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ORIGINAL RESEARCH

Epidemiology, Risk Factors, and External Validation of Predictive Models for Multidrug-Resistant Bacterial Infections in Diabetic Foot Ulcers

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Objective: This study aimed to investigate the epidemiological characteristics and risk factors of multidrug-resistant bacterial (MDRB) infections in diabetic foot ulcer (DFU) and externally validate existing predictive models for MDRB, *Pseudomonas aeruginosa* (*PSA*), and *methicillin-resistant Staphylococcus aureus* (*MRSA*) infections.

Methods: A retrospective analysis of 344 patients diagnosed with DFU identified key clinical and laboratory variables associated with outcomes. Univariate and multivariate logistic regression identified risk factors, while receiver operating characteristic (ROC) curves and calibration analyses assessed model validity.

Results: MDRB infections were linked to longer hospitalization, lower hemoglobin, higher hs-CRP, and higher osteoporosis prevalence. Significant risk factors included prolonged hospitalization, osteomyelitis, osteoporosis, prior antimicrobial use, and respiratory rate. *PSA* infections correlated with myocardial infarction and peripheral vascular disease, while no significant risk factors were identified for *MRSA*. External validation showed poor discriminatory ability (AUC: 0.501 for MDRB, 0.505 for *PSA*, 0.569 for *MRSA*) and calibration performance, indicating poor generalizability of existing models in our cohort.

Conclusion: MDRB infections in DFUs are associated with specific clinical characteristics and risk factors. However, existing predictive models demonstrated limited utility in our dataset, emphasizing the need for model refinement and inclusion of additional risk factors. Future research should focus on improving predictive models and developing targeted antimicrobial strategies to enhance clinical outcomes in diabetic foot infections.

Keywords: diabetic foot ulcers, multidrug-resistant bacteria, risk factors, predictive models, model validation

Introduction

Diabetic foot ulcers (DFUs) represent one of the most serious complications in patients with diabetes, affecting approximately 6.3% of diabetic individuals worldwide,[1] with even higher rates reported in some regions.[2] The spectrum of infections associated with DFUs is broad, ranging from superficial cellulitis to deep necrotizing infections, abscess formation, and osteomyelitis. If not appropriately managed, these infections can lead to amputation, severely diminishing patients' quality of life. Moreover, DFUs not only significantly increase disability and mortality rates but also impose a heavy economic burden on health-care systems.[1]

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In recent years, the rising prevalence of multidrug-resistant bacterial (MDRB) infections in DFUs has emerged as a major clinical challenge.[3] MDRB infections extend hospital stays, escalate treatment costs, and heighten the risk of lower extremity amputations.[4] The microbial spectrum in diabetic foot infections (DFI) is complex, with organisms ranging from common skin commensals to highly resistant nosocomial pathogens.[3] Among Gram-positive isolates, *Staphylococcus aureus*—both methicillin-susceptible (*MSSA*) and methicillin-resistant (*MRSA*)—remains the single most prevalent pathogen, followed by coagulase-negative *staphylococci* such as *Staphylococcus epidermidis* and *enterococci* (including vancomycin-resistant strains).[3] Gram-negative bacilli are frequently encountered, especially *Escherichia coli* (often ESBL-producers), *Klebsiella pneumoniae, Proteus mirabilis* and *Pseudomonas aeruginosa* (*PSA*).[3] Anaerobes (*Peptostreptococcus spp., Bacteroides spp.)* and opportunistic yeasts (*Candida spp.)* may also participate, particularly in chronic or previously treated wounds.[3] Alarmingly, recent Asian multicentre data indicate that 60–70% of *E. coli* and 50% of *K. pneumoniae* isolates from DFUs now harbour ESBLs, while MRSA rates exceed 50% in tertiary centres.[3] The presence of these resistant strains[5] complicates treatment decisions and underscores the necessity for accurate risk assessment.[6]

Although previous studies have investigated the epidemiological characteristics and risk factors associated with MDRB infections,[7] significant variability exists in their applicability across different regions and populations. With the global increase in antibiotic resistance, research focusing on resistant pathogens in DFIs has intensified. For instance, geographic and institutional variations have been noted.[6] Farkas et al[8] reported prevalence rates of 6.5% for *PSA* and 11.1% for *MRSA* in infectious foot ulcers from two urban hospitals in the United States, while Kim et al[9] found corresponding rates of 23% and 6% in a case–control study on DFIs. Beyond clinical outcomes, the economic toll of MDRB-related treatment failure is substantial: prolonged hospitalization, additional surgical procedures, and escalated drug costs can double or triple the expense of managing a single DFI.[10] In the EU alone, resistant infections already generate over €1.5 billion in excess health-care costs annually,[10] and similar projections from China indicate that unchecked resistance could add hundreds of millions of dollars to national expenditures.[11] Recognizing these financial consequences reinforces the urgency of accurate, region-specific prediction models to guide empiric therapy and curb further economic burden.

To address these challenges, Farkas et al[8] developed a regression-based nomogram that quantifies the risk of isolating resistant pathogens in DFIs, demonstrating predictive performance for both *PSA* (AUC = 0.85) and *MRSA* (AUC = 0.72). Similarly, Yi-ni Ma et al[12] introduced a nomogram for predicting MDRB infections in DFU patients, achieving a promising AUC of 0.773. Predictive models could identify patients at high risk for antibiotic resistance before culture results are available, enabling clinicians to avoid ineffective or overly broad empiric regimens and thus curtail unnecessary exposure.[13] By integrating models into computerized decision-support systems, hospitals can translate retrospective insights into real-time prescribing guidance. Although risk prediction models have been proposed, each utilizes different parameters, which complicates the process for clinicians in determining the most suitable tool for their practice. Moreover, there remains a lack of externally validated data on these models. External validation, which involves testing models using data from independent cohorts, is crucial for evaluating a model's reproducibility (ie, its ability to provide accurate predictions in similar populations) and portability across diverse clinical settings.[14] In general, predictive models tend to perform better in the cohorts from which they were derived compared to other cohorts due to differences in case mix and outcome rates.

In this study, we analyze clinical data from 344 DFU patients to further elucidate the epidemiological characteristics and risk factors associated with MDRB infections. Additionally, we aim to externally validate the predictive performance of the models proposed by Farkas et al[8] and Yi-ni Ma et al[12] in different patient populations. This investigation is crucial not only for enhancing the identification of resistant pathogens in DFIs but also for informing more precise antimicrobial strategies, ultimately improving clinical outcomes in this vulnerable patient group.

Methods

Study Design and Population

This study was a retrospective observational study designed to externally validate two previously published predictive models for MDRB infections, *PSA*, and *MRSA* in patients with DFUs. External validation was performed on DFI patients

consecutively admitted to Shaoguan First People's Hospital—a major tertiary referral centre at the heart of Shaoguan City and one of only two such hospitals in northern Guangdong Province—from January 2022 to November 2024.

The inclusion criteria as follows: (1) Met the 1999 WHO Diabetes Diagnostic Criteria; (2) Met the diagnostic criteria of *DF* in "Guidelines for the Prevention and Control of Type 2 Diabetes in China (2017 Edition)"[15] and "Chinese Guideline on Prevention and Management of *DF* (2019 Edition)";[16–19] (3) The clinical identification of infection relied on the manifestation of at least two signs among these: localized swelling or hardening, redness encircling the ulcer, tenderness or pain in the area, elevated temperature, and pus-like discharge. As for diagnosing osteomyelitis, it was determined through imaging in accordance with the recommended guidelines.[20]

The patients with incomplete clinical data or microbiological data; malnutrition circulatory ulcers of the lower limbs caused by varicose veins; and foot ulcers caused by other diseases were excluded from the study.

This study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of Shaoguan First People's Hospital (approval No. (2025)31). Because the study was retrospective, the requirement for informed consent was waived. All patient data were anonymized and de-identified prior to analysis.

Data Collection

Aside from the baseline demographic and laboratory parameters, the following risk factors previously evaluated for association with MDRB, *PSA*, and *MRSA* in DFUs were identified from the existing literature and were collected retrospectively from the medical record: age, gender, course of diabetes, fasting blood glucose, glycosylated hemoglobin (HbA1c),[6] hemoglobin concentration, Charlson Comorbidity Index (CCI)[8] and their corresponding indicators, high-sensitivity C-reactive protein (hs-CRP), procalcitonin, white blood cell count, systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature, ulcer surface area,[21] presence of osteomyelitis,[22] osteoporosis,[8] gangrene,[21] amputation history,[23] previous hospitalization,[22] prior use of antibacterial drugs,[6] types of antibacterial drugs,[8] and ICU admission days. IDSA Severity Score[21] was calculated based on the Infectious Diseases Society of America (IDSA) guidelines for DFUs. Data on MDRB, *PSA*, and *MRSA* infections were confirmed through microbiological testing. If no antibiotic was given, or the antibiotic administered prior to culture collection was lacking known spectrum of activity against the microorganism eventually isolated, the microorganism was considered not to have been covered by antibiotics empirically.

Microbiological Studies

Culture specimens were gathered in a sterile manner either during ulcer debridement or as part of the amputation procedure for infected areas, with all below-the-knee amputations being included for sampling. After debriding the wound and cleansing the surrounding tissue with povidone iodine, samples were taken from the infected site. For most cases, specimens were obtained through deep tissue biopsy and bone debridement during surgery. In addition, some high-quality deep tissue swabs were collected in line with guidelines to ensure proper sampling for culture.[20]

Data Imputation and Validation

The pattern of missing data in the original dataset was analyzed using Little's MCAR test,[24] which revealed a χ^2 value of 367.768 ($P = 0.031$), indicating that the dataset was not missing completely at random (MCAR). Consequently, simply removing data with a missing rate >10% may introduce bias.

To address missing values in the dataset, we employed a multiple imputation approach using the random forest algorithm, implemented in R via the mice package. Specifically, we generated five complete datasets through multiple imputation, with the random forest method (method = 'rf') selected for its ability to handle complex relationships and non-linear patterns in the data. This approach ensures robust estimation of missing values while preserving the underlying distribution of the variables.

The imputed datasets were exported as CSV files for further analysis. To validate the consistency between the original and imputed data, we performed a distribution comparison for key variables, including cholesterol, creatinine, estimated glomerular filtration rate, fasting blood glucose, HbA1c, hemoglobin concentration, hs-CRP, procalcitonin, triglyceride, and white blood cell count.

For each variable, we constructed histograms to visualize the distribution of values before and after imputation. Additionally, we conducted independent *t*-tests to assess whether there were statistically significant differences in the means of the variables between the original and imputed datasets. The results demonstrated no significant differences in the distributions of the variables across all imputed datasets ($P > 0.05$), indicating that the imputation process preserved the statistical properties of the original data (detailed in Supplementary Figure 1).

Among the five imputed datasets, we selected the first imputed dataset (Dataset 1) for subsequent statistical analyses. This selection was based on the stability and consistency of the imputed values, as well as the alignment of variable distributions with the original dataset. The distribution comparisons and statistical validation are illustrated in the accompanying figures (detailed in Supplementary Figure 1), which show the alignment of variable distributions between the original and imputed datasets. This validation step ensures the reliability of the imputed data for subsequent analyses.

Statistical Analysis

Continuous variables were described using means and standard deviations if they followed a normal distribution, as determined by the Shapiro–Wilk test (or Kolmogorov–Smirnov test) of normality. Categorical variables were presented as frequencies. Key clinical variables between our dataset and the original models were compared to assess generalizability. For categorical variables, chi-square tests were used. For continuous variables, t-tests were used if the data were normally distributed; otherwise, non-parametric tests (eg, Mann–Whitney *U*-test) were applied. Univariate analysis was used to screen for strong risk factors from the 21 potential factors identified. Following univariate analysis, variables with a p-value < 0.1 were included in multivariate logistic regression models to adjust for confounding factors. Following the methodologies of previous studies,[14] we generated ROC curves and calculated AUC values to evaluate the discriminatory efficacy of the three clinical prediction models, contextualized to our regional data. For models built using the logistic formula, calibration curves were plotted to elucidate the disparity between the predicted and actual probabilities of occurrence. All statistical analyses were performed using R software (version 4.0.3), MedCalc Statistical Software version 18.2.1 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2018), and Prism 9 software to plot the above ROC, AUC, calibration curves, etc. $P < 0.05$ was considered statistically significant.

Results

Comparison of Clinical and Laboratory Characteristics Between MDRB and Non-MDRB Patients in DFUs

A total of 344 patients with DFUs were included in this retrospective observational study, with 231 patients in the non-MDRB group and 113 patients in the MDRB group. The baseline characteristics and clinical outcomes of the two groups are summarized in Table 1.

Patients with MDRB infections exhibited higher IDSA Severity Scores (>3, 47.49% vs 35.06%, $P = 0.0235$), longer hospitalization durations (24.30 ± 15.25 days vs 17.75 ± 13.01 days, $P < 0.0001$), lower hemoglobin concentration (110.5 ± 22.61 g/L vs 103.1 ± 21.63 g/L, $P = 0.0009$), higher levels of hs-CRP (70.33 ± 82.12 mg/L vs 45.89 ± 62.05 mg/L, $P = 0.0023$), higher mean pulse rate (89.96 ± 11.86 bpm vs 86.23 ± 12.47 bpm, $P = 0.0065$), and lower mean respiration rate (17.74 ± 1.076 bpm vs 18.13 ± 1.266 bpm, $P = 0.0051$) compared to non-MDRB patients. Additionally, MDRB patients had a higher prevalence of osteoporosis (15.93% vs 7.79%, $P = 0.0208$) and lower prior antimicrobial drug use (35.50% vs 21.24%, $P = 0.0072$). Cerebrovascular disease (31.60% vs 20.35%, $P = 0.0292$) was more common in the non-MDRB group. No significant differences were observed in age, course of diabetes, types of antibacterial drugs (≥2), fasting blood glucose, HbA1c, osteomyelitis, triglyceride, cholesterol, CCI (their corresponding indicators were provided in the Supplementary Table 1), white blood cell count, or procalcitonin levels between the groups.

Risk Factors Associated with MDRB Infections in DFUs

Univariate analysis comparing patients with and without MDRB infections indicated no statistical significance for age, Course of Diabetes, Types of antibacterial drugs, CCI (data not showed), osteomyelitis, and several other variables. Conversely, significant associations were found between MDRB infections and variables such as hemoglobin

Table 1 Comparison of Clinical and Laboratory Parameters Between MDRB and Non-MDRB Groups

	Non-MDRB (n = 231)	MDRB (n = 113)	*P* Values*
Age (years)	65.67 ± 12.32	63.96 ± 11.22	0.126
Amputation (Yes, %)	13 (5.63%)	4 (3.54%)	0.4029
CCI	6.08 ± 1.89	5.7 ± 1.81	0.1637
Cholesterol (mmol/L)	4.20 ± 1.40	4.21 ± 1.62	0.9563
Course of Diabetes (years)	11.26 ± 7.05	12.09 ± 6.92	0.3079
Course of Diabetes > 10 years (Yes, %)	131 (56.71%)	72 (63.72%)	0.2155
Creatinine (umol/L)	174.10 ± 250.00	199.20 ± 275.90	0.3983
Diastolic pressure (mmHg)	77.74 ± 10.69	79.88 ± 12.64	0.2225
Estimated glomerular filtration rate (mL/min)	71.26 ± 42.23	64.42 ± 38.23	0.204
Fasting blood glucose (mmol/L)	9.43 ± 4.75	10.49 ± 5.26	0.0618
Gangrene (Yes, %)	88 (38.06%)	47 (41.59%)	0.5337
Gender (male, %)	143 (61.90%)	68 (60.18%)	0.7581
HbA1c (%)	9.08 ± 2.74	9.05 ± 2.41	0.9172
Hemoglobin concentration (g/L)	110.5 ± 22.61	103.1 ± 21.63	0.0009*
Hs-CRP (mg/L)	45.89 ± 62.05	70.33 ± 82.12	0.0023*
Hospitalization days (days)	17.75 ± 13.01	24.30 ± 15.25	<0.0001*
ICU hospitalization days (days)	0.09 ± 0.89	0.04 ± 0.38	0.5584
IDSA Severity > 3 (Yes, %)	81 (35.06%)	54 (47.49%)	0.0235*
Osteomyelitis (Yes, %)	52 (22.51%)	36 (31.86%)	0.0625
Osteoporosis (Yes, %)	18 (7.79%)	18 (15.93%)	0.0208*
Previous hospitalization (Yes, %)	127 (54.98%)	60 (53.10%)	0.7431
Previous MRSA infection (Yes, %)	2 (0.09%)	1 (0.09%)	0.9886
Previous use of antibacterial drugs (Yes, %)	82 (35.50%)	24 (21.24%)	0.0072*
Procalcitonin (ng/mL)	0.45 ± 1.75	0.34 ± 0.78	0.5355
Pulse (bpm)	86.23 ± 12.47	89.96 ± 11.86	0.0065*
Respiration (bpm)	18.13 ± 1.27	17.74 ± 1.08	0.0051*
Smoke (Yes, %)	62 (28.14%)	25 (22.12%)	0.3457
Systolic pressure (mmHg)	136.1 ± 19.59	138.0 ± 21.27	0.4276
Temperature (°C)	36.65 ± 0.46	36.66 ± 0.49	0.5551
Triglyceride (mmol/L)	1.48 ± 0.85	1.33 ± 0.74	0.1049
Types of antibacterial drugs (≥2, %)	28 (12.12%)	15 (13.27%)	0.7624
Ulcer surface area (cm^2)	19.71 ± 30.24	20.55 ± 28.92	0.8076
White blood cell count ($\times 10^9$/L)	10.11 ± 5.44	11.01 ± 4.97	0.137

Note: *Indicates statistically significant data.

concentration (OR = 0.99, 95% CI: 0.98–1.00, $P = 0.0039$), hs-CRP levels (OR = 1.00, 95% CI: 1.00–1.01, $P = 0.0029$), hospitalization days (OR = 1.03, 95% CI: 1.02–1.05, $P = 0.0001$), IDSA Severity > 3 (OR = 1.70, 95% CI: 1.07–2.68, $P = 0.0238$), osteoporosis (OR = 2.24, 95% CI: 1.12–4.50, $P = 0.0243$), previous use of antimicrobial drugs (OR = 0.49, 95% CI: 0.29–0.83, $P = 0.0061$), Pulse (OR = 1.02, 95% CI: 1.01–1.04, $P = 0.0087$), respiration rate (OR = 0.74, 95% CI: 0.60–0.92, $P = 0.0036$), With Cerebrovascular disease (OR = 0.55, 95% CI: 0.32–0.94, $P = 0.0262$), and With Immunosuppressive drugs (OR = 2.05E-09, $P = 0.028$).

Multivariate logistic regression analysis confirmed that hospitalization days (OR = 1.02, 95% CI: 1.01–1.04, $P = 0.0134$), osteomyelitis (OR = 3.27, 95% CI: 1.28–8.37, $P = 0.0133$), osteoporosis (OR = 3.01, 95% CI: 1.34–6.74, $P = 0.0074$), previous use of antimicrobial drugs (OR = 0.40, 95% CI: 0.22–0.73, $P = 0.0029$), and respiration rate (OR = 0.75, 95% CI: 0.60–0.95, $P = 0.0036$) were significantly associated with MDRB infections, as detailed in Table 2.

Table 2 Univariate and Multivariate Analysis of Risk Factors for MDRB Infections

	Univariate OR	95% CI	B	*P Value**	Multivariate OR	(95% CI)	B	*P Value**
Age	0.99	0.97 to 1.01	−0.01	0.2148				
Amputation	0.62	0.20 to 1.93	−0.47	0.3883				
CCI	0.92	0.81 to 1.04	−0.09	0.1599				
Cholesterol	1.00	0.86 to 1.17	0.004	0.9562				
Course of Diabetes	1.02	0.99 to 1.05	0.02	0.3081				
Course of Diabetes > 10 years	1.34	0.84 to 2.13	0.29	0.2129				
Creatinine	1.00	1.00 to 1.00	0.0004	0.4039				
Diastolic pressure	1.02	1.0 to 1.08	0.02	0.1029				
Estimated glomerular filtration rate	1.00	0.99 to 1.00	−0.004	0.1426				
Fasting blood glucose	1.04	1.00 to 1.09	0.04	0.0645	1.008	0.96 to 1.07	0.01	0.7665
Gangrene	1.16	0.73 to 1.83	0.15	0.5333				
Gender	0.93	0.59 to 1.47	−0.07	0.7575				
HbA1c	1.00	0.91 to 1.09	−0.01	0.9169				
Hemoglobin concentration	0.99	0.98 to 1.00	−0.02	0.0039*	0.989	0.98 to 1.00	−0.01	0.0706
Hs-CRP	1.01	1.00 to 1.01	0.01	0.0029*	1.003	1.00 to 1.01	0.003	0.2427
Hospitalization days	1.03	1.02 to 1.05	0.03	0.0001*	1.024	1.01 to 1.04	0.02	0.0134*
ICU hospitalization days	0.88	0.57 to 1.38	−0.12	0.5179				
IDSA Severity > 3	1.70	1.07 to 2.68	0.53	0.0238*	0.540	0.22 to 1.34	−0.62	0.1817
Osteomyelitis	1.61	0.97 to 2.66	0.48	0.065	3.273	1.28 to 8.37	1.19	0.0133*
Osteoporosis	2.24	1.12 to 4.50	0.81	0.0243*	3.010	1.34 to 6.74	1.10	0.0074*
Previous hospitalization	0.93	0.59 to 1.46	−0.08	0.7423				
Previous MRSA infection	1.02	0.09 to 11.40	0.02	0.9857				
Previous use of antibacterial drugs	0.49	0.29 to 0.83	−0.71	0.0061*	0.397	0.22 to 0.73	−0.92	0.0029*
Procalcitonin	0.94	0.76 to 1.16	−0.07	0.4969				
Pulse	1.03	1.01 to 1.04	0.03	0.0087*	1.024	1.00 to 1.05	0.02	0.0543
Respiration	0.74	0.60 to 0.92	−0.30	0.0036*	0.754	0.60 to 0.95	−0.28	0.0145*
Smoke	0.77	0.46 to 1.32	−0.26	0.3409				
Systolic pressure	1.01	0.99 to 1.02	0.01	0.4086				
Temperature	1.05	0.65 to 1.69	0.05	0.8415				
Triglyceride	0.78	0.58 to 1.06	−0.25	0.0948	0.800	0.57 to 1.13	−0.22	0.2017
Types of antibacterial drugs	1.11	0.57 to 2.17	0.10	0.7623				
Ulcer surface area	1.00	0.99 to 1.01	0.001	0.8076				
White blood cell count	1.03	0.99 to 1.08	0.03	0.142				

Note: *Indicates statistically significant data.

Comparison of Clinical Characteristics Between PSA and Non-PSA Groups in DFUs

About 317 patients in the non-*PSA* group and 27 patients in the *PSA* group were included in this study. The baseline characteristics and clinical outcomes of the two groups are summarized in Table 3. Patients with *PSA* infections exhibited lower diastolic blood pressures (73.44 ± 10.57 mmHg vs 78.86 ± 11.37 mmHg, $P = 0.0142$), lower HbA1c levels (8.156 ± 2.610% vs 9.104 ± 2.649%, $P = 0.0366$), lower pulse rates (82 ± 12.05 bpm vs 87.89 ± 12.52 bpm, $P = 0.0458$) and higher prevalence of myocardial infarction (18.52% vs 2.21%, $P = 0.0015$) compared to non-PSA patients. No significant differences were observed in age, amputation, CCI (their corresponding indicators were provided in the Supplementary Table 2), course of diabetes, gangrene, gender, hospitalization days, IDSA Severity > 3, previous hospitalization, previous use of antibacterial drugs or other variables between the groups.

Risk Factors Associated with PSA Infections in DFUs

Univariate analysis comparing patients with and without *PSA* infections indicated significant associations with variables such as cholesterol levels (OR = 0.70, 95% CI: 0.48–1.02, $P = 0.0425$), diastolic blood pressure (OR = 0.96, 95% CI: 0.92–0.99, $P = 0.0149$), estimated glomerular filtration rate (OR = 0.99, 95% CI: 0.98–1.00, $P = 0.0432$), pulse rate (OR = 0.96, 95% CI: 0.93–0.99, $P = 0.0143$), ulcer surface area (OR = 0.98, 95% CI: 0.95–1.00, $P = 0.0229$), and myocardial infarction (OR = 10.06,

Table 3 Comparison of Clinical and Laboratory Parameters Between PSA and Non-PSA Groups

	Non-*PSA* (n = 317)	*PSA* (n = 27)	*P* Values*
Age (years)	64.77 ± 11.92	69.07 ± 12.17	0.1139
Amputation (Yes, %)	14 (4.42%)	3 (11.11%)	0.1396
CCI	5.96 ± 1.89	6.63 ± 1.96	0.0947
Cholesterol (mmol/L)	4.24 ± 1.48	3.72 ± 1.07	0.1084
Course of Diabetes (years)	11.42 ± 7.00	12.45 ± 7.37	0.4236
Course of Diabetes > 10 years (Yes, %)	186 (58.68%)	17 (62.96%)	0.6895
Creatinine (umol/L)	186.20 ± 266.60	173.10 ± 220.20	0.8038
Diastolic pressure (mmHg)	78.86 ± 11.37	73.44 ± 10.57	0.0142*
Estimated glomerular filtration rate (mL/min)	69.88 ± 41.76	54.26 ± 26.35	0.0551
Fasting blood glucose (mmol/L)	9.74 ± 4.88	9.37 ± 5.67	0.3034
Gangrene (Yes, %)	123 (38.80%)	12 (44.44%)	0.6822
Gender (male, %)	195 (61.51%)	16 (59.26%)	0.8389
HbA1c (%)	9.10 ± 2.65	8.16 ± 2.61	0.0366*
Hemoglobin concentration (g/L)	108.00 ± 22.82	105.20 ± 21.92	0.5724
Hs-CRP (mg/L)	55.90 ± 71.89	42.63 ± 45.89	0.3466
Hospitalization days (days)	20.01 ± 14.11	20.00 ± 14.44	0.9983
ICU hospitalization days (days)	0.07 ± 0.78	0 (0%)	>0.9999
IDSA Severity > 3 (Yes, %)	125 (39.43%)	10 (37.04%)	0.8412
Osteomyelitis (Yes, %)	80 (25.24%)	8 (29.63%)	0.6453
Osteoporosis (Yes, %)	34 (10.73%)	2 (7.41%)	0.755
Previous hospitalization (Yes, %)	171 (53.94%)	16 (59.26%)	0.5562
Previous MRSA infection (Yes, %)	3 (0.95%)	0 (0%)	0.621
Previous use of antibacterial drugs (Yes, %)	95 (29.97%)	11 (40.74%)	0.3924
Procalcitonin (ng/mL)	0.43 ± 1.54	0.22 ± 0.33	0.4872
Pulse (bpm)	87.89 ± 12.52	82.00 ± 12.05	0.0458*
Respiration (bpm)	18.04 ± 1.28	18.00 ± 1.11	0.8753
Smoke (Yes, %)	80 (25.24%)	7 (25.93%)	>0.9999
Systolic pressure (mmHg)	137.40 ± 20.14	129.70 ± 20.82	0.0641
Temperature (°C)	36.66 ± 0.48	36.55 ± 0.29	0.2286
Triglyceride (mmol/L)	1.43 ± 0.79	1.45 ± 1.04	0.8946
Types of antibacterial drugs (≥2, %)	28 (12.12%)	15 (13.27%)	0.7624
Ulcer surface area (cm^2)	21.24 ± 30.53	9.58 ± 17.89	0.0514
White blood cell count ($\times 10^9$/L)	10.50 ± 5.28	9.95 ± 5.81	0.6045

Note: *Indicates statistically significant data.

95% CI: 2.95–34.31, $P = 0.0009$), without statistical significance for Amputation, IDSA Severity > 3, CCI (their corresponding indicators were provided in the Supplementary Table 3) and Renal disease, as detailed in Table 4.

Multivariate logistic regression analysis confirmed that myocardial infarction (OR = 23.34, 95% CI: 3.58–152.31, $P = 0.001$) and peripheral vascular disease (OR = 0.12, 95% CI: 0.02–0.88, $P = 0.0365$) were identified as significant risk factors for *PSA* infections, as detailed in Table 4.

Comparison of Clinical Characteristics Between MRSA and Non-MRSA Groups and Risk Factors Analysis in DFUs

About 325 patients in the non-*MRSA* group and 19 patients in the *MRSA* group were included in this study. The baseline characteristics and clinical outcomes of the two groups are summarized in Supplementary Table 4. No significant between-group differences were observed for any variable, possibly because the low number of *MRSA*-infected patients reduced statistical power. Univariate analysis comparing patients with and without *MRSA* infections indicated significant associations with variables such as Temperature (OR = 0.21, 95% CI: 0.04–1.26, $P = 0.0444$), and connective tissue

Table 4 Univariate and Multivariate Analysis of Risk Factors for PSA Infections

	Univariate OR	95% CI	B	*P Value**	Multivariate OR	(95% CI)	B	*P Value**
Age	1.03	1.00 to 1.07	0.03	0.0712	1.04	0.99 to 1.10	0.04	0.1404
Amputation = 1	2.71	0.73 to 10.07	1.00	0.1757				
CCI	1.21	0.99 to 1.47	0.19	0.0661	0.75	0.50 to 1.13	−0.29	0.1692
Cholesterol	0.70	0.48 to 1.02	−0.36	0.0425*	0.66	0.42 to 1.05	−0.41	0.0781
Course of Diabetes	1.02	0.97 to 1.08	0.02	0.4848				
Course of Diabetes > 10 years = 1	1.20	0.53 to 2.70	0.18	0.662				
Creatinine	1.00	1.00 to 1.00	0.00	0.8442				
Diastolic pressure	0.96	0.92 to 0.99	−0.05	0.0149*	0.99	0.94 to 1.05	−0.01	0.8242
Estimated glomerular filtration rate	0.99	0.98 to 1.00	−0.01	0.0432*	0.99	0.97 to 1.00	−0.01	0.1288
Fasting blood glucose	0.98	0.90 to 1.07	−0.02	0.6491				
Gangrene = 1	1.26	0.57 to 2.79	0.23	0.5667				
Gender = 1	0.91	0.41 to 2.03	−0.09	0.8179				
HbA1c	0.85	0.71 to 1.01	−0.16	0.0501	0.98	0.79 to 1.20	−0.02	0.822
Hemoglobin concentration	0.99	0.98 to 1.01	−0.01	0.4897				
Hs-CRP	1.00	0.99 to 1.00	0.00	0.3587				
Hospitalization days	1.00	0.97 to 1.03	0.00	0.9697				
IDSA Severity > 3 = 1	0.90	0.40 to 2.04	−0.10	0.8061				
Osteomyelitis = 1	1.25	0.53 to 2.96	0.22	0.6207				
Osteoporosis = 1	0.67	0.15 to 2.94	−0.41	0.5719				
Previous hospitalization = 1	1.24	0.56 to 2.76	0.22	0.5932				
Previous use of antibacterial drugs = 1	1.61	0.72 to 3.59	0.47	0.2552				
Procalcitonin	0.62	0.21 to 1.78	−0.48	0.2386				
Pulse	0.96	0.93 to 0.99	−0.04	0.0143*	0.98	0.94 to 1.01	−0.02	0.2021
Respiration	1.00	0.72 to 1.38	0.00	0.9794				
Smoke = 1	1.04	0.42 to 2.54	0.04	0.9371				
Systolic pressure	0.98	0.96 to 1.00	−0.02	0.0553	0.97	0.95 to 1.00	−0.03	0.0743
Temperature	0.49	0.15 to 1.60	−0.70	0.1894				
Triglyceride	1.04	0.65 to 1.65	0.04	0.8808				
Types of antibacterial drugs = 1	1.67	0.60 to 4.67	0.51	0.3504				
Ulcer surface area	0.98	0.95 to 1.00	−0.02	0.0229*	0.97	0.94 to 1.00	−0.03	0.0622
White blood cell count	0.98	0.91 to 1.06	−0.02	0.6334				
With Myocardial infarction = 1	10.06	2.95 to 34.31	2.31	0.0009*	23.34	3.58 to 152.31	3.15	0.001*
With Peripheral vascular disease = 1	0.20	0.04 to 1.09	−1.61	0.0998	0.12	0.02 to 0.88	−2.12	0.0365*

Note: *Indicates statistically significant data.

disease (OR = 3150000000, $P = 0.0156$), without statistical significance for Amputation, Previous *MRSA* infection and Osteomyelitis. Multivariate logistic regression analysis confirmed no variables were identified as significant risk factors for *MRSA* infections (detailed in Supplementary Table 5).

External Validation of the MDRB Infection Prediction Model of Yi-Ni Ma et al in 2021 in Diabetic Foot

To assess the disparities between our collected clinical data and the predictive model for MDRB infections in DFUs proposed by Yi-ni Ma et al in 2021, we conducted a comparative analysis.

In our dataset, the proportion of patients using two or more types of antibacterial drugs was significantly lower than that reported in the model data (Figure 1a). Similarly, the proportion of patients with a history of previous antibacterial drug use was also reduced in our cohort. Moreover, fewer patients in our cohort had a disease duration of less than 10 years than in the reference study, whereas the prevalence of osteoporosis did not differ between the two groups. Despite these differences, the general trends in variable distributions remained consistent between the two datasets. Regarding

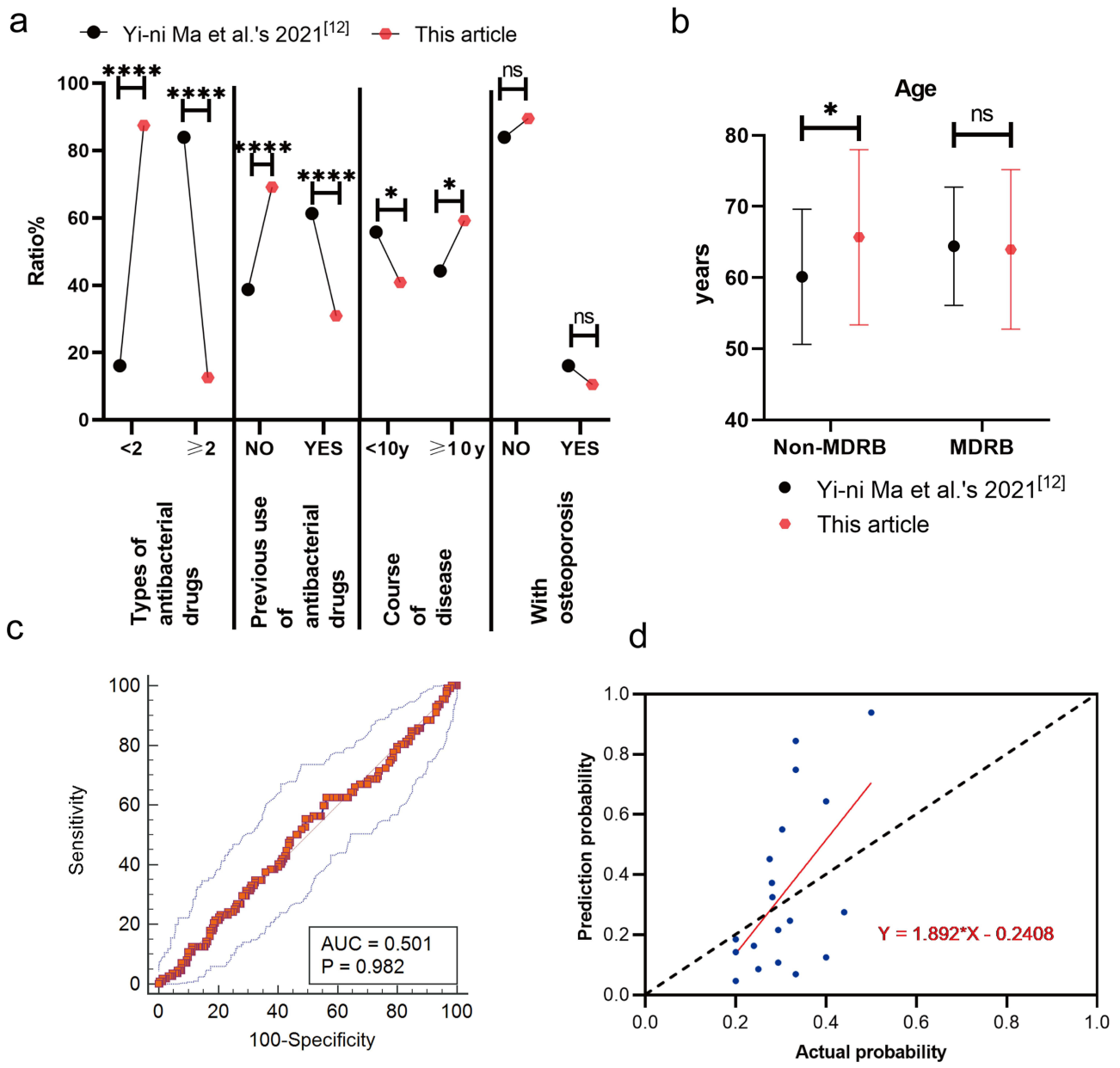

Figure 1 External validation results of the MDRB infection prediction model in DFU. (**a**) Comparison of key clinical variables between the dataset from Yi-ni Ma et al (2021) and our independent dataset. The proportion of patients using ≥2 types of antibacterial drugs, previous antibacterial drug use, and disease duration <10 years were significantly lower in our dataset, while no significant difference was found in the prevalence of osteoporosis. Statistical significance is indicated as ns: not significant, *$P < 0.05$, and ****$P < 0.0001$. (**b**) Comparison of patient age between Non-MDRB and MDRB groups in the two datasets. A significant difference was observed in the Non-MDRB group (*$P < 0.05$), while no significant difference was found in the MDRB group (ns: not significant). (**c**) ROC curve for the predictive model in our dataset. The AUC was 0.501, indicating poor discrimination performance. (**d**) Calibration curve assessing the agreement between predicted and actual probabilities of MDRB infection. The red line represents the fitted regression line, with the equation Y = 1.892X – 0.2408, showing a tendency for the model to underestimate the risk of MDRB infection in our dataset.

patient age, our analysis showed that non-MDRB patients in our dataset were significantly older than those reported by Yi-ni Ma et al, whereas no significant difference was observed in the MDRB group (Figure 1b).

To evaluate the external validity of the predictive model, we constructed a receiver operating characteristic (ROC) curve, which yielded an area under the curve (AUC) of 0.501, suggesting that the model had a poor predictive ability in our independent dataset (Figure 1c). Furthermore, calibration analysis revealed a systematic underestimation of MDRB infection risk, with the predicted probabilities deviating significantly from the actual observed probabilities (Figure 1d). The linear regression equation derived from the calibration curve demonstrated a weak correlation between predicted and actual values, further confirming the model's limited generalizability.

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External Validation of Predictive Models for PSA and MRSA Infections in DFUs

To evaluate the performance of the predictive models for *PSA* and *MRSA* infections in DFUs, we conducted external validation using our clinical data.

The proportion of patients with gangrene in our dataset was significantly lower than that reported in the original model data, while the proportion of patients with a history of amputation was significantly higher. In our dataset, the proportions of patients with an IDSA Severity > 3 or renal disease were also lower, though these differences did not reach statistical significance. Notably, all patients in our dataset had diabetes, which is a significant difference from the original model data where patients without diabetes were also included (Figure 2a).

The ROC curve analysis for the *PSA* model showed an AUC of 0.505, indicating limited ability to distinguish between patients with and without *PSA* infections in our dataset (Figure 2b). Additionally, the calibration curve revealed a linear relationship between predicted and actual probabilities, with the regression equation Y = 0.5488X+0.03734 (Figure 2c). The slope of the regression line being less than 1 suggests that the model slightly underestimated the actual probability of *PSA* infections.

The proportion of patients with a history of *MRSA* infection differed significantly between the two datasets, whereas the difference in osteomyelitis rates was not statistically significant (Figure 2d). The *MRSA* model exhibited an AUC of 0.569 (Figure 2e), reflecting poor discriminatory capacity in distinguishing *MRSA* cases from non-cases, only slightly better than random chance. The calibration curve, represented by the equation Y = 3.122X−0.1174 (Figure 2f), demonstrated that the model overestimated infection probability in low-risk patients and underestimated it in high-risk patients, with a regression line slope exceeding 1.

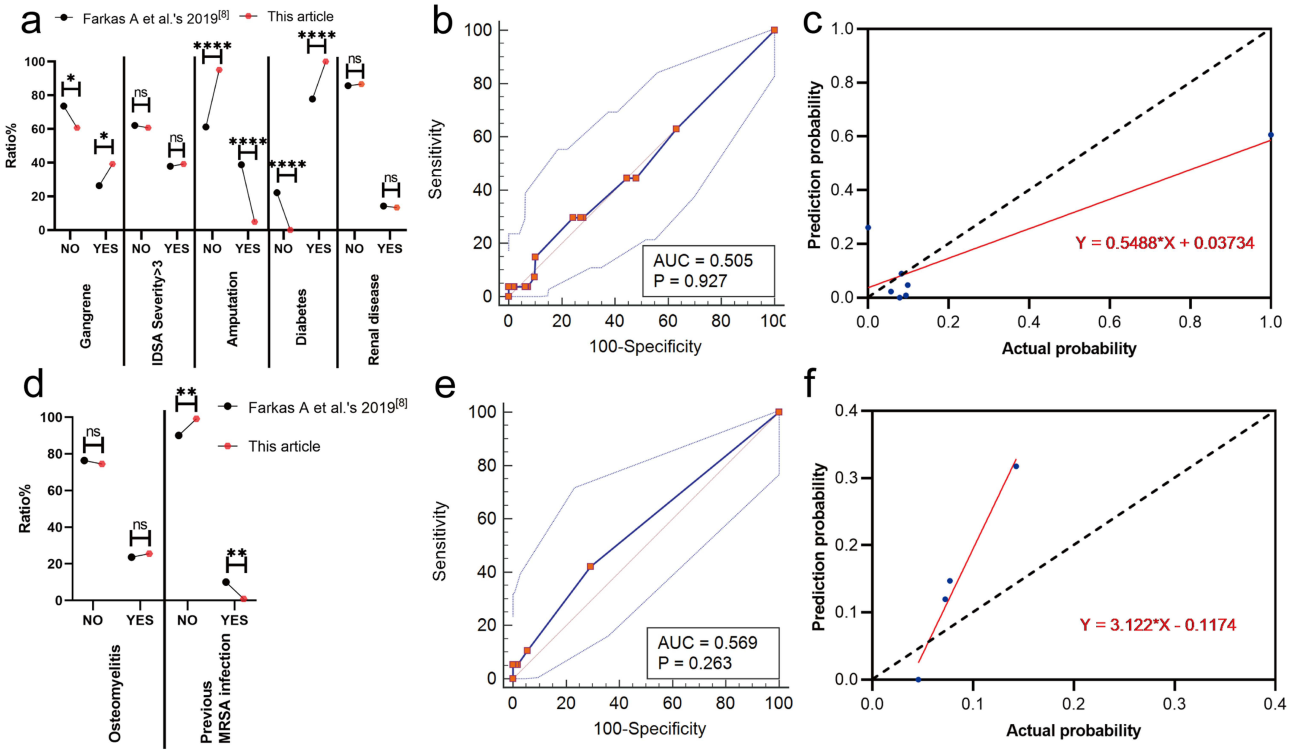

Figure 2 External validation of predictive models for *PSA* and *MRSA* infections in DFUs. (**a**) Comparison of key clinical variables between our dataset and the original model data. The proportion of patients with gangrene and with amputation differed significantly between the two datasets, whereas the differences in IDSA severity > 3 and renal disease were not statistically significant. Notably, all patients in our dataset had diabetes, whereas the original model included patients without diabetes. Statistical significance is indicated as ns: not significant, **P* < 0.05, and *****P* < 0.0001. (**b**) ROC curve for the *PSA* predictive model in our dataset. The AUC was 0.505, indicating poor discriminatory ability of the model in distinguishing patients with and without *PSA* infections. (**c**) Calibration curve for the *PSA* predictive model. The red line represents the fitted regression line with the equation Y = 0.5488X+0.03734, showing that the model slightly underestimated the actual probability of *PSA* infections in our dataset. (**d**) Comparison of key clinical variables between our dataset and the original model data. The proportion of patients with a history of MRSA infection differed significantly between the two datasets, whereas the difference in osteomyelitis rates was not statistically significant. Statistical significance is indicated as ns: not significant, and ***P* < 0.01. (**e**) ROC curve for the *MRSA* predictive model in our dataset. The AUC was 0.569, indicating limited discriminatory ability of the model in distinguishing patients with and without *MRSA* infections. (**f**) Calibration curve for the *MRSA* predictive model. The red line represents the fitted regression line with the equation Y = 3.122X−0.1174, showing that the model overestimated the probability of *MRSA* infections in low-risk cases and underestimated it in high-risk cases.

Antimicrobial Susceptibility of All Isolated Pathogens

In total, 113 non-duplicate isolates were recovered from 344 DFU episodes. Supplementary Table 6 summarises the species distribution: Gram-positive organisms predominated (62/113, 54.9%), with *Staphylococcus aureus* (34/113, 30.1%) the single most common pathogen, followed by *Staphylococcus haemolyticus* (8/113, 7.1%) and *Enterococcus faecalis* (5/113, 4.4%). Gram-negative bacteria accounted for 49/113 (43.4%) of isolates, led by *Proteus mirabilis* (20/113, 17.7%) and *Escherichia coli* (10/113, 8.8%); *Klebsiella pneumoniae, Proteus hauseri*, and *Klebsiella oxytoc*a were also frequently identified. *Candida parapsilosis* and *Candida tropicalis* were each isolated once.

Supplementary Table 7 lists the detailed resistance profiles for every organism. *MRSA* was detected in 19/34 (55.88%) *S. aureus* isolates, and vancomycin-resistant enterococci were not seen. Among Gram-negatives, ESBL production was confirmed in 7/10 (70%) *E. coli* and 2/4 (50%) *K. pneumoniae*. Resistance rates to commonly tested agents were: cefuroxime axetil 95% (19/20) in *P. mirabilis*, erythromycin 94% (32/34) in *S. aureus*, co-trimoxazole 75% (3/4) in *K. pneumoniae*, and levofloxacin 50% (2/4) in *K. oxytoca*. The carbapenems (imipenem, meropenem) retained full activity against all Enterobacterales tested, and tigecycline/colistin remained active against the single Acinetobacter baumannii isolate. These data provide a comprehensive overview of the antimicrobial resistance landscape in our DFU cohort beyond the *Pseudomonas aeruginosa* and *MRSA* subgroups.

Discussion

This study investigated the epidemiological characteristics and risk factors of MDRB infections among DFU patients, while also externally validating predictive models for MDRB, *PSA*, and *MRSA* infections. Our findings not only highlighted key clinical differences between infection groups but also revealed significant limitations in the predictive models when applied to our dataset, underscoring the need for further model refinement and the incorporation of additional risk factors to enhance clinical utility.

Our analysis demonstrated that patients with MDRB infections experienced considerably longer hospital stays, lower hemoglobin levels, higher hs-CRP levels, increased heart rates, reduced respiratory rates, and a higher prevalence of osteoporosis compared to patients without MDRB infections. Notably, prior antibacterial drug use was significantly lower in the MDRB group. Multivariate logistic regression confirmed that prolonged hospitalization, the presence of osteomyelitis, osteoporosis, prior antibacterial use, and respiratory rate were key risk factors for MDRB infection. While our findings regarding prolonged hospitalization and osteomyelitis align with previous research,[4,22] the observation of a lower respiratory rate in the MDRB group is a novel finding that may indicate its potential as a predictive factor, meriting further investigation in larger studies. These results suggest that MDRB infections are closely related to patients' overall health, inflammatory response, and past antibacterial use patterns. As demonstrated in the Italian teaching-hospital cohort,[25] active surveillance for MDRB colonization is therefore essential: it flags high-risk patients early, guides prompt isolation and decolonization, and provides local resistance data that curtail empirical broad-spectrum prescribing. By linking these surveillance results to our findings of heightened inflammatory markers, hospitals can implement targeted antimicrobial stewardship to prevent both clinical deterioration and further amplification of resistance.

In comparing *PSA* infection with non-*PSA* infection cases, we found that patients with *PSA* infection had lower diastolic blood pressure, HbA1c, and heart rates, along with a higher incidence of myocardial infarction. Multivariate analysis identified myocardial infarction and peripheral vascular disease as significant risk factors, suggesting that *PSA* infections are closely linked to underlying cardiovascular conditions. This relationship might be attributable to the virulence characteristics of *PSA* and its adaptation to the diabetic foot environment.[26] Additionally, although *PSA*-infected patients exhibited smaller ulcer areas, possibly reflecting a more localized invasive behavior, previous studies[26] have typically focused on *PSA*'s role in more widespread infections. A systematic review emphasizes that *P. aeruginosa* can exhibit localized invasion in early stages through flagella, the type III secretion system, alginate-based biofilms, and quorum sensing, while later progressing to widespread dissemination via efflux pumps and mature biofilms.[27] This discrepancy indicates that *PSA* infection may present varying clinical features depending on the stage of infection.

Regarding *MRSA* infection, most clinical characteristics did not differ significantly between *MRSA* and non-*MRSA* groups; however, univariate analysis revealed that body temperature and the presence of connective tissue disease were

significantly associated with *MRSA* infection. Despite these findings, no independent risk factors were identified in the multivariate analysis, suggesting a complex and heterogeneous nature of *MRSA* infections. A comprehensive review underscores that MRSA manifests as a highly heterogeneous pathogen capable of causing both localized skin/soft-tissue infections and life-threatening systemic disease, with its clinical presentation shaped by strain-specific virulence factors —such as PVL, TSST-1 and biofilm determinants—together with host immune status, thereby explaining why traditional risk-factor models often fail to identify consistent predictors.[28] However, our *MRSA* sample comprised only 19 patients, so the study was underpowered to detect clinically meaningful differences between *MRSA* and non-*MRSA* groups. This limitation may explain why, in contrast to earlier reports,[3] we did not observe a significant association between pre-*MRSA* infection and prior antibacterial use. We therefore explicitly acknowledge that the present findings require confirmation in larger cohorts and recommend either pooling data with additional centres or extending the study period to increase the number of *MRSA* cases.

The external validation of the MDRB, *PSA*, and *MRSA* predictive models, originally proposed by Farkas et al (2019) and Yi-ni Ma et al (2021), revealed limited performance in both discriminatory ability and calibration. Our clinical data yielded AUC values of 0.501, 0.505, and 0.569 for the respective models, indicating poor predictive accuracy. Significant differences in key variables such as gangrene, amputation, and diabetes between our dataset and the original model data likely contributed to these suboptimal results. Although there was some alignment between predicted and observed probabilities, the overall performance of the models was insufficient for reliable clinical application. This underscores the necessity for further refinement of these models or the integration of additional risk factors to enhance their generalizability across diverse patient populations.

Our findings should be interpreted in light of several limitations. First, this single-center retrospective study may be subject to selection bias and limited generalizability to other health-care settings. However, their regional scope still contributes valuable insights to the wider understanding of DFIs. Second, although multiple imputation was used only for non-core variables, the key predictors required by the validated models were >95% complete. Nevertheless, any remaining missing data inherent to the retrospective design could still have modestly affected the models' predictive performance in our cohort. Third, the *PSA* (n = 27) and *MRSA* (n = 19) subgroups were too small to achieve adequate statistical power, increasing the risk of false-negative associations. Finally, marked heterogeneity in patient characteristics between our cohort and the external validation datasets likely contributed to the observed poor model performance, further limiting the conclusions that can be drawn regarding broader applicability. Future research should involve multicenter collaborations and prospective designs to further validate and optimize these predictive models, thereby enhancing their predictive ability and clinical applicability.

Conclusion

MDRB infections in DFUs are linked to a distinct set of clinical characteristics and risk factors. In our cohort, however, existing predictive models showed limited utility, underscoring the need for refinement and the inclusion of additional variables. Future work should therefore pursue three complementary goals: (1) elucidating the molecular mechanisms that drive resistance, (2) developing novel broad-spectrum antibacterial agents, and (3) constructing personalized treatment strategies grounded in robust, multicenter datasets. By integrating these approaches, we can enhance both the accuracy of risk prediction and the clinical management of diabetic foot infections, ultimately improving patient outcomes.

Disclosure

The authors have no competing interests to declare that are relevant to the content of this article.

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