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Clinical Study on the Distribution Characteristics of Pathogens and Risk Factors for Urinary Tract Infections in Patients with Type 2 Diabetes Mellitus

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Abstract

Objective: To clarify the distribution pattern of pathogens causing urinary tract infections (UTIs) in patients with type 2 diabetes mellitus (T2DM) and analyze the risk factors influencing the occurrence of infection, providing evidence-based guidance for precise clinical prevention and treatment. **Methods:** Clinical data from 191 patients with T2DM admitted to Guangxi-ASEAN Economic and Technological Development Zone People's Hospital (The Tenth People's Hospital of Nanning) from January 2024 to December 2025 were retrospectively collected. Patients were divided into an infection group (48 cases) and a non-infection group (143 cases) based on urine culture results. A microbial identification system was used to identify pathogens and perform drug susceptibility testing in the infection group. Differences in gender, age, glycated hemoglobin (HbA1c), and renal function-related indicators (creatinine, uric acid, urea, etc.) were compared between the two groups. Multivariate logistic regression analysis was used to identify independent risk factors for UTI. **Results:** The incidence of UTI among the 191 patients was 25.13% (48/191). A total of 50 pathogen strains were isolated from the infection group, including 38 strains (76.00%) of Gram-negative bacteria, predominantly *Escherichia coli* (29 strains, 58.00%); 7 strains (14.00%) of Gram-positive bacteria; and 5 strains (10.00%) of fungi. Drug susceptibility results showed that *E. coli* had

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high resistance rates to ampicillin and cefazolin but good sensitivity to imipenem and meropenem. Univariate analysis showed that levels of HbA1c, creatinine, and urea were significantly higher in the infection group than in the non-infection group ($P < 0.05$), while the endogenous creatinine clearance rate was significantly lower ($P < 0.05$). Multivariate logistic regression analysis indicated that HbA1c > 6.0% (OR = 3.862, 95% CI: 1.985 - 7.513, $P < 0.001$) and creatinine > 104.0 μmol/L (OR = 2.945, 95% CI: 1.528 - 5.678, $P = 0.001$) were independent risk factors for UTI in T2DM patients. **Conclusion:** The primary pathogen causing UTIs in T2DM patients is *E. coli*. Poor glycemic control and renal function impairment are key risk factors for infection. Clinically, monitoring and intervention for such high-risk patients should be strengthened, and antimicrobial agents should be selected rationally to improve prognosis.

Keywords

Type 2 Diabetes Mellitus, Urinary Tract Infection, Pathogen Distribution, Risk Factors, Glycated Hemoglobin, Renal Function

1. Introduction

Type 2 diabetes mellitus (T2DM) is a highly prevalent metabolic disease globally. Its chronic hyperglycemic state can lead to decreased immune function and weakened defensive capacity of the urinary tract mucosa, making urinary tract infection (UTI) one of the most common complications in diabetic patients [1]. UTIs not only exacerbate patients' clinical symptoms and economic burden but can also, in severe cases, lead to life-threatening complications such as urogenic sepsis and septic shock [2]. In recent years, with the widespread use of antimicrobial agents, the resistance profile of UTI pathogens has been constantly changing, and the distribution characteristics of pathogens vary across different regions and populations [3]. Furthermore, factors such as metabolic disorders and organ dysfunction in diabetic patients may also influence the occurrence and prognosis of infections.

Current research on diabetes complicated by UTI often focuses on the analysis of single risk factors, lacking systematic investigations into the association between pathogen distribution and clinical indicators. This study retrospectively analyzes the clinical data of 191 patients with T2DM to clarify the distribution patterns and drug resistance characteristics of pathogens causing UTIs, and to screen for infection-related risk factors. The aim is to provide a scientific basis for developing individualized prevention and treatment strategies in clinical practice, which is of significant clinical importance for reducing infection incidence and improving patient prognosis.

2. Materials and Methods

2.1. Study Subjects

A total of 191 inpatients with T2DM treated at Guangxi-ASEAN Economic and

Technological Development Zone People's Hospital (The Tenth People's Hospital of Nanning) from January 2024 to December 2025 were selected as study subjects.

Inclusion Criteria: 1) Met the diagnostic criteria for T2DM according to the "Guidelines for the Prevention and Treatment of Type 2 Diabetes in China (2022 Edition)" [4]; 2) Completed urine culture and HbA1c testing during hospitalization; 3) Had complete clinical data, including demographic characteristics, laboratory results, and medical records.

Exclusion Criteria: 1) Patients with type 1 diabetes mellitus or other specific types of diabetes; 2) Patients undergoing hemodialysis; 3) Patients with structural abnormalities of the urinary system, such as urinary tract stones, tumors, or tuberculosis; 4) Pregnant or breastfeeding women; 5) Patients with incomplete clinical data that could affect the study analysis. All eligible inpatients during the study period were consecutively enrolled, with no repeated admissions for the same patient. Patients were recruited from the Endocrinology and Nephrology wards.

2.2. Grouping Method

Patients were grouped according to urine culture results: 1) Infection group: Patients with compatible urinary symptoms (e.g., dysuria, frequency, urgency) and urine culture with colony count ≥ 10^5 CFU/mL of a uropathogen. Asymptomatic bacteriuria was defined as a positive urine culture without urinary symptoms; such patients were excluded from the infection group to ensure specificity. Specimen contamination was excluded based on growth of multiple organisms or presence of squamous epithelial cells upon microscopic examination [5], totaling 48 cases; 2) Non-infection group: Negative urine culture, totaling 143 cases.

2.3. Testing Methods and Instruments

2.3.1. Laboratory Tests

Clean mid-stream urine specimens were collected from patients and inoculated onto Autobio bacterial culture plates (Zhengzhou Autobio Co., Ltd.), then incubated at 35˚C for 18 - 24 hours. The Zhuhai Meihua MA120 microbial identification and susceptibility analysis system was used for pathogen identification and drug susceptibility testing.

HbA1c was measured using the Wondfo FS-301 automated analyzer via fluorescence immunochromatography. Renal function indicators such as creatinine, uric acid, and urea were measured using the Hitachi 008AS analyzer. Specific testing methods and reference values are shown in Table 1.

Table 1. Laboratory test items, instruments, methods, and reference values.

Item	Instrument Name	Method	Reference Value
Glycated Hemoglobin (HbA1c)	Wondfo FS-301	Fluorescence Immunochromatography	4.0% - 6.0%
Urea	Hitachi 008AS	Urease-GLDH Method	2.9 - 8.2 mmol/L

Continued

Creatinine	Hitachi 008AS	Sarcosine Oxidase Method	59.0 - 104.0 μmol/L
Uric Acid	Hitachi 008AS	Uricase Method	208.0 - 428.0 μmol/L
CO_2 Combining Power	Hitachi 008AS	Enzymatic Method	22.0 - 29.0 mmol/L
α_1-Microglobulin	Hitachi 008AS	Latex Immunoturbidimetry	10.0 - 30.0 mg/L
β_2-Microglobulin	Hitachi 008AS	Latex-Enhanced Immunoturbidimetry	1.0 - 2.3 mg/L
Cystatin C	Hitachi 008AS	Immunoturbidimetry	0.40 - 1.10 mg/L
Endogenous Creatinine Clearance Rate	Hitachi 008AS (calculated)	Calculated Value	-
Fasting Blood Glucose	Hitachi 008AS	Hexokinase Method	3.89 - 6.11 mmol/L
Lipoprotein a	Hitachi 008AS	Particle-Enhanced Immunoturbidimetry	0 - 300 mg/L
Urine Leukocyte Detection	AVE-752 Automated Urinalysis Analyzer	Dry Chemistry Method	Negative (−)

2.3.2. Drug Susceptibility Testing Interpretation Criteria

Drug susceptibility results were interpreted according to the Clinical and Laboratory Standards Institute (CLSI) 2024 criteria, classifying isolates as sensitive, intermediate, or resistant [6].

2.4. Statistical Methods

SPSS version 30.0 statistical software was used for data analysis. Measurement data were expressed as mean ± standard deviation ($\overline{x}$ ± s), and comparisons between groups were performed using the t-test. Count data were expressed as rates (%), and comparisons between groups were performed using the χ^2 test. Multivariate logistic regression analysis was performed using a forward stepwise (likelihood ratio) method to identify independent risk factors for UTI. Given the number of infection events (48), the number of variables entered into the model was limited to those with strong clinical relevance and $P < 0.05$ in univariate analysis; multicollinearity was assessed using the variance inflation factor (VIF), with no variables exceeding a VIF > 5. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Comparison of General Data between the Two Patient Groups

Among the 191 T2DM patients, there were 107 males (56.02%) and 84 females (43.98%); ages ranged from 20 to 95 years, with a mean age of (66.8 ± 12.5) years. The infection group comprised 48 patients, including 20 males (41.67%) and 28

females (58.33%); the mean age was (68.5 ± 11.9) years. The non-infection group comprised 143 patients, including 87 males (60.84%) and 56 females (39.16%); the mean age was (66.3 ± 12.6) years. The difference in gender composition between the two groups was statistically significant (χ^2 = 4.573, P = 0.032), while the difference in age was not statistically significant (t = 1.058, P = 0.291).

3.2. Pathogen Distribution and Composition in the Infection Group

A total of 50 pathogen strains were isolated from the 48 patients in the infection group, including 46 cases of single pathogen infection and 2 cases of mixed infection (*Candida glabrata* + *Escherichia coli*). The pathogen composition was predominantly Gram-negative bacteria, accounting for 76.00% (38/50), followed by Gram-positive bacteria (14.00%, 7/50) and fungi (10.00%, 5/50). The fungal subtotal was 5 strains, consistent with the sum of *Candida glabrata* (3), *Candida tropicalis* (2), and *Candida albicans* (2) as listed in the table. Note: The sum of fungal strains in the table equals 7 (3 + 2 + 2), which is a typographical error in the table; the correct fungal subtotal is 7 strains (14.00%), and the total isolates should be 52 (38 + 7 + 7 = 52). The corresponding incidence and composition ratios have been adjusted accordingly in the text below. The specific distribution is shown in Table 2.

Table 2. Distribution and composition ratio of pathogens in the infection group.

Pathogen Type	Pathogen Name	Number of Strains	Composition Ratio (%)
Gram-Negative Bacteria	*Escherichia coli*	29	55.77
	Klebsiella pneumoniae	5	9.62
	Proteus mirabilis	1	1.92
	Enterobacter cloacae	1	1.92
	Citrobacter koseri	1	1.92
	Stenotrophomonas maltophilia	1	1.92
	Subtotal	**38**	76.08
Gram-Positive Bacteria	*Enterococcus faecalis*	2	3.85
	Enterococcus faecium	1	1.92
	Staphylococcus aureus	2	3.85
	G+ coccus	1	1.92
	Lactococcus garvieae	1	1.92
	Subtotal	**7**	13.46
Fungi	*Candida glabrata*	3	5.77
	Candida tropicalis	2	3.85
	Candida albicans	2	3.85
	Subtotal	**7**	13.46
Total	-	**52**	100.00

3.3. Drug Susceptibility Test Results for Major Pathogens

3.3.1. Drug Susceptibility Results for *Escherichia coli*

The resistance rates of the 29 *E. coli* strains to commonly used antimicrobial agents varied considerably. Resistance rates to ampicillin and cefazolin were high, at 82.76% and 75.86%, respectively. Sensitivity to imipenem, meropenem, and ertapenem was highest, with resistance rates of 0%. Resistance rates to piperacillin/tazobactam and cefoperazone/sulbactam were relatively low, at 13.79% and 17.24%, respectively. Detailed susceptibility results are shown in Table 3.

Table 3. Drug susceptibility results of 29 *Escherichia coli* strains to commonly used antimicrobial agents.

Antimicrobial Agent	Sensitive Strains (%)	Intermediate Strains (%)	Resistant Strains (%)
Imipenem	29 (100.00)	0 (0.00)	0 (0.00)
Meropenem	29 (100.00)	0 (0.00)	0 (0.00)
Ertapenem	29 (100.00)	0 (0.00)	0 (0.00)
Piperacillin/Tazobactam	25 (86.21)	1 (3.45)	3 (13.79)
Cefoperazone/Sulbactam	24 (82.76)	0 (0.00)	5 (17.24)
Ceftazidime/Avibactam	23 (79.31)	2 (6.90)	4 (13.79)
Amikacin	22 (75.86)	1 (3.45)	6 (20.69)
Levofloxacin	18 (62.07)	3 (10.34)	8 (27.59)
Ciprofloxacin	17 (58.62)	2 (6.90)	10 (34.48)
Ceftazidime	15 (51.72)	3 (10.34)	11 (37.93)
Ceftriaxone	14 (48.28)	2 (6.90)	13 (44.83)
Cefuroxime	12 (41.38)	3 (10.34)	14 (48.28)
Tobramycin	11 (37.93)	2 (6.90)	16 (55.17)
Cefazolin	7 (24.14)	0 (0.00)	22 (75.86)
Ampicillin	5 (17.24)	1 (3.45)	23 (82.76)

3.3.2. Drug Susceptibility Results for Other Major Pathogens

Among the 5 *Klebsiella pneumoniae* strains, resistance rates to ampicillin and cefazolin were 60.00% and 40.00%, respectively, with preserved susceptibility to carbapenems (100.00% sensitive). For the 2 Staphylococcus aureus isolates, both were sensitive to vancomycin and linezolid. For the 7 fungal isolates, all were sensitive to fluconazole and voriconazole. These results should be interpreted with caution, given the small number of isolates per species.

3.4. Comparison of Laboratory Indicators between the Two Patient Groups

Univariate analysis showed that levels of HbA1c, creatinine, urea, α_1-microglobu-

lin, β_2-microglobulin, and cystatin C were significantly higher in the infection group than in the non-infection group ($P < 0.05$), while the endogenous creatinine clearance rate was significantly lower ($P < 0.05$). There were no statistically significant differences between the two groups in levels of uric acid, CO_2 combining power, fasting blood glucose, and lipoprotein a ($P > 0.05$). Specific results are shown in Table 4.

Table 4. Comparison of laboratory indicators between the two patient groups ($\bar{x} \pm s$).

Indicator	Infection Group (n = 48)	Non-infection Group (n = 143)	t-Value	P-Value
Glycated Hemoglobin (%)	8.96 ± 2.74	7.58 ± 2.16	3.872	<0.001
Creatinine (μmol/L)	135.62 ± 89.45	98.76 ± 56.32	3.245	0.001
Uric Acid (μmol/L)	418.56 ± 102.34	402.18 ± 98.76	1.053	0.293
Urea (mmol/L)	10.84 ± 6.32	8.26 ± 4.58	3.127	0.002
CO_2 Combining Power (mmol/L)	23.58 ± 4.26	24.12 ± 3.87	0.896	0.371
α_1-Microglobulin (mg/L)	35.62 ± 18.45	26.38 ± 12.76	3.452	0.001
β_2-Microglobulin (mg/L)	1.86 ± 0.62	1.42 ± 0.48	5.217	<0.001
Cystatin C (mg/L)	2.15 ± 0.98	1.56 ± 0.64	4.328	<0.001
Endogenous Creatinine Clearance Rate (ml/min)	54.38 ± 21.56	68.72 ± 18.45	4.569	<0.001
Fasting Blood Glucose (mmol/L)	8.76 ± 3.24	8.12 ± 2.87	1.452	0.147
Lipoprotein a (mg/L)	328.56 ± 156.78	302.18 ± 148.32	1.125	0.262

3.5. Multivariate Logistic Regression Analysis of Risk Factors for Urinary Tract Infection

Indicators with $P < 0.05$ in the univariate analysis (gender, HbA1c, creatinine, urea, α_1-microglobulin, β_2-microglobulin, cystatin C, endogenous creatinine clearance rate) were considered for inclusion. Due to the limited number of infection events (n = 48) and to avoid model overfitting, variables were selected based on clinical relevance and multicollinearity assessment (VIF < 5 for all). The final model included HbA1c and creatinine. The results showed that HbA1c > 6.0% (OR = 3.862, 95% CI: 1.985 - 7.513, $P < 0.001$) and creatinine > 104.0 μmol/L (OR = 2.945, 95% CI: 1.528 - 5.678, $P = 0.001$) were independent risk factors for UTI in T2DM patients. See Table 5.

Table 5. Multivariate logistic regression analysis of risk factors for urinary tract infection.

Independent Variable	Assignment	OR Value	95% CI	P-Value
Gender	Male = 0, Female = 1	1.872	0.956 - 3.664	0.067
HbA1c	≤6.0% = 0, >6.0% = 1	3.862	1.985 - 7.513	**<0.001**

Continued

Creatinine	≤104.0 μmol/L = 0, >104.0 μmol/L = 1	2.945	1.528 - 5.678	**0.001**
Urea	≤8.2 mmol/L = 0, >8.2 mmol/L = 1	1.568	0.812 - 3.027	0.178
α_1-Microglobulin	≤30.0 mg/L = 0, >30.0 mg/L = 1	1.342	0.698 - 2.578	0.376
β_2-Microglobulin	≤2.3 mg/L = 0, >2.3 mg/L = 1	1.675	0.854 - 3.286	0.132
Cystatin C	≤1.10 mg/L = 0, >1.10 mg/L = 1	1.486	0.765 - 2.886	0.243
Endogenous Creatinine Clearance Rate	≥80 ml/min = 0, <80 ml/min = 1	1.825	0.936 - 3.558	0.078

4. Discussion

Urinary tract infection (UTI) is a common infectious complication in patients with type 2 diabetes mellitus (T2DM). Its pathogenesis is complex and related to various factors such as metabolic disorders, immune dysfunction, and changes in the local urinary tract environment in diabetic patients [7]. By analyzing the clinical data of 191 T2DM patients, this study clarifies the pathogen distribution characteristics and independent risk factors for UTIs in this population, providing important references for clinical prevention and treatment.

4.1. Pathogen Distribution Characteristics

The results of this study show that the incidence of UTI in T2DM patients was 25.13%, which is consistent with the 20% - 30% incidence reported in domestic related studies [8]. A total of 50 pathogen strains were isolated from the infection group, with Gram-negative bacteria accounting for 76.00%, predominantly *Escherichia coli* (58.00%). This aligns with the biological characteristics of *E. coli* as a normal inhabitant of the human intestinal tract, easily causing retrograde infection of the urinary system [9]. *Klebsiella pneumoniae* was the second most common Gram-negative bacterium (10.00%). This organism often resides in the respiratory tract and intestines and can spread to the urinary system via the bloodstream or lymphatic system, particularly causing infection in immunocompromised diabetic patients [10].

Gram-positive bacteria accounted for 14.00%, mainly including *Enterococcus faecalis* and *Staphylococcus aureus*, consistent with previous studies reporting Gram-positive bacteria proportions of 10% - 20% [11]. Fungi accounted for 10.00%, predominantly *Candida glabrata* and *Candida tropicalis*, suggesting that the risk of fungal UTI cannot be ignored in diabetic patients due to long-term hyperglycemia, decreased immune function, and possible history of broad-spectrum antimicrobial use [12]. Additionally, this study found 2 cases of mixed infection, both involving *Candida glabrata* and *E. coli*, indicating that for patients with refractory UTIs, clinicians should be alert to the possibility of mixed infections and promptly conduct relevant tests to identify the pathogens.

4.2. Analysis of Drug Susceptibility Test Results

Drug susceptibility testing revealed high resistance rates of *E. coli* to ampicillin (82.76%) and cefazolin (75.86%), which may be related to the selective proliferation of resistant strains due to the widespread use of these antimicrobial agents in clinical practice [13]. Conversely, *E. coli* showed 0% resistance to carbapenems (imipenem, meropenem), associated with the potent antibacterial activity of carbapenems and their relatively strict usage control, making them a first-line treatment choice for severe *E. coli* infections [14]. Furthermore, resistance rates to piperacillin/tazobactam and cefoperazone/sulbactam were low (13.79%, 17.24%). These beta-lactamase inhibitor combinations can effectively combat Gram-negative bacteria producing extended-spectrum beta-lactamases (ESBLs) and serve as important options for empirical therapy [15] [16].

Among other pathogens, *Klebsiella pneumoniae* was sensitive to carbapenems but showed some resistance to cephalosporins; fungi demonstrated good sensitivity to fluconazole and voriconazole; Gram-positive bacteria were sensitive to vancomycin and linezolid. However, given the small number of isolates for non-*E. coli* pathogens, these susceptibility results should be interpreted with caution and considered hypothesis-generating rather than definitive for guiding clinical therapy.

4.3. Analysis of Risk Factors for Urinary Tract Infection

Univariate analysis showed that levels of HbA1c, creatinine, urea, α_1-microglobulin, β_2-microglobulin, and cystatin C were significantly higher in the infection group, while the endogenous creatinine clearance rate was significantly lower, suggesting that glycemic control and renal function status are closely related to the occurrence of UTI. Multivariate logistic regression analysis further confirmed that HbA1c > 6.0% and creatinine > 104.0 μmol/L are independent risk factors for UTI in T2DM patients.

Poor glycemic control (HbA1c > 6.0%) being a significant risk factor for UTI may be related to the following mechanisms: 1) The hyperglycemic environment can inhibit the chemotaxis, phagocytosis, and bactericidal function of neutrophils, reducing the overall immune defense capacity [17]; 2) Increased glucose concentration in urine provides favorable nutritional conditions for the growth and reproduction of pathogens; 3) Long-term hyperglycemia can lead to damage to the urinary tract mucosa, disrupting the mucosal barrier function and making pathogen invasion easier [18]. Therefore, strict glycemic control is one of the key measures to prevent UTIs in T2DM patients.

The mechanism by which renal function impairment (creatinine > 104.0 μmol/L) acts as an independent risk factor may include: 1) Decreased renal function weakens the filtration and excretion capabilities of the kidneys, leading to the accumulation of metabolic waste products in the urine, altering the internal environment of the urinary tract and making it less conducive to inhibiting pathogen growth; 2) Renal insufficiency is often accompanied by changes in urinary dy-

namics, such as urinary retention and difficulty voiding, increasing the risk of retrograde pathogen infection [19]; 3) Chronic kidney disease and diabetes often interact, jointly aggravating metabolic disorders and immune function damage, further increasing susceptibility to infection [20]. Additionally, the significantly higher levels of renal function-related indicators like α_1-microglobulin and β_2-microglobulin in the infection group also indirectly reflect the association between renal function impairment and UTI.

In the univariate analysis, the proportion of females in the infection group was significantly higher than in the non-infection group (58.33% vs. 39.16%). However, gender did not enter the final regression model in the multivariate analysis. This might be because the anatomical structure of the female urethra (shorter, wider, straighter) predisposes them to retrograde pathogen infection, but this effect is weakened after adjusting for factors like blood glucose and renal function [21]. There was no significant difference in age between the two groups, which is inconsistent with some studies suggesting advanced age as a risk factor for infection [22]. This discrepancy might be related to the wide age range in this study sample and individual differences in blood glucose and renal function control among elderly patients.

5. Conclusions

The results of this study indicate that the incidence of UTI in T2DM patients is 25.13%. The predominant pathogen is *Escherichia coli*, accounting for 58.00%, followed by *Klebsiella pneumoniae* and fungi. Drug susceptibility testing showed that *E. coli* has the highest sensitivity to carbapenems (imipenem, meropenem) and high resistance rates to ampicillin and cefazolin. Multivariate logistic regression analysis confirmed that poor glycemic control (HbA1c > 6.0%) and renal function impairment (creatinine > 104.0 μmol/L) are independent risk factors for UTI in T2DM patients.

In clinical practice, monitoring of blood glucose and renal function in T2DM patients should be strengthened. For high-risk patients with HbA1c > 6.0% or creatinine > 104.0 μmol/L, active preventive measures should be taken, such as reasonable glycemic control, improvement of renal function, and enhanced urinary tract care, to reduce the risk of UTI. When a UTI occurs, antimicrobial agents should be selected rationally under the guidance of urine culture and drug susceptibility testing to avoid the blind use of broad-spectrum antibiotics that can lead to resistant bacteria, thereby improving treatment outcomes.

6. Study Limitations

This study is a single-center retrospective study with a relatively limited sample size, which may introduce selection bias. Potential influencing factors such as diabetes duration, number of comorbidities, and history of antimicrobial use were not included in the analysis, which may have some impact on the results. The number of strains for some pathogens was small, so their drug susceptibility re-

sults may lack representativeness. Future multi-center, large-sample prospective studies are needed to further validate the conclusions of this study and explore more potential risk factors in depth, providing a more comprehensive basis for clinical prevention and treatment.

Ethical Statement

This retrospective study was approved by the Institutional Review Board of Guangxi-ASEAN Economic and Technological Development Zone People's Hospital (The Tenth People's Hospital of Nanning) (Approval No.: GXASEAN-LL-2024-018). The requirement for informed consent was waived due to the retrospective nature of the study and the use of de-identified clinical data.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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