Research Square

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Combined hemoglobin glycation index and RDW/LDL-C ratio predict severe sepsis and/or septic shock in diabetic patients with Enterobacteriaceae bloodstream infections

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Abstract

Objective

To investigate the predictive value of hemoglobin glycation index (HGI) and red cell distribution width/low-density lipoprotein cholesterol ratio (RDW/LDL-C) for progression to severe sepsis and/or septic shock following *Enterobacteriaceae* bloodstream infection in diabetic patients.

Methods

This retrospective study included 203 diabetic patients with concomitant *Enterobacteriaceae* bloodstream infections. Clinical data were collected, and the HGI and RDW/LDL-C were calculated. Patients were grouped into quartiles (Q1-Q4) based on combined indicator quartiles. Multivariate logistic regression analysis was performed to assess the association with severe infection risk, and predictive performance was evaluated using ROC curves.

Results

Patients in the severe group exhibited significantly higher HGI and RDW/LDL-C levels compared to the non-severe group (both $p < 0.05$). Multivariate analysis showed that after adjusting for source of infection (Model 1) and comorbidities (Model 2), with Q1 as the reference group, Q2 and Q4 were independent predictors of severe sepsis and/or septic shock, respectively. ROC curve analysis indicated that the combined HGI-RDW/LDL-C index had an area under the curve (AUC) of 0.760 (95% CI: 0.693–0.826) for predicting severe sepsis and/or septic shock. Furthermore, the proportion of *Klebsiella pneumoniae* infections and antibiotic resistance patterns exhibited specific distributions within the high combined index group.

Conclusion

The HGI-RDW/LDL-C composite index serves as an independent risk factor for progression to severe sepsis and/or septic shock following *Enterobacteriaceae* bloodstream infection in diabetic patients, demonstrating good predictive value.

Introduction

Patients with diabetes may have a higher risk of bloodstream infections, typically exhibiting poorer clinical outcomes, longer hospital stays, and a significantly increased risk of mortality [1, 2]. Diabetic patients experience impaired immune function, microcirculatory disorders, and reduced tissue repair capacity due to prolonged hyperglycemia. This puts patients particularly vulnerable to infections, leading to acute systemic infections that may advance to sepsis and multiple organ failure. Research

demonstrates that individuals with diabetes possess a 2 to 6-fold increased risk of acquiring bloodstream infections relative to non-diabetic individuals[3], and the mortality rate for severe sepsis ranges from approximately 10% to 40%[4, 5]. Research conducted by Hernando Gómez *et al.* demonstrated that hospitalized patients with type 2 diabetes and sepsis who are administered metformin experience decreased mortality rates within 90 days [6]. In recent years, the increasing prevalence of diabetes has rendered diabetic patients with concurrent bloodstream infections a significant focus and problem in clinical management.

Blood glucose control serves as a core indicator in diabetes management. HbA1c is a metabolic byproduct resulting from the attachment of glucose to hemoglobin in the body. It accurately reflects a diabetic patient's blood glucose control over the preceding 2 to 3 months [7]. The hemoglobin glycation index (HGI) is a novel metric proposed by Hempe *et al*. in 2002 to quantify variations in glycated hemoglobin levels among individual patients [8]. He *et al* analyzed the trajectory of the dynamic HGI and its impact on survival in patients with sepsis. Trajectory analysis indicated that patients in the rising trajectory group faced markedly higher death risks at both 28 days and 90 days compared to the stable group, whereas patients in the descending trajectory group demonstrated significantly lower mortality risks [9]. HGI was independently associated with the risk of sepsis-related encephalopathy and short-term prognosis, serving as a biomarker for prognostic risk stratification [10].

Red blood cell distribution width (RDW) reflects red blood cell volume heterogeneity. Elevated RDW was associated with acute or chronic heart failure, acute pancreatitis, sepsis, acute pulmonary embolism, and acute kidney injury [11]. Elevated RDW was independently associated with increased short-term and long-term all-cause mortality in patients with acute pancreatitis and sepsis [12]. Studies suggested that RDW-CV may serve as a simple and useful biomarker for detecting tubular injury in patients with type 2 diabetes [13]. Additionally, most diabetic patients exhibit dyslipidemia. Low-density lipoprotein cholesterol (LDL-C) is a lipoprotein that transports cholesterol. Studies indicated that LDL-C levels were closely associated with cardiovascular risk in diabetic patients [14]. Feng *et al.* demonstrated that among hospitalized patients with infections, lower measured LDL-C levels were significantly associated with increased risks of sepsis and ICU admission [15].

Currently, most relevant studies focus on comparing the epidemiology of bloodstream infections between diabetic and non-diabetic patients. However, in-depth exploration of the association between different metabolic levels and the prognosis of bloodstream infections caused by various pathogens in diabetic patients remains limited. Therefore, this study aims to systematically analyze the relationship between blood glucose, inflammation-metabolism level and the severity of clinical outcomes in diabetic patients following *Enterobacteriaceae* bloodstream infections. This analysis seeks to provide evidence-based support for optimizing glucose and lipid management strategies and improving clinical outcomes in diabetic patient population.

Materials and methods

Study population

This study enrolled 203 patients with type 2 diabetes diagnosed with *K. pneumoniae* or *E. coli* bloodstream infections admitted to Taizhou Hospital in Zhejiang Province from January 2023 to October 2025 through the departments of Emergency Medicine, Infectious Diseases, Endocrinology, and Critical Care Medicine. Inclusion Criteria: (1) Patients with diabetes must meet satisfy the diagnostic criteria specified in the Chinese Guidelines for the Prevention and Treatment of Type 2 Diabetes (2020 Edition), with comprehensive admission blood glucose records and regular blood glucose monitoring records during hospitalization. (2) Fulfilled the diagnostic criteria for bloodstream infection: a. At least one blood culture with detection of the corresponding pathogen; b. Clinical evidence of infection (*e.g.*, fever > 38°C, chills, or hypotension). Exclusion criteria: Age < 18 years old, pregnant women, incomplete case records, transfer to another hospital during the study period. The definitions of sepsis and septic shock were based on the Third International Consensus Definition of Sepsis and septic shock (Sepsis-3) [16]. Sepsis accompanied by hypotension, hypoperfusion, or organ failure was designated as severe sepsis [17]. We categorized the participants into two categories based on clinical diagnostic information and patient severity: the severe sepsis and/or septic shock group and the non-severe sepsis and/or septic shock group. The study was approved by the Helsinki ethics committee at our institution.

Microbiological methods

All specimen collection and testing were conducted in accordance with the Chinese Guidelines for Clinical Laboratory Operations. Two separate sets of blood cultures were routinely collected, with 10 mL of blood collected into one aerobic and one anaerobic bottle. Blood cultures were incubated in the BacT/Alert system (bioMérieux, France) for a duration of 5 days. The isolates were identified as *K. pneumoniae* and *E. coli* using MALDI-TOF mass spectrometry (bioMérieux, France). Antibiotic susceptibility was tested using the VITEK 2 compact system (bioMérieux Vitek Inc., France) with microbroth dilution. Partial susceptibility tests were performed by the disk diffusion method on Mueller-Hinton agar. Antibiotic susceptibility results were interpreted according to Clinical and Laboratory Standards Institute (CLSI) guidelines. *E. coli* ATCC 25922 and *K. pneumoniae* ATCC 700603 served as quality control strains.

Data Collection

Review the electronic medical record system to collect and administer all patient information. Recorded clinical information includes gender, age, underlying conditions, primary infection site, clinical scores, comorbidities, laboratory test results, microbiological data, medication history, and clinical outcomes. Laboratory results included all blood parameters measured concurrently with the collection of the patient's first positive blood culture after admission, encompassing procalcitonin, C-reactive protein, lactate, oxygenation index, complete blood count, biochemical profile, coagulation function, and other relevant diagnostic indicators.

Using fasting plasma glucose (FPG) values as the independent variable and measured HbA1c values as the dependent variable for all patients, we assessed the linear relationship between the two. A linear regression equation was then established to calculate predicted HbA1c values (Predicted HbA1c = 7.969 + 0.008 × FPG). and calculated the HGI value (HGI = measured HbA1c value - predicted HbA1c value) [18]. Patients were divided into four quartile groups based on the combination of HGI and RDW/LDL-C: Q1 (low HGI and low RDW/LDL-C), Q2 (low HGI and high RDW/LDL-C), Q3 (high HGI and low RDW/LDL-C), and Q4 (high HGI and high RDW/LDL-C).

Statistical analysis

This study employed SPSS 23.0 (SPSS Inc., Chicago, IL, USA) for statistical analysis. Graphs and charts were generated using R software. Non-normally distributed variables were expressed as median (interquartile range) [M (P25, P75)], with intergroup comparisons performed using the *Mann-Whitney U* test. Categorical variables were characterized by frequencies and percentages, with intergroup comparisons using the chi-square (χ^2) test or Fisher's exact test. Factors with statistically significant differences in univariate analysis were incorporated into a multivariate logistic regression model to identify independent predictors. All tests were two-sided, with $p < 0.05$ deemed statistically significant.

Results

This study encompassed 203 patients, consisting of 71 individuals in the non-severe sepsis/septic shock group and 132 individuals in the severe sepsis/septic shock group. Demographic and clinical characteristics were presented in Table 1. No significant differences were observed between groups in age, gender, BMI, smoking, or drinking (all $p > 0.05$). Among patients in the severe group, the proportion of respiratory tract infections was significantly higher than that in the non-severe group (14.4% *vs.* 2.8%, $p = 0.019$), while the proportion of primary infections was significantly lower (17.4% *vs.* 31.0%, $p = 0.041$). No statistically significant difference in bacterial makeup (*K. pneumoniae vs. E. coli*) was observed between the two groups. The use of hypoglycemic agents prior to admission was also slightly lower in the severe group (61.4% vs. 76.1%, $p = 0.050$). Patients in the severe group more frequently received carbapenem antibiotics (75.8% *vs.* 57.7%, $p = 0.013$), presented with thrombocytopenia (15.9% *vs.* 1.4%, $p = 0.003$), ICU admission (26.5% *vs.* 4.2%, $p < 0.001$), and mortality in hospital (9.8% *vs.* 0%, $p = 0.015$) were significantly higher than in the non-severe group.

Table 1
Demographics, clinical characteristics of diabetic patients with *Enterobacteriaceae* bloodstream infections

Characteristics	Non- serious sepsis and/ or septic shock group (n = 71)	Serious sepsis and/ or septic shock group (n = 132)	*p* value
Age (years)	66.0 (57.0–74.0)	65.0 (57.0- 74.2)	0.785
Gender, n (%)			0.566
Male	28 (39.4)	59 (44.7)	
Female	43 (60.6)	73 (55.3)	
BMI	24.1 (22.4–26.8)	24.4 (21.8–27.0)	0.889
Smoking, n (%)	12 (16.9)	20 (15.2)	0.901
Drinking, n (%)	8 (11.3)	12 (9.1)	0.803
Clinical symptoms			
Fever	38 (53.5)	82 (62.1)	0.299
Nausea	5 (7.0)	7 (5.3)	0.850
Weakness	10 (14.1)	15 (11.4)	0.735
Abdominal.pain	8 (11.3)	15 (11.4)	1.000
Bacteria, n (%)			1.000
K. pneumoniae	40 (56.3)	75 (56.8)	
E. coli	31 (43.7)	57 (43.2)	
ESBLs	14 (19.7)	33 (25.0)	0.499
Source.of.infection, n (%)			
Respiratory system	2(2.8)	19 (14.4)	**0.019**
Urinary.tract	27 (38.0)	58 (43.9)	0.506
Original.infection	22 (31.0)	23 (17.4)	**0.041**
Liver- gallbladder and pancreas	15(21.1)	32(24.2)	0.743
Others	2(2.8)	2(1.5)	0.612
Infection.type, n (%)			0.821
Community-acquired	68 (95.8)	124 (93.9)	
Hospital-acquired	3 (4.2)	8 (6.1)	

Characteristics	Non- serious sepsis and/ or septic shock group (n = 71)	Serious sepsis and/ or septic shock group (n = 132)	*p* value
Comorbidities, n(%)			
Hypertension	44 (62.0)	65 (49.2)	0.113
Tumor	13 (18.3)	12 (9.1)	0.093
Liver cirrhosis	5 (7.0)	9 (6.8)	1.000
Cardiovascular	25 (35.2)	64 (48.5)	0.095
Chronic pulmonary disease	4 (5.6)	5 (3.8)	0.801
Use of hypoglycemic agents before admission	54 (76.1)	81 (61.4)	0.050
Complications.of.diabetes (%)			
Diabetic kidney disease	7 (9.9)	18 (13.6)	0.577
Diabetic cardiovascular diseases	7 (9.9)	13 (9.8)	1.000
Diabetic neuropathy	7 (9.9)	15 (11.4)	0.927
Diabetic ketoacidosis	14 (19.7)	24 (18.2)	0.937
Diabetic retinopathy	5 (7.0)	14 (10.6)	0.563
Diabetic.foot ulcers	1 (1.4)	4 (3.0)	0.813
Multiple.organ.failure	1 (1.4)	12 (9.1)	0.067
Thrombocytopenia	1(1.4)	21(15.9)	**0.003**
Antibiotic drugs			
Carbapenems	41 (57.7)	100 (75.8)	**0.013**
Cephalosporins	10 (14.1)	12 (9.1)	0.393
Beta-lactamase inhibitors	49 (69.0)	97 (73.5)	0.608
Quinolones	2 (2.8)	3 (2.3)	1.000
ICU admission	3 (4.2)	35 (26.5)	**< 0.001**
Mortality in hospital	0(0)	13(9.8)	**0.015**
Hospital length of stay, median (IQR) (days)	10.0 (9.0- 14.5)	12.0 (9.0–16.0)	0.082

Laboratory results (Table 2) showed that patients in the severe group had significantly higher levels of Neu%, CRP, PCT, LAC, Cre, D-Dimer, and HbA1c compared to the non-severe group ($p < 0.05$ for all), while

PLT and ALB were significantly lower ($p < 0.01$ for both). Notably, HGI and the RDW/LDL-C ratio were also significantly elevated in the severe group ($p = 0.047$ and $p < 0.001$).

Table 2
Laboratory findings of diabetic patients with *Enterobacteriaceae* bloodstream infections on the collection date of the first positive blood culture

Characteristics	Non- serious sepsis and/ or septic shock group (n = 71)	Serious sepsis and/ or septic shock group (n = 132)	*p* value
WBC (10^9/L)	11.7 (8.5–15.0)	12.8 (9.1–17.2)	0.105
Neu %	88.4 (80.4–92.3)	91.0 (87.1–94.2)	**< 0.001**
Hb (g/L)	116.0 (99.0- 131.0)	117.0 (101.8–133.0)	0.825
PLT (10^9/L)	197.0 (154.5- 246.5)	151.0 (99.2- 216.2)	**0.001**
CRP (mg/L)	110.1 (43.0- 204.1)	173.9 (102.9- 232.2)	**0.001**
PCT (ng/mL)	1.4 (0.5–11.6)	16.7 (3.4–65.1)	**< 0.001**
LAC (mmol/L)	2.0 (1.4–2.4)	2.5 (1.7–3.5)	**0.002**
PaO2/FiO2	353.5 (317.8–390.0)	348.0 (272.0- 410.0)	0.419
Cre (μmol/L)	71.0 (56.0–98.0)	85.5 (61.8- 144.5)	**0.011**
ALB (g/L)	33.2 (29.4–37.8)	29.1 (26.2–31.8)	**< 0.001**
D-Dimer (mg/L)	1.8 (0.8–2.9)	2.9 (1.5–5.9)	**< 0.001**
FIB (g/L)	5.9 (4.8–6.8)	6.0 (5.0- 7.1)	0.576
HbA1c (%)	8.7 (7.4–10.1)	9.6 (7.7–11.8)	**0.019**
GLU (mg/dL)	187.2 (136.7- 226.8)	194.4 (154.9- 235.3)	0.327
HGI	-1.0 (-1.9- 0.6)	0.1(-1.9-2.0)	**0.047**
RDW/LDL	5.4 (4.4–7.7)	8.3 (5.6–11.4)	**< 0.001**

Abbreviations: WBC white blood cells, Neu% neutrophil ratio, Hb hemoglobin, PLT platelets, CRP C-reactive protein, PCT procalcitonin, LAC Lactic acid, PaO2/FiO2 Partial pressure of arterial oxygen/Fraction of inspired oxygen, ALB albumin, Cr creatinine, FIB fibrinogen, HbA1c Glycated Hemoglobin A1c, GLU glucose

Further multivariate analysis (Table 3) evaluated the relationship between quartiles of the combined HGI-RDW/LDL-C index and the risk of developing severe sepsis and/or septic shock. Compared with Q1 as the reference, adjusted odds ratios for Q2 and Q4 were significantly elevated after adjusting for source of infection (Model 1) or underlying disease (Model 2). In Model 1, Q2 OR = 4.632, 95% CI: 1.922–11.163; Q4 OR = 9.580, 95% CI: 3.478–26.389; Model 2: Q2 OR = 4.458, 95% CI: 1.820-10.917; Q4 OR = 11.337, 95% CI: 3.909–32.879). ROC curve analysis (Fig. 1) showed that the combined HGI-RDW/LDL-C index

predicted severe sepsis and/or septic shock with an area under the curve (AUC) of 0.760 (95% CI: 0.693–0.826).

Table 3
Univariable and multivariate analysis for diabetic patients of *Enterobacteriaceae* bloodstream infections with severe sepsis and/ or septic shock

HGI-RDW/LDL	Unadjusted OR (95%CI)	*p* value	Model 1		Model 2	
			Adjusted OR (95%CI)	*p* value	Adjusted OR (95%CI)	*p* value
Q1	Reference		Reference		Reference	
Q2	4.176(1.801–9.684)	**0.001**	4.632(1.922–11.163)	**0.001**	4.458(1.820-10.917)	**0.001**
Q3	2.041(0.927–4.491)	0.076	2.272(0.982–5.255)	0.055	2.260(0.959–5.326)	0.062
Q4	8.776(3.313–23.247)	**< 0.001**	9.580(3.478–26.389)	**< 0.001**	11.337(3.909–32.879)	**< 0.001**
Model 1 Source.of.infection were included in multivariate analysis						
Model 2 Comorbidities were included in multivariate analysis						

Figure 2A illustrated the distribution differences between *K. pneumoniae* and *E. coli* across different quartiles (Q1–Q4) of HGI-RDW/LDL-C levels. *K. pneumoniae* infections were most prevalent in Q4 (62.0%), while *E. coli* infections were least common in Q4 (38.8%). Severe sepsis and/or septic shock occurred more frequently at HGI-RDW/LDL levels Q2 and Q4 (as shown in Fig. 2B).

Heatmap analysis (Fig. 3) illustrated the antibiotic resistance rates of *K. pneumoniae* and *E. coli* across different HGI-RDW/LDL-C level groups. At HGI-RDW/LDL-C levels Q1 and Q2, *K. pneumoniae* exhibited relatively high resistance rates to multiple antibiotics, particularly second-generation cephalosporins. Additionally, carbapenem-resistant strains emerged at the Q1 level. For *E. coli*, relatively high resistance rates to cephalosporins were primarily concentrated at the Q2 level.

Discussion

This retrospective study analyzed clinical data from 203 patients with type 2 diabetes who developed bloodstream infections caused by *K. pneumoniae* or *E. coli*. Results indicated that both low HGI/high RDW/LDL-C and high HGI/high RDW/LDL-C profiles were significantly associated with the risk of severe sepsis and/or septic shock. These combined indicators demonstrated independent predictive value in multivariate analysis, suggesting their potential as biomarkers for assessing infection severity in diabetic patients.

First, this study further confirms the association between poor glycemic control and adverse infection outcomes. HbA1c levels were significantly elevated in the severe group, consistent with previous research [19] indicating that prolonged hyperglycemia leads to multiple immune dysfunction, including impaired neutrophil chemotaxis, phagocytosis, and bactericidal activity; compromised lymphocyte proliferation; and monocyte/macrophage dysfunction [20]. This state of “immune paralysis” prevents diabetic patients from effectively eliminating pathogens, leading to the swift spread and worsening of diseases. Concurrently, microcirculatory dysfunction and tissue hypoxia induced by hyperglycemia foster an environment conducive to pathogen proliferation while hindering tissue healing mechanisms [21]. Additionally, HGI—as an indicator reflecting the association between individual blood glucose fluctuations and target organ damage, was significantly elevated in the severe group, suggesting that blood glucose fluctuations may influence the progression of the infection more than average blood glucose levels alone.

In this study, patients in the severe group exhibited elevated inflammatory markers (CRP, PCT) and signs of organ injury (elevated LAC, BUN, D-Dimer; decreased ALB), signifying uncontrolled systemic infection and multi-organ involvement. Hyperglycemia may be a principal catalyst of this detrimental cycle. Infection stimulates the synthesis of inflammatory markers, including CRP and PCT, while concurrently inhibiting insulin secretion or its receptor interactions. Additionally, substances produced by infections, including lipopolysaccharide (LPS), stimulate Toll-like receptors and autoimmune responses, ultimately resulting in disruptions in energy metabolism and insulin resistance [22].

Secondly, the RDW/LDL-C ratio, serving as a composite indicator of inflammation and metabolic disorders, demonstrated a strong correlation with infection severity in this study. Elevated RDW typically reflects heightened inflammatory states and oxidative stress. In diabetic patients, prolonged hyperglycemia leads to increased production of reactive oxygen species (ROS), interleukins (IL), and TNF-α, disrupting erythropoiesis in the bone marrow. This results in heterogeneous volumes among newly formed red blood cells, thereby elevating RDW. Conversely, low LDL-C may be associated with lipid metabolism disorders and malnutrition during the acute phase of infection. These findings suggest that an elevated RDW/LDL-C ratio may synergistically with HGI reflect metabolic-inflammatory imbalance during infectious stress, thereby influencing sepsis progression.

Additionally, this study is the first to investigate the distribution differences of the combined HGI-RDW/LDL-C indicator across different pathogen infections. *K. pneumoniae* infections were more prevalent in the high HGI-RDW/LDL-C group, and patients in this group also exhibited distinct antibiotic resistance patterns. This may be related to how hyperglycemia and hyperinflammatory states influence the immune microenvironment, thereby altering pathogen colonization and resistance expression—a finding warranting further investigation.

This study has several limitations. First, as a single-center retrospective study, the potential for selection bias may be present. The external validity of these findings requires further validation in multicenter, prospective, large-sample studies. Furthermore, this study did not dynamically monitor the trends of

these indicators throughout the hospitalization period or their relationship with treatment response and prognostic evolution, potentially failing to fully reflect the metabolic and inflammatory dynamics during the disease course.

Conclusion

In summary, among diabetic patients with combined *Enterobacteriaceae* bloodstream infections, the composite indicator HGI-RDW/LDL-C—reflecting the interaction between blood glucose fluctuations and inflammation-metabolism, is an independent risk factor for progression to severe sepsis and/or septic shock and holds predictive value. This indicator facilitates early identification of high-risk patients, providing a basis for optimizing management strategies for blood glucose, lipids, and anti-infective therapy.

Declarations

Ethics approval and consent to participate

The Institutional Medical Ethics Committee of Taizhou Hospital of Zhejiang Province granted approval for this retrospective study, with a waiver of informed consent because the medical records of the subjects were deidentified from the Medical Records and Statistics Room to ensure patient confidentiality. The use of the raw data and the study's protocol was permitted by the Institutional Medical Ethics Committee of Taizhou Hospital of Zhejiang Province, and all methods were performed following the relevant guidelines and regulations.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Author Contribution

P Z had roles in the study design, data analysis, literature search, and writing of the manuscript. SX L had roles in guiding research and clinical management. FF X and QF Z had roles in data collection and

interpretation. All authors have read and agreed with the final manuscript.

Data Availability

The datasets generated and analyzed during the current study are not publicly available due to privacy or ethical restrictions but are available from the corresponding author on reasonable request.

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Figures

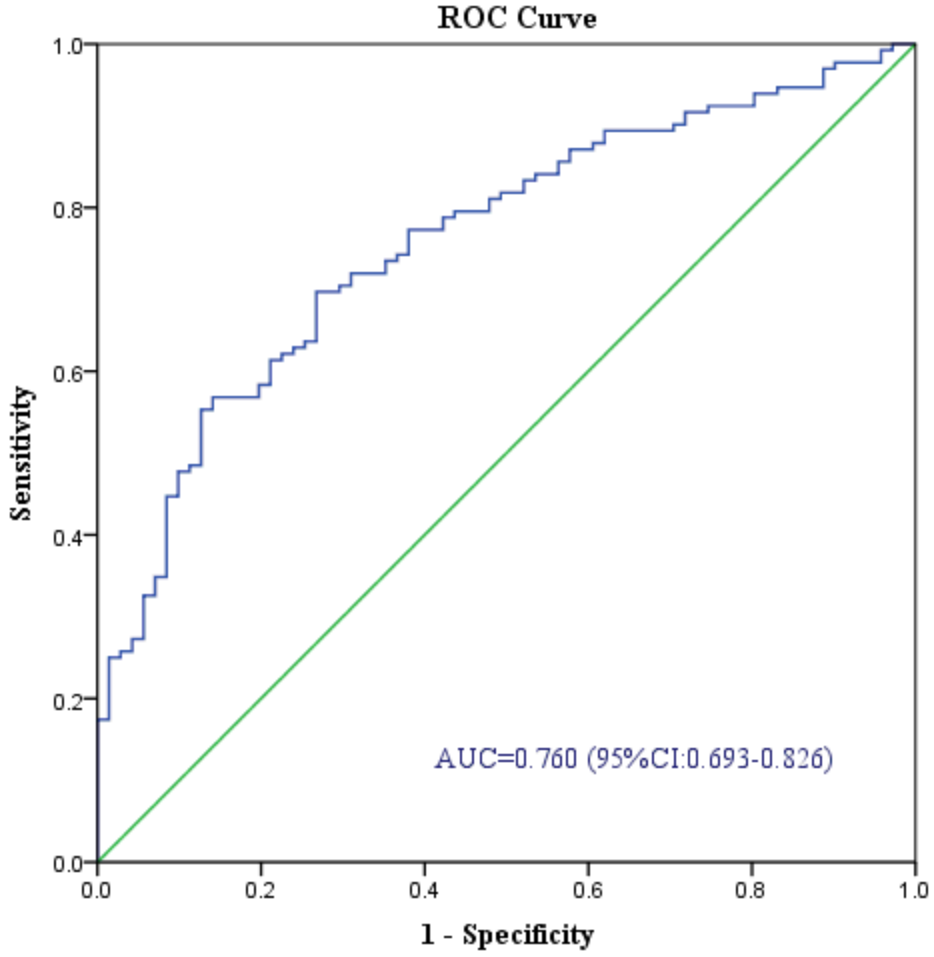


Figure 1

ROC curve of HGI-RDW/LDL-C for severe sepsis and/or septic shock following *Enterobacteriaceae* bloodstream infection in diabetic patients

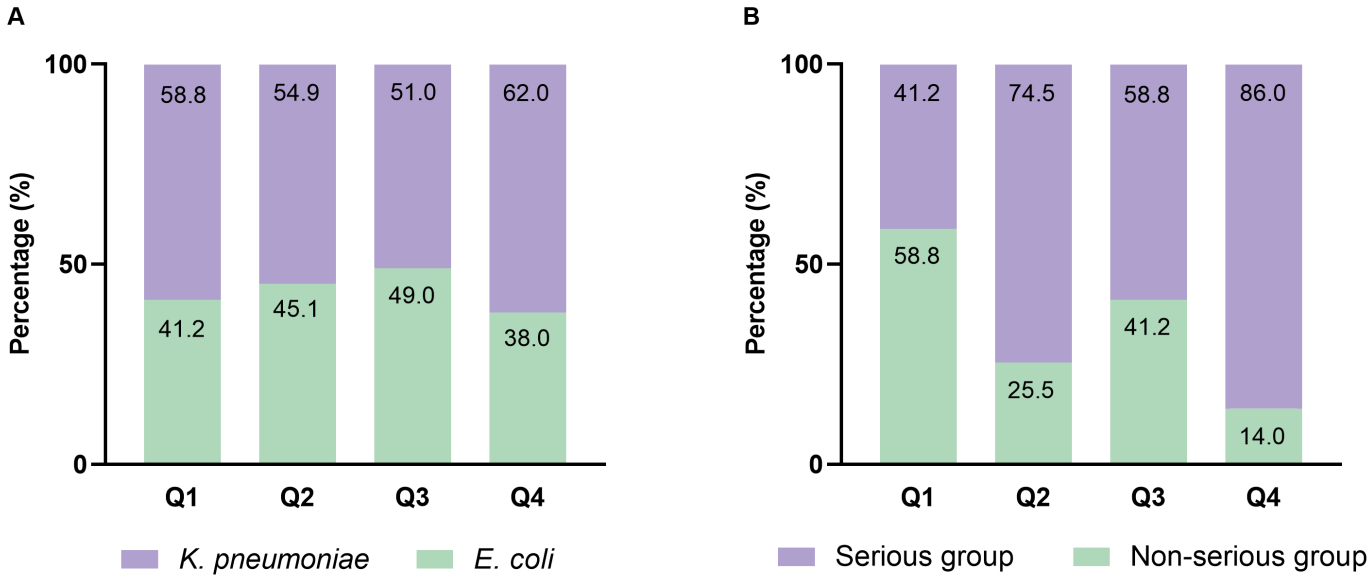


Figure 2

Distribution of different bacterial strains and severe vs. non-severe group in patient cohorts stratified by HGI-RDW/LDL-C levels

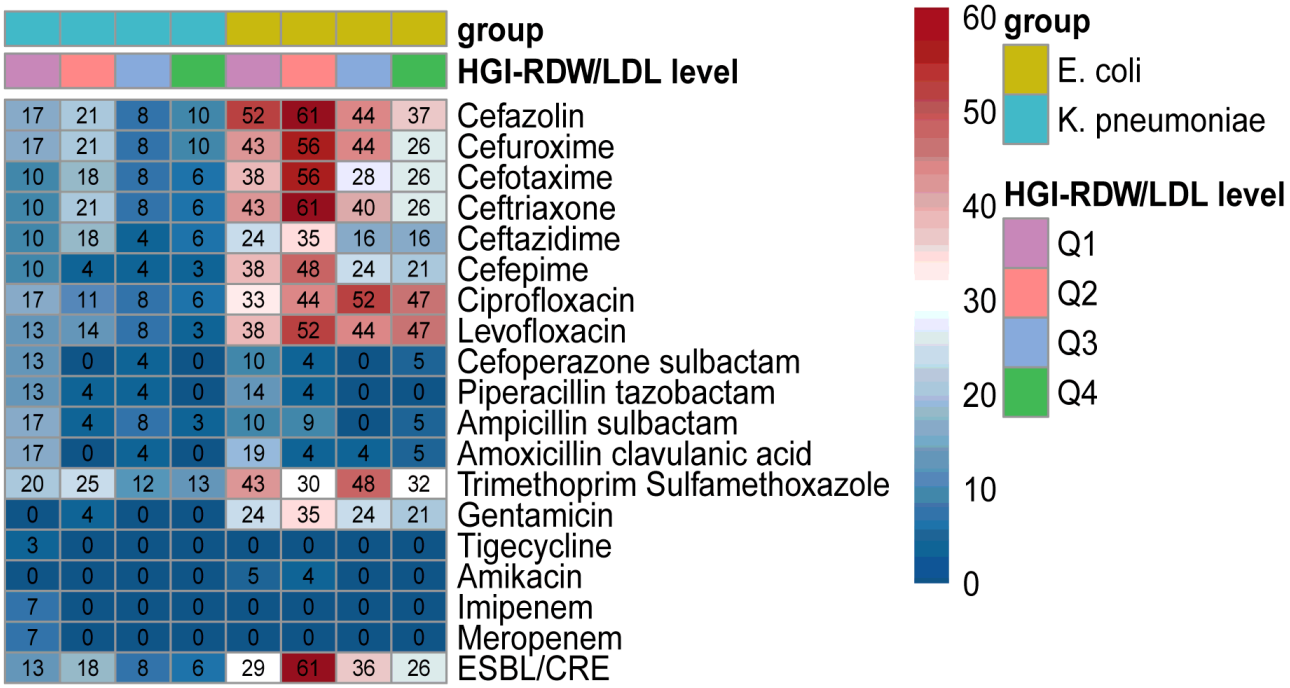


Figure 3

Heatmap depicting antimicrobial susceptibility profiles of *K. pneumoniae* and *E. coli* isolates across patient groups stratified by HGI-RDW/LDL-C levels