susceptibility Testing

Strain identification and susceptibility testing were performed using the VITEK-2 system (BioMerieux, France) and validated by the Kirby-Bauer disk diffusion method. Quality control included: (1) daily calibration with control strains (*Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853); (2) retesting ≥5% of strains per batch (minimum 5 strains); (3) recalibration and data review if results deviated from CLSI 2024 standards.[11] Results were interpreted as susceptible, intermediate, or resistant, with resistance rate calculated as the percentage of resistant strains among total strains. Testing was conducted by our hospital's microbiology lab, with data managed by the Infection Control Department.

Antibacterial Drug Usage Data

The hospital HIS rational drug use system collects data on the use of antibacterial drugs. The WHO-defined daily dose (DDD) serves as the standard reference for calculating antimicrobial agents' consumption in DDD units. DDDs quantify prescribing frequency, with higher values indicating stronger clinical preference for an agent. The calculation formula is as follows:

DDDs = Annual drug total consumption/Drug DDD value.

Data Analysis

Data analysis used SPSS 27.0 and R 4.5.1: (1) Pearson correlation analysis (significance level α=0.05) was conducted to assess the relationship between the resistance rate of *S. marcescens* and DDDs of antimicrobials. (2) Multiple linear regression was used to explore independent, linear correlations. The model used *S. marcescens* resistance rate as the dependent variable and statistically significant antimicrobial DDDs from the previous quarter as independent variables. The stepwise method was applied for variable selection. It requires linear relationships, independent and normally

distributed residuals, homoscedasticity, and no multicollinearity among independent variables. (3) The final regression model is subjected to threefold validation. Bayesian analysis used Markov Chain Monte Carlo (MCMC) simulation (10,000 iterations; weakly informative priors) in SPSS 27.0. Significance required: 95% credible interval excluding zero and posterior probability >0.95. Bootstrap Validation: Conduct 3000 BCa resamples; require original coefficient within 95% CI and CI not crossing zero. Winsorized Regression: Apply 1% bilateral winsorization, re-model. Accept if $|\Delta\beta\%| < 10\%$ and $p<0.05$ remains significant ($\Delta\beta\% = [(\beta\_winsorized - \beta\_original)/\beta\_original] \times 100\%$) and the significance level ($p<0.05$).

Results

Isolation Rate of *S. marcescens*

In the past four years, 16190 strains of pathogens were detected in our hospital, among which 522 strains of *S. marcescens* were isolated, accounting for 3.22% of the total number of bacteria. The total χ^2 value was 16.365, less than the critical value (21.026), P>0.05, and there was no significant difference in the isolation rate of *S. marcescens*. The total number of pathogens and *S. marcescens* detected in each quarter are shown in Table 1. It can be seen that the detection rate of *S. marcescens* is 1.96%–4.35%. Of the 522 isolates of *S. marcescens*, 452 (86.59%) came from respiratory tract, 31 (5.94%) from blood flow, 29 (5.56%) from urine, and the remaining 10 (1.91%) from other sources. According to the statistics of the departments submitted for examination, the top 3 departments with the number of isolates of *S. marcescens* were 265 (50.77%) in surgery, 139 (26.63%) in ICU and 85 (16.28%) in internal medicine.

Usage of Antibacterial Drugs

The DDDs of commonly used antimicrobial agents in the past four years are shown in Table 2.

β-lactam antibiotics continue to dominate, with high DDDs for piperacillin tazobactam, cefoperazone-sulbactam, and levofloxacin. Over the four years, the usage of cefuroxime, piperacillin-tazobactam, and gentamicin showed a significant upward trend.

Table 1 Detection of *Serratia marcescens*

	***Serratia marcescens* Number/Strain**	**Total Bacterial Count/Strain**	**Percentage of *Serratia marcescens* Strains Isolates Relative to Total Hospital Isolates/%**	**χ^2 Value**
Q2 2021	55	1264	4.35	5.023
Q3 2021	51	1367	3.73	1.110
Q4 2021	38	1213	3.13	0.029
Q1 2022	37	1190	3.11	0.045
Q2 2022	49	1335	3.67	0.841
Q3 2022	39	1248	3.13	0.035
Q4 2022	32	1210	2.64	1.244
Q12023	28	1059	2.64	1.090
Q2 2023	23	1172	1.96	5.757
Q4 2023	38	1112	3.42	0.134
Q1 2024	30	1000	3.00	0.150
Q2 2024	29	970	2.99	0.160
Q3 2024	36	1023	3.52	0.284
Q4 2024	37	1027	3.60	0.467
Total	522	16,190	3.22	16.365

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Table 2 The DDDs of Commonly Used Antimicrobial Agents

	TZP	CXM	CAZ	CRO	CFS	CMZ	IPM	MEM	AMK	GEN	LVX
Q1 2021	2022.11	356.75	1247.00	429.50	2432.00	610.00	148.75	542.83	171.80	114.67	1914.00
Q2 2021	3170.89	411.50	2223.00	815.50	2912.00	1126.00	182.75	904.17	115.00	215.67	2464.00
Q3 2021	3124.93	843.25	1486.25	680.00	3534.50	676.50	340.25	1070.00	197.80	103.33	2683.00
Q4 2021	2775.21	640.75	842.75	989.00	3392.50	1698.50	176.25	925.83	234.20	121.33	2400.00
Q1 2022	3204.96	1140.25	861.00	1237.50	3698.25	1545.00	172.50	1142.33	311.00	98.67	2203.00
Q2 2022	3187.93	1941.50	1190.00	1394.50	4447.00	1270.75	147.00	834.67	321.80	127.67	2164.00
Q3 2022	3427.39	2521.00	1013.25	1013.00	3695.25	937.75	53.25	995.50	198.20	137.00	2241.00
Q4 2022	3479.46	1746.25	925.25	1048.50	3583.25	598.50	121.75	924.83	103.20	141.67	1526.00
Q1 2023	4148.68	1225.50	881.50	839.00	5182.50	414.50	409.25	795.00	140.60	257.00	1683.00
Q3 2023	2944.61	1554.00	1424.50	909.50	3025.00	1332.50	171.75	706.17	263.60	315.00	1969.00
Q4 2023	3769.07	1378.00	1224.25	1276.00	2684.75	1477.50	186.25	610.17	397.20	424.33	2224.00
Q1 2024	4715.36	1618.75	970.50	1671.00	3803.38	1799.50	117.50	508.50	304.80	295.00	2256.00
Q2 2024	4010.79	2401.50	996.50	1611.50	4960.00	1742.25	190.25	692.17	300.20	392.00	1646.00
Q3 2024	3604.82	2830.75	837.00	972.00	5470.13	1624.50	176.50	645.50	309.20	558.33	1804.00

Abbreviations: TZP, Piperacillin/Tazobactam; CXM, Cefuroxime; CAZ, Ceftazidime; CRO, Ceftriaxone; CFS, Cefoperazone/Sulbactam; CMZ, Cefmetazole; IPM, Imipenem; MEM, Meropenem; AMK, Amikacin; GEN, Gentamicin; LVX, Levofloxacin.

Drug Resistance of *S. marcescens*

The isolates of *S. marcescens* were highly susceptible to amikacin and tigecycline, with resistance rates below 5%. They also showed susceptibility to piperacillin-tazobactam, ceftazidime, ertapenem, imipenem, meropenem, trimethoprim-sulfamethoxazole, and tigecycline, with resistance rates below 10%. Resistance to cefuroxime exceeded 90%, while resistance to amoxicillin-clavulanate remained above 60%. From 2021 to 2024, resistance rates to ceftriaxone, ceftazidime, cefoxitin, imipenem, meropenem, ertapenem, and ceftazidime decreased overall, while resistance to levofloxacin increased. For more details, as shown in Table 3.

Pearson Correlation Analysis

Pearson correlation analysis showed that *S. marcescens* resistance to ceftazidime, cefoperazone-sulbactam, and imipenem correlated with the DDDs of multiple antibiotics. In contrast, resistance to amoxicillin-clavulanic acid, cefuroxime, cefoxitin, cefepime, amikacin, and levofloxacin each correlated with only one antibiotic's DDD (Table 4).

Table 3 Drug Resistance of *Serratia marcescens*

	AMC	CXM	CAZ	CRO	FEP	CFX	CFS	ETP	IPM	MEM	AMK	LVX	SXT	TGC
Q2 2021	79.40	98.00	21.10	35.30	8.80	25.50	2.50	7.80	12.80	10.50	3.60	5.30	5.30	0.00
Q3 2021	72.10	93.90	2.00	4.10	0.00	26.50	0.00	0.00	0.00	0.00	0.00	11.80	0.00	0.00
Q4 2021	83.80	94.60	7.70	21.60	2.60	13.50	2.60	2.70	5.10	0.00	0.00	12.80	2.60	0.00
Q1 2022	75.70	94.60	2.70	2.70	2.70	18.90	2.70	2.70	2.70	2.70	0.00	10.80	0.00	0.00
Q2 2022	88.00	92.00	6.00	6.00	4.00	32.00	6.00	4.00	6.00	2.00	0.00	8.00	6.00	0.00
Q3 2022	69.20	92.30	2.60	15.40	2.60	20.50	2.60	2.60	2.60	3.30	2.60	5.10	2.60	0.00
Q4 2022	84.40	96.90	3.10	10.00	0.00	9.40	3.10	0.00	6.30	0.00	0.00	3.10	3.10	0.00
Q1 2023	64.30	92.90	0.00	10.70	0.00	14.30	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Q2 2023	60.90	87.00	4.30	8.70	0.00	8.70	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Q4 2023	60.50	84.20	5.30	10.50	0.00	15.80	0.00	0.00	0.00	0.00	0.00	2.60	5.30	0.00
Q1 2024	60.00	96.70	3.30	10.00	3.30	10.00	0.00	0.00	0.00	0.00	0.00	10.00	3.30	0.00
Q2 2024	65.50	82.80	3.40	10.30	3.40	13.80	0.00	3.40	3.40	3.40	0.00	3.40	0.00	0.00
Q3 2024	77.10	91.40	2.80	8.60	0.00	17.10	0.00	2.90	0.00	0.00	0.00	27.80	2.80	0.00
Q4 2024	70.30	86.50	2.70	18.90	0.00	13.50	0.00	0.00	0.00	0.00	0.00	24.30	2.70	0.00

Abbreviations: AMC, Amoxicillin/Clavulanic; CXM, Cefuroxime; CAZ, Ceftazidime; CRO, Ceftriaxone; FEP, Cefepime; CFX, Cefoxitin; CFS, Cefoperazone/Sulbactam; ETP, Ertapenem; IPM, Imipenem; MEM, Meropenem; AMK, Amikacin; LVX, Levofloxacin; SXT, Trimethoprim/Sulfamethoxazole; TGC, Tigecycline.

Table 4 Correlation of *Serratia marcescens* Resistance Rates (Columns) with Antibiotic DDDs (Rows)

	TZP	CXM	CAZ	CRO	CFS	CMZ	IPM	MEM	AMK	GEN	LVX
AMC-RR	−0.398	−0.108	−0.026	−0.176	−0.069	0.000	−0.145	0.565[a]	−0.081	−0.501	0.391
CXM-RR	−0.562[a]	−0.336	0.207	−0.357	−0.487	−0.318	−0.162	0.347	−0.187	−0.474	0.292
CAZ-RR	−0.609[a]	−0.481	0.099	−0.572[a]	−0.414	−0.355	0.079	−0.261	−0.132	−0.285	0.035
CRO-RR	−0.452	−0.094	0.032	−0.493	−0.136	−0.411	0.036	−0.354	−0.073	−0.068	−0.101
FEP-RR	−0.472	−0.536[a]	−0.046	−0.215	−0.506	−0.051	−0.109	−0.243	0.169	−0.365	0.238
CFX-RR	−0.533[a]	−0.482	0.289	−0.108	−0.313	0.166	−0.205	0.253	−0.043	−0.409	0.195
CFS-RR	−0.469	−0.223	−0.197	−0.123	−0.174	−0.011	−0.137	0.630[a]	0.093	−0.677[b]	0.413
ETP-RR	−0.419	−0.411	−0.117	−0.093	−0.255	0.028	−0.096	−0.163	0.080	−0.413	0.112
IPM-RR	−0.557[a]	−0.355	−0.057	−0.392	−0.407	−0.274	−0.216	0.056	−0.123	−0.579[a]	0.257
MEM-RR	−0.516	−0.431	−0.064	−0.256	−0.368	−0.109	−0.234	−0.364	−0.034	−0.370	0.012
AMK-RR	−0.567[a]	−0.243	0.080	−0.276	−0.222	−0.276	−0.174	−0.301	−0.028	−0.336	−0.081
LVX-RR	0.087	0.311	0.010	0.206	0.391	0.519	0.064	−0.119	0.368	0.555[a]	−0.022
SXT-RR	−0.468	0.061	−0.028	−0.148	−0.242	0.083	−0.182	0.002	0.410	−0.012	−0.007

Notes: [a]P<0.05, [b]P<0.01.

Abbreviations: TZP, Piperacillin/Tazobactam; CXM, Cefuroxime; CAZ, Ceftazidime; CRO, Ceftriaxone; CFS, Cefoperazone/Sulbactam; CMZ, Cefmetazole; IPM, Imipenem; MEM, Meropenem; AMK, Amikacin; GEN, Gentamicin; LVX, Levofloxacin; AMC, Amoxicillin/Clavulanic; FEP, Cefepime; CFX, Cefoxitin; ETP, Ertapenem; SXT, Trimethoprim/Sulfamethoxazole; TGC, Tigecycline.

Correlation Analysis

To assess independent linear correlations, we utilized multiple linear regression models. Models 1–3 included multiple independent variables, while Models 4–9 incorporated single independent variables. Table 5 shows the key parameters and test values for each regression model: regression coefficients (β) quantify the impact of independent variables on the dependent variable ($p<0.05$ indicates significance), the F-value assesses overall model significance, VIF<5 demonstrates low multicollinearity, R^2 represents explanatory power, and a Durbin-Watson value near 2 confirms residual independence. Diagnostic plots for Models 1–3 are shown in Figures 1–3. The standardized residual histograms (Figures 1a, 2a and 3a) approximate a normal distribution across all groups. The normal probability (P-P) plots (Figures 1b, 2b and 3b) demonstrate points clustering closely along the diagonal line, confirming the normality of residuals. The residual scatter

Table 5 Linear Regression Analysis of *Serratia marcescens* Resistance and DDDs

Model	Dependent Variable	Independent Variable	Unstandardized Coefficients		Standardized Coefficients	t (p)	*95% Confidence Interval for β*		R^2	F	VIF	Durbin-Watson
			β	Standard Error			Lower Limit	Upper Limit				
1	CAZ-RR	TZP-DDDs	−0.005	0.002	−0.609	−2.660 (0.021)	−0.009	0.000	0.371	7.078	1.000	2.080
2	IPM-RR	GEN-DDDs	−0.015	0.006	−0.579	−2.458 (0.030)	−0.028	−0.002	0.335	6.043	1.000	1.914
3	CFS-RR	GEN-DDDs	−0.009	0.003	−0.677	−3.182 (0.008)	−0.015	−0.003	0.458	10.126	1.000	1.655
4	CXM-RR	TZP-DDDs	−0.004	0.002	−0.562	−2.355 (0.036)	−0.008	0.000	0.316	5.548	1.000	2.670
5	CFX-RR	TZP-DDDs	−0.006	0.003	−0.533	−2.180 (0.050)	−0.011	0.000	0.284	4.751	1.000	1.938
6	AMK-RR	TZP-DDDs	0.000	0.000	−0.567	−2.384 (0.035)	−0.002	0.000	0.321	5.683	1.00	1.969
7	AMC-RR	MEM-DDDs	0.027	0.011	0.565	2.370 (0.035)	0.002	0.052	0.319	5.615	1.000	1.414
8	LVX-RR	GEN-DDDs	0.032	0.014	0.555	2.313 (0.039)	0.002	0.063	0.308	5.348	1.000	1.013
9	FEP-RR	CXM-DDDs	−0.002	0.001	−0.536	−2.199 (0.048)	−0.003	0.000	0.287	4.835	1.000	1.879

Abbreviations: TZP, Piperacillin/Tazobactam; CXM, Cefuroxime; CAZ, Ceftazidime; CFS, Cefoperazone/Sulbactam; IPM, Imipenem; MEM, Meropenem; AMK, Amikacin; GEN, Gentamicin; LVX, Levofloxacin; AMC, Amoxicillin/Clavulanic; FEP, Cefepime; CFX, Cefoxitin.

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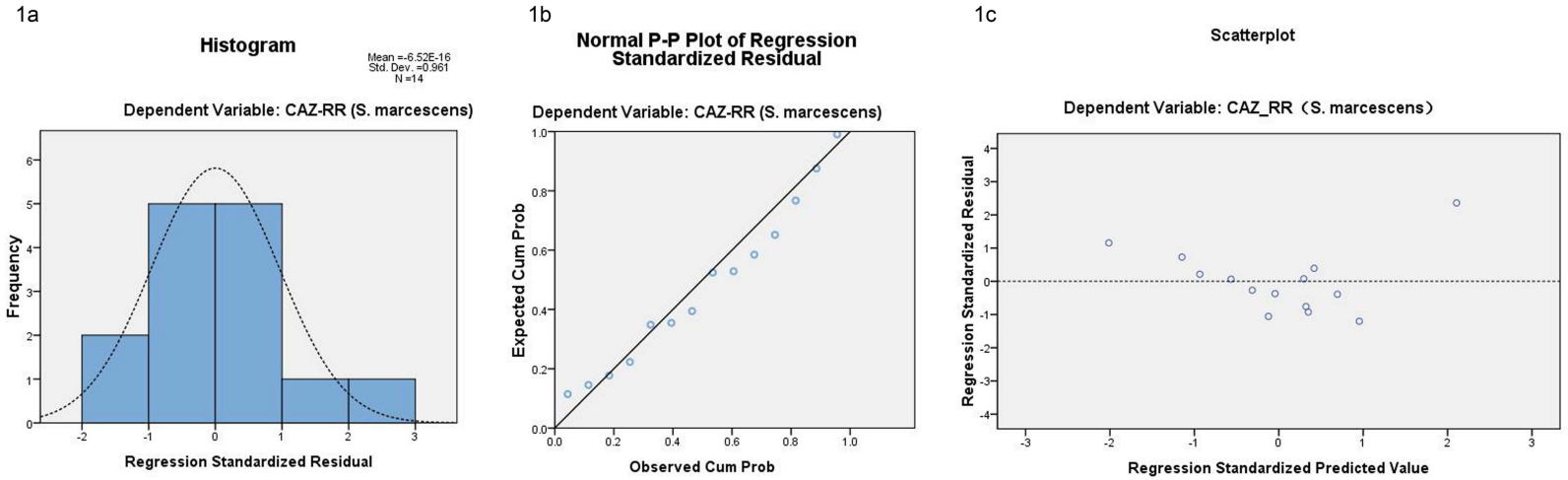

Figure 1 Regression diagnostic plots for Model 1. (**a**). Histogram of standardised residuals (normality assessment), (**b**). Normal Q-Q plot (residual normality verification), (**c**). Scatterplot of Residuals versus fitted values (homoscedasticity assessment).

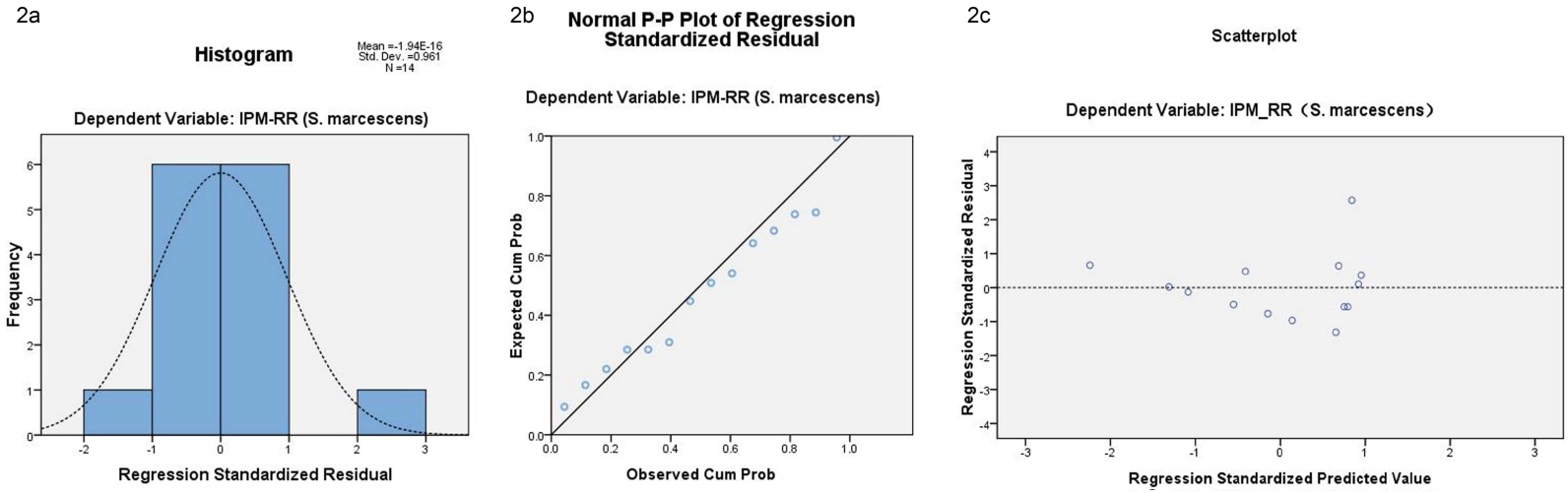

Figure 2 Regression diagnostic plots for Model 2. (**a**). Histogram of standardised residuals (normality assessment), (**b**). Normal Q-Q plot (residual normality verification), (**c**). Scatterplot of Residuals versus fitted values (homoscedasticity assessment).

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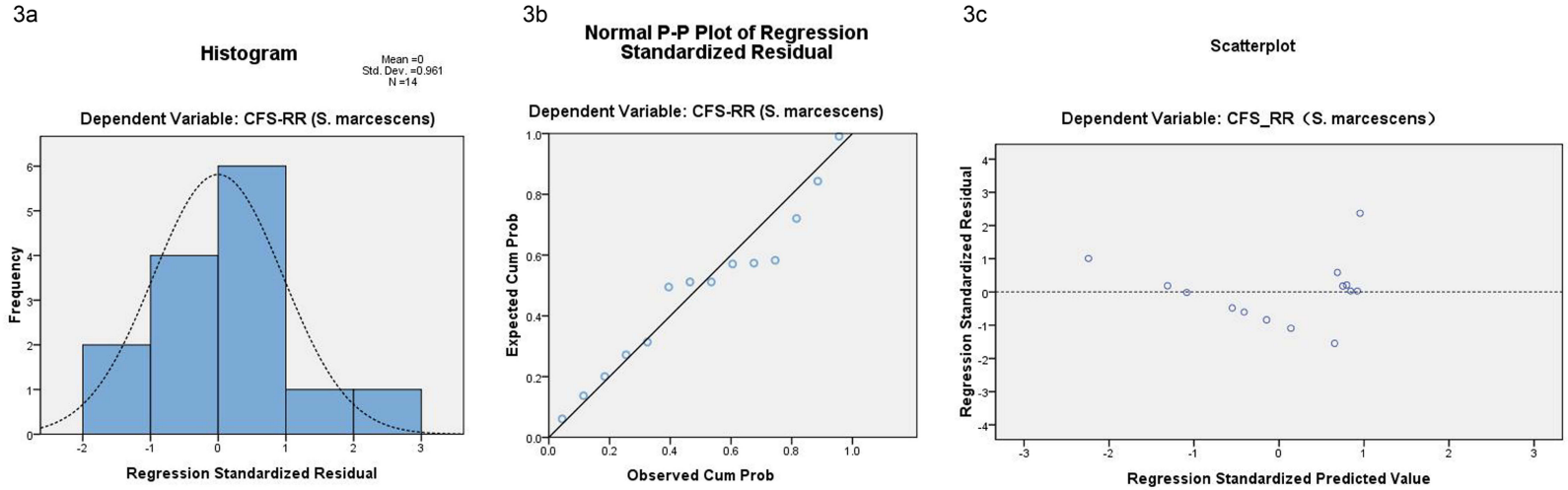

Figure 3 Regression diagnostic plots for Model 3. (**a**). Histogram of standardised residuals (normality assessment), (**b**). Normal Q-Q plot (residual normality verification), (**c**). Scatterplot of Residuals versus fitted values (homoscedasticity assessment).

plots (Figures 1c, 2c and 3c) show evenly distributed points within the ±3 range for all groups, indicating homoscedasticity and absence of influential outliers.

Robustness Verification

The final regression model is subjected to threefold validation (Table 6). Multiple robustness validations consistently demonstrated negative correlations for IPM-RR/GEN, CFS-RR/GEN, CFX-RR/TZP, and FEP-RR/CXM. Bayesian posterior means were less than zero (95% HPD excluding zero), Bootstrap confidence intervals were entirely negative, and Winsorized regression coefficients were highly consistent with the original model, with minimal changes such as +0.41% for IPM-RR/GEN.

The robustness validation for the AMC-RR/MEM and LVX-RR/GEN groups supports the original positive trend. Bayesian analysis shows posterior means significantly greater than zero, and Winsorized regression reinforces this with positive coefficients and confidence intervals excluding zero. Bootstrap results are borderline, primarily reflecting insufficient estimation precision rather than a change in effect direction. All three validation methods have consistent positive point estimates, with effect sizes exceeding the clinical threshold ($|\beta| > 0.02$), confirming the biological validity of the positive trend.

The triple validation showed consistent negative trends for CAZ-RR/TZP, CXM-RR/TZP, and AMK-RR/TZP. Bayesian and Winsorized regression results were statistically significant, while Bootstrap analysis results were borderline, reflecting limited estimation accuracy due to the sample size. The effect sizes were small ($|\beta| < 0.005$) and did not reach the clinical threshold ($|\beta| > 0.02$), but the consistent trends warrant validation through enhanced analytical approaches in future investigations.

Discussion

S. marcescens, first identified in 1819 by Venetian pharmacist Bartolomeo Bizio, was initially seen as a low-pathogenicity environmental saprophyte. However, its pathogenic potential was revealed in the 1950s through fatal urinary tract infections. It can cause infections in multiple systems, including respiratory, neurological, abdominal, cardiovascular, musculoskeletal, and ocular.[12] Recently, *S. marcescens* has gained attention as an emerging pathogen worldwide, provoking infections and outbreaks in debilitated individuals, particularly newborns and patients in ICU.[13] *S. marcescens* resists disinfectants, persists in the environment, and colonizes medical devices and surfaces. Its invasiveness and antimicrobial resistance make it a major hospital-acquired pathogen.

In the past four years, a total of 522 strains of *S. marcescens* were detected in our hospital, accounting for 3.22% of the total bacterial count in the hospital. The clinical isolated samples of *S. marcescens* mainly come from the respiratory

Table 6 Robustness Verification

	Bayesian		Bootstrap		Winsorized		
	β	(95% CI)	β	(95% CI)	β	(95% CI)	$\Delta\beta$%
CAZ-RR/TZP	−0.0047	[−0.0086, −0.0009]	−0.0047	[−0.0122, 0.0000]	−0.0043	[−0.0081, −0.0006]	−7.65%
IPM-RR/GEN	−0.0151	[−0.0285, −0.0017]	−0.0151	[−0.0315,-0.0070]	−0.0152	[−0.0280, −0.0023]	0.41%
CFS-RR/GEN	−0.0088	[−0.0148, −0.0028]	−0.0088	[−0.0165, −0.0040]	−0.0089	[−0.0147, −0.00031]	0.87%
CXM-RR/TZP	−0.0041	[−0.0080, −0.0003]	−0.0041	[−0.0065, 0.0009]	−0.0042	[−0.0082, −0.0002]	0.81%
CFX-RR/TZP	−0.0056	[−0.0113, -2.477×10^{-6}]	−0.0056	[−0.0099, −0.0020]	−0.0059	[−0.0116, -1.565×10^{-4}]	4.36%
AMK-RR/TZP	−0.0010	[−0.0019, -8.526×10^{-5}]	−0.0010	[−0.0023, 0.0000]	−0.0010	[−0.0019, -4.371×10^{-5}]	−1.26%
AMC-RR/MEM	0.0271	[0.0022, 0.0519]	0.0271	[−0.0050, 0.0477]	0.0269	[0.0018, 0.0519]	−0.78%
LVX-RR/GEN	0.0323	[0.0019, 0.0628]	0.0323	[−0.0098, 0.0601]	0.0324	[0.0015, 0.0634]	0.24%
FEP-RR/CXM	−0.0018	[−0.0035, -1.593×10^{-5}]	−0.0018	[−0.0041, −0.0002]	−0.0017	[−0.0033, -1.035×10^{-5}]	−4.48%

Notes: Validation: Bayesian analysis used MCMC (10k iterations; 95% CI≠0 and posterior probability >0.95); Bootstrap validation employed 3k BCa resamples (95% CI≠0); Winsorized regression applied 1st/99th percentile winsorization with |Δβ%|<10% and sustained significance (p<0.05), where $\Delta\beta$% = [(β_winsorized − β_original) / β_original] × 100%.

Abbreviations: TZP, Piperacillin/Tazobactam; CXM, Cefuroxime; CAZ, Ceftazidime; CFS, Cefoperazone/Sulbactam; IPM, Imipenem; MEM, Meropenem; AMK, Amikacin; GEN, Gentamicin; LVX, Levofloxacin; AMC, Amoxicillin/Clavulanic; FEP, Cefepime; CFX, Cefoxitin.

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tract, accounting for 86.59%, and the proportion of samples from blood, urine, secretions, ducts, etc. is relatively small. This suggests that when the immune system is weakened, the respiratory tract is a common site for *S. marcescens* infection, calling for clinical prevention and control. This finding aligns with relevant literature.[14,15] The presence of *S. marcescens* can exacerbate the condition of patients with compromised immune systems.[16] Furthermore, studies have indicated that this bacterium may lead to severe acute infections, resulting in respiratory distress even in individuals with normal immune function.[17] *S. marcescens* is mainly found in surgical and intensive care unit (ICU), emphasizing the need for better infection control. This aligns with Chen Jian et al's findings.[18] Major risk factors include serious underlying diseases, major surgeries, ventilator use, tracheostomies, invasive exams, and prolonged high-dose antibiotics, which are common among ICU and surgical patients.

S. Marcescens contains R factors or R plasmids that can carry multiple resistance genes, leading to its natural resistance to first generation cephalosporins, ampicillin, and macrolides.[18] The study showed that *S. marcescens* had a resistance rate of over 90% to cefuroxime and a high resistance rate to amoxicillin-clavulanic, consistent with Li Jin et al.[19] The isolated strains of *S. marcescens* showed sensitivity to cefoperazone-sulbactam, cefepime, ertapenem, imipenem, meropenem, amikacin, trimethoprim-sulfamethoxazole, and tigecycline, with a resistance rate of less than 10%, consistent with previous reports.[20] *S. marcescens* shows high sensitivity to amikacin and tigecycline, with resistance rates below 5%. Compared with the national data of bacterial resistance monitoring in CHINET in 2023,[4] the resistance rate of 522 strains of *S.* marcescens to cefuroxime is slightly higher than the national average level. The drug sensitivity results to ceftriaxone, ceftazidime, levofloxacin, amikacin, trimethoprim-sulfamethoxazole, and tigecycline are relatively consistent with the national data, while the resistance rate to cefepime, cefoxitin, cefoperazone-sulbactam, ertapenem, imipenem and meropenem is lower than the national level. Clinically, third-generation cephalosporins, aminoglycosides, and quinolones treat *S. marcescens* infections, with carbapenems for severe MDR strains. Overuse of carbapenems has coincided with an increasing detection rate of carbapenem-resistant *S. marcescens*, hindering control and treatment.[21] Notably, studies demonstrate that *S. marcescens* exhibits intrinsic resistance to polymyxins. Studies show *S. marcescens* is naturally resistant to polymyxins,[6] if it also produces carbapenemases, treatment gets harder.[22] Clinicians should choose antibiotics wisely to control and prevent outbreaks of *S. marcescens* infections.

Reports indicate that developing a new antimicrobial drug from research to clinical use generally takes 5 to 10 years. In contrast, bacteria can develop resistance in as few as 2 years.[23] Thus, slowing bacterial resistance is just as critical as enhancing antimicrobial drug efficacy. The study showed resistance to cefoperazone-sulbactam and imipenem had independent negative linear relationships with gentamicin DDDs; resistance to cefoxitin correlated negatively with piperacillin-tazobactam DDDs; resistance to cefepime showed a negative association with cefuroxime DDDs. These four relationships were strongly supported by consistent results from Bayesian, Bootstrap, and Winsorized regression. In addition, amoxicillin-clavulanic resistance positively correlated with meropenem DDDs, and levofloxacin resistance positively correlated with gentamicin DDDs. These positive trends were supported by triple robustness testing. Concurrently, analyses of *S. marcescens* isolates revealed negative linear correlations of resistance to ceftazidime, cefuroxime, and amikacin with piperacillin-tazobactam DDDs. Although these associations were directionally consistent across all robustness validation methods, their effect sizes fell below prespecified clinical thresholds, warranting further studies to explore these potential relationships. The recurrent involvement of piperacillin-tazobactam in resistance patterns warrants attention. Existing studies have shown that *S. marcescens* has the ability to form biofilms, which can hinder antibiotic penetration, alter bacterial metabolic states, and thus enhance bacterial drug resistance.[24] Although research on *S. marcescens* is limited, studies on other Gram-negative bacteria can offer insights. Research has demonstrated that use of piperacillin-tazobactam reduces rates of ceftazidime-resistant *Klebsiella pneumoniae*, which is similarly a member of the *Enterobacteriaceae* family.[25] The mechanism may be related to biofilm inhibition. Studies have shown that sub-minimal inhibitory concentration (sub-MIC) concentrations of piperacillin-tazobactam can effectively reduce biofilm formation by inhibiting the adhesiveness and motility of *Escherichia coli*,[26] and reduce *Pseudomonas aeruginosa* biofilm formation in a dose-dependent manner, with the strongest inhibitory effect at MIC/2 concentration.[27] Whether increased use of piperacillin-tazobactam reduces *S. marcescens* resistance to ceftazidime by inhibiting biofilm-mediated resistance barriers remains unclear, and relevant mechanisms require further research through

constructing in vitro biofilm models and conducting in vivo antibacterial experiments. Zhao Ningqiu et al[28] found that different antimicrobial agents may share resistance mechanisms, such as overexpression of efflux pumps, changes in cell membrane permeability, inactivation of antimicrobial compounds, and modification of their targets. These mechanisms can cause cross-resistance or co-resistance between drugs.

From a biological perspective, these associations may involve complex mechanisms. Negative correlations may reveal potentialistic synerg inhibitory effects between antimicrobial drugs, suggesting that increased use of certain drugs can suppress the rise in resistance to target drugs, indicating that rational combination or rotation of antimicrobial drugs can effectively reduce resistance risks. Positive correlations suggest the presence of cross-resistance or co-resistance mechanisms, implying that increased use of one class of antimicrobial drugs may simultaneously or subsequently lead to increased resistance to other structurally or functionally similar drugs. Hospitals should optimize antibiotic management strategies, including targeted antibiotic rotation, limiting high-risk drug use, and adhering to data-driven guidelines. These measures can improve patient care, curb the spread of *S. marcescens* resistance, and preserve the long-term efficacy of essential antimicrobials.

The resistance mechanisms of *S. marcescens* are complex, as it inherently exhibits resistance to multiple antibiotics, such as polymyxin and cephalothin. It can produce specific β-lactamases induced by drugs, include cephalosporinase (AmpC), extended-spectrum β-lactamases (ESBLs), carbapenemases, etc. These enzymes are capable of hydrolyzing the β-lactam ring of β-lactam antibiotics, rendering the antibiotics inactive and thus enabling the bacteria to develop resistance to the corresponding antibiotics. Research on carbapenem resistance mainly focuses on serine carbapenemases, such as KPC enzyme, OXA-48, and metallo-enzymes.[29] The resistance genes encoding carbapenemases in *S. marcescens* are mainly KPC-2,[30] NDM-1,[31] IMP-1, IMP-10, and it may carry multiple resistance genes, presenting a multi-drug-resistant phenotype.[32] Relevant reports have shown that the synergistic effect of high-yield chromosome-mediated loss of AmpC enzyme and porin resulting in decreased permeability can also cause drug resistance to carbapenilic antibiotics.[33] Moreover, reduced outer membrane permeability and overactive efflux pumps in the inner membrane are key contributors to increased drug resistance in *S. marcescens*.[34]

Currently, there is a scarcity of global data regarding how *S. marcescens* develops resistance in response to antimicrobial exposure. This aspect remains a relatively unexplored area within *S. marcescens* research. Our study used multiple linear regression to analyze the independent, linear correlation between *S. marcescens* resistance rates and antibiotic use one quarter in advance. We also validated our results using three methods: Bayesian, which enhances reliability; Bootstrap, which improves model adaptability; Winsorized regression, which controls the impact of outliers. Our quarterly time-series design (longitudinal study) is more effective at capturing macro trends compared to cross-sectional studies.[9,35] However, the limited observation period restricts the number of data points in similar longitudinal studies.[36,37] To compensate, we optimized our methodology through triple validation to ensure model stability. Future research could further investigate the impact of continuous antibiotic use on resistance through randomized controlled trials and explore resistance mechanisms. We hope this study offers a unique perspective to guide antibiotic management.

The rapid emergence and spread of resistant bacteria in hospitals are due to multiple factors, including improper antimicrobial use creating high selective pressure, inconsistent infection control measures leading to patient-to-patient transmission, inter-hospital transfer of resistance, and complex links between resistance and antimicrobial use.[38] Clinicians should strictly control antimicrobial use, standardize dosages and durations, and avoid misuse that can trigger resistance. Tailoring treatments based on infection type and susceptibility results can reduce resistance risks. Healthcare facilities need to enhance resistance monitoring, strengthen multidisciplinary collaboration, and enforce strict antimicrobial use regulations. Regular analysis of resistance data can guide rational prescribing. Infection control measures, including "one use, one disinfection", isolating patients with resistant infections, and using dedicated equipment, are essential. Hand hygiene training and rapid response to clustered cases are crucial to break transmission chains. Understanding the correlation between *S. marcescens* resistance rates and antimicrobial use is crucial for clinical resistance control.

Conclusion

Over the past four years, our hospital identified 522 *S. marcescens* strains (3.22% of all isolates), with 86.59% from respiratory samples. This indicates that the respiratory tract is a common site for *S. marcescens* infection, necessitating clinical prevention and control measures. Most strains were sensitive to cefoperazone-sulbactam, cefepime, ertapenem, imipenem, meropenem, amikacin, trimethoprim-sulfamethoxazole, and tigecycline, with resistance rates <10%. Our study found significant correlations between *S. marcescens* resistance and antibiotic usage. Negative correlations showed that strategic antimicrobial use can reduce resistance rates, while positive correlations indicated higher co-resistance risks. These results highlight the need for hospitals to implement antibiotic rotation, limit high-risk drug use, and enhance supervision to improve patient outcomes and curb resistance.

Highlights

1. This study is the first to deeply investigate the macro-level quantitative relationship between *S. marcescens* drug resistance and antibiotic use, filling a research gap in this area.
2. Using multiple linear regression models, we identified independent linear correlations between *S. marcescens* resistance rates and the use of various antibiotics.
3. Our findings provide a scientific basis for rational and optimized antibiotic use in clinical practice, helping to delay the emergence of resistant bacteria and combat the threat of antibiotic resistance.

Ethics Approval

This study was reviewed and approved by the Ethics Committee of Wenzhou Hospital of Integrated Traditional Chinese and Western Medicine (NO. 2025-L104). Informed consent was obtained from the patient.

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Disclosure

The authors report no conflicts of interest in this work.

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