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Predictive Modeling of Linezolid-Associated Hyponatremia in Critical Care: A Biomarker-Augmented Risk Framework

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Abstract

Background: Hyponatremia, a frequent yet potentially life-threatening electrolyte imbalance, poses heightened risks in intensive care contexts. This investigation sought to explore contributory factors linked to hyponatremia following linezolid administration in critically ill (CI) individuals and to formulate a robust predictive framework.
Methods: A retrospective evaluation was conducted on clinical records and follow-up data from 200 CI patients who received linezolid therapy. To isolate key determinants, logistic regression modeling was utilized, followed by validation using Receiver Operating Characteristic (ROC) curve analysis. A nomogram-based risk assessment tool was then constructed, with calibration tested via the Hosmer-Lemeshow goodness-of-fit approach.
Findings: Adverse reactions were recorded in 23.5% of the cohort. Statistically significant disparities ($P < 0.05$) emerged between CI and non-CI patients across several variables, including linezolid serum levels, therapy duration (DOM), baseline sodium values (BSS), estimated glomerular filtration rate (eGFR), white blood cell (WBC) count, total bilirubin (TBIL), albumin (ALB), and key biomarkers (NGAL, suPAR, Cystatin C), as well as concurrent spironolactone usage. The Z-score presented the highest diagnostic efficacy for hyponatremia, with a threshold of -3.24. The model demonstrated an 85.5% predictive accuracy, and the nomogram—based on multivariate regression and fit assessment—exhibited excellent alignment with actual outcomes.
Interpretation: Independent predictors of hyponatremia included DOM, drug concentration, BSS, eGFR, and TBIL. Incorporation of novel biomarker profiles modestly improved model precision, suggesting added value in patient risk stratification. The developed tool offers promise for early detection and intervention in vulnerable ICU populations.

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INTRODUCTION

Hyponatremia, a frequently encountered yet often overlooked electrolyte disorder, is characterized by abnormally low concentrations of sodium in the blood. Its clinical presentation ranges widely depending on patient-specific variables such as age, progression rate, and the degree of sodium depletion. In its milder forms, patients may exhibit non-specific symptoms like headache, lethargy, or mild nausea. As the condition worsens, however, more alarming manifestations can arise, including convulsions, persistent vomiting, altered mental status, and neuromuscular disturbances such as spasms and seizures (1,2). Critically ill (CI) individuals, owing to their complex medical states and exposure to intensive pharmacological therapies, are at especially

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high risk, making hyponatremia a serious concern in this population (3).

Among the pharmacological agents frequently administered in these settings is linezolid, a synthetic oxazolidinone antibiotic used to treat Gram-positive bacterial infections, has been occasionally linked to hyponatremia. (4). While it has demonstrated efficacy in mitigating water retention associated with antidiuretic hormone resistance by enhancing renal excretion of free water and raising serum sodium (5,6), paradoxically, linezolid has also been implicated in causing or worsening hyponatremia. Several reports have documented beneficial effects of linezolid on serum sodium restoration (7,8), though treatment efficacy appears to vary depending on individual patient characteristics.

Existing literature (9) highlights a range of possible contributors to linezolid-associated hyponatremia, including comorbidities, drug dosage, treatment duration, fluid balance, demographic parameters, and concurrent medications. Notably, baseline sodium concentration, C-reactive protein (CRP) levels, and age have also been identified as relevant indicators (10). Recently, attention has turned to biomarkers that may refine risk prediction. Molecules such as neutrophil gelatinase-associated lipocalin (NGAL), soluble urokinase plasminogen activator receptor (suPAR), and cystatin C—each reflecting renal stress, immune activation, and filtration capacity—have emerged as promising adjuncts in risk stratification for drug-induced hyponatremia.

However, most investigations to date remain qualitative or observational in nature, often lacking structured, quantitative models capable of accurately forecasting the onset of this condition in CI patients (11). This gap underscores the need for more robust, data-driven tools.

To address this, the present study sought to develop a nomogram-based predictive model for evaluating the likelihood of hyponatremia in linezolid-treated CI patients. Nomograms serve as intuitive graphical tools that synthesize complex statistical relationships into clinically usable formats. By combining conventional clinical data with biomarker insights, the proposed model aims to enable early identification of high-risk individuals. Utilizing data from 200 CI patients collected over a three-year span—with six-month follow-up—this research endeavors to reveal actionable risk indicators, ultimately contributing to improved therapeutic decision-making and patient outcomes.

Materials and Methods

Study Population

This retrospective study reviewed the medical records of 200 patients admitted to the intensive care unit and treated with linezolid at ** Hospital between September 2019 and September 2022. The cohort included 112 males (56%) and 88 females (44%), ranging in age from 32 to 78 years, with a mean age of 59.6 ± 13.5 years. The average body weight was recorded at 67.3 ± 11.5 kg. Institutional ethics approval was obtained from the ** Hospital Ethics Committee prior to data extraction.

To be eligible for inclusion, patients had to meet all of the following criteria:

1. A clinical diagnosis of hyponatremia attributed to linezolid therapy.
2. Minimum linezolid administration duration of three days.
3. Positive microbiological evidence of Gram-positive cocci infection.
4. Use of linezolid in either oral or intravenous form.
5. Informed participation and demonstrable treatment adherence.

Patients were excluded if they met any of the following conditions:

- Baseline serum sodium concentration ≤ 134 mmol/L prior to initiating linezolid therapy.
- Pregnancy or lactation.
- Active malignancy.
- Absence of baseline serum sodium (BSS) data.
- Pre-existing infections such as urinary tract, gastrointestinal, or biliary infections.
- Incomplete laboratory datasets.

Research Design

A historical cohort of 200 ICU patients receiving linezolid therapy was analyzed to assess the occurrence of hyponatremia. All participants were monitored over a six-month follow-up period. Collected variables included demographic characteristics, treatment duration (DOM), organ function assessments, existing comorbidities, and pre- and post-treatment laboratory profiles. Parameters evaluated encompassed BSS, albumin (ALB), total protein, alanine aminotransferase (ALT), total bilirubin (TBIL), procalcitonin (PCT), creatinine, serum urea, CRP, potassium, and interleukin-6 (IL-6).

To evaluate renal and inflammatory stress, serum levels of NGAL, suPAR, and cystatin C were measured within the first three days of initiating linezolid therapy using validated immunoassay kits under standardized laboratory conditions. Internal quality control procedures were followed in accordance with the manufacturer's specifications. All biomarker values were handled as continuous variables and analyzed alongside classical risk indicators.

Liver status was classified using the Child-Pugh score (12), while renal function was estimated via the simplified Modification of Diet in Renal Disease (MDRD)

formula (13). All patients received linezolid at a dosage of 600 mg every 12 hours. The average treatment course lasted 17.6 ± 8.7 days.

Diagnostic Criteria

Hyponatremia was defined in accordance with the 2014 European Clinical Practice Guidelines, with BSS < 135 mmol/L indicating hyponatremia and BSS < 125 mmol/L considered indicative of severe hyponatremia.

Adverse Reaction Classification

Adverse events were assessed using the classification system outlined in the "Manual for Adverse Drug Reaction Reporting and Evaluation" (14), which categorizes reactions into six levels: confirmed, highly probable, probable, possible, unlikely, and indeterminate. Only the first three classifications—confirmed, highly probable, and probable—were regarded as definitive evidence of adverse reaction incidence.

Statistical Analysis

All statistical procedures were carried out using SPSS version 23.0. Quantitative variables were described using means ± standard deviations and compared using independent sample t-tests. For longitudinal intra-group comparisons, repeated measures ANOVA was applied. Categorical variables were expressed as proportions and compared using the chi-square test.

Predictive modeling and visualization were conducted using version 4.2.1 of relevant statistical software, and nomogram development was supported by the rms package. Bootstrapping with 2,000 replications was used for internal model validation. Relationships among continuous variables were explored using Pearson correlation coefficients.

Univariate and multivariate logistic regression analyses (LRA) were employed to determine the odds ratios (OR) and 95% confidence intervals (CI) for variables associated with hyponatremia. Variables reaching statistical significance at $P < 0.05$ in univariate analysis were carried forward into the multivariate model. Predictive performance was quantified using ROC curve analysis. Model calibration was assessed via the Hosmer-Lemeshow goodness-of-fit test, with $P < 0.05$ indicating statistically significant lack of fit.

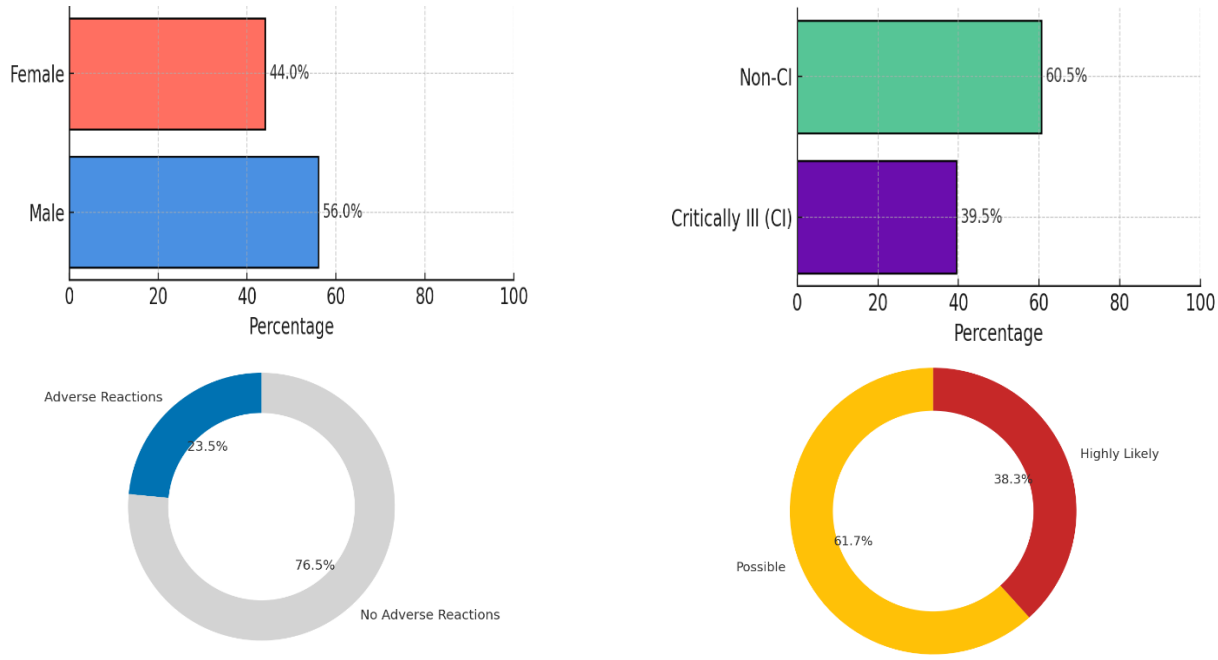

Figure 1. A: gender distribution; B: number of CI and non-CI patients; C: IoAR; D: assessment results

Results

Basic Characteristics of the Patient Cohort

A total of 200 patients were included in the analysis, comprising 112 males (56%) and 88 females (44%) as shown in Figure 1A. Among them, 79 individuals (39.5%) were classified within the critically ill (CI) subgroup, while 121 (60.5%) were categorized as non-CI patients (Figure 1B).

Adverse drug reactions were identified in 47 participants, corresponding to an overall incidence rate

of 23.5% (Figure 1C). Causality analysis further revealed that 29 of these cases were deemed "possible," and 18 were assessed as "highly likely" in relation to linezolid exposure (Figure 1D).

Overview of Study Participants

As presented in Table 1, there were no statistically significant differences between the critically ill (CI) and non-CI patient groups in terms of demographic features, baseline serum sodium (BSS) levels, or the types of infections observed. The two cohorts were thus comparable across key baseline characteristics, supporting the validity of subsequent group-based analyses.

Table 1. Brief information of patients

Item	CI patients group (n = 79)	Non-CI patients group (n = 121)	χ2/t	P
Cases	79	121		
Gender (males/females)	34/45	84/37	4.76	0.09
Age (years old)	64.9 ± 4.5	62.4 ± 5.7	-0.94	0.08
BMI (kg/m2)	24.5 ± 1.6	24.3 ± 2.3	3.67	0.47
Temperature (℃)	37.8 ± 0.5	37.6 ± 0.4	0.92	0.27
Heart rate (beats/min)	91.6 ± 1.7	88.8 ± 2.5	1.65	0.87
WBC count (109/L)	16.2 ± 2.5	15.7 ± 4.3	0.93	0.35
RBC count (109/L)	154.7 ± 13.5	147.3 ± 12.4	1.86	0.73
DOM (days)	9.19 ± 4.53	7.4 ± 3.06	1.83	0.19
BSS (mmol/L)	158.2 ± 4.67	148.2 ± 4.51	0.59	0.61
Combined infection (cases (%))				
Pulmonary infection	45 (56.96%)	44 (36.36%)	0.34	0.71
Intracranial infection	19 (24.05%)	53 (43.80%)	0.01	0.89
Other infections	15 (18.99%)	24 (19.83%)	0.26	0.83

Single-Factor Analysis of Linezolid-Associated Hyponatremia

Findings summarized in Table 2 indicate significant disparities ($P < 0.05$) between the critically ill and non-critically ill groups across several clinical parameters. Notable variables include linezolid plasma concentration, duration of medication (DOM), baseline serum sodium (BSS), estimated glomerular filtration rate (eGFR), white blood cell (WBC) count, total bilirubin (TBIL), albumin (ALB), and the concomitant use of spironolactone.

Furthermore, biomarker analysis revealed markedly elevated levels of neutrophil gelatinase-associated lipocalin (NGAL), soluble urokinase plasminogen activator receptor (suPAR), and cystatin C in CI patients presenting with hyponatremia. Each of these biomarkers showed strong statistical significance ($P < 0.01$), underscoring their potential role in the underlying mechanisms of linezolid-related hyponatremia.

Logistic Regression Analysis (LRA)

A multivariate logistic regression was conducted to identify independent predictors of severe hyponatremia, with the condition treated as the dependent variable. The model incorporated duration of medication (DOM), linezolid concentration, baseline serum sodium (BSS), estimated glomerular filtration rate (eGFR), and total bilirubin (TBIL) as clinical input variables.

In addition, biomarker indicators—NGAL, suPAR, and Cystatin C—were also integrated into the model. All three demonstrated statistical significance, with suPAR emerging as the most robust predictor (OR = 1.669, $P < 0.001$). The final model confirmed that each of these factors was independently associated with an elevated risk of developing hyponatremia ($P < 0.05$), as detailed in Table 3.

ROC Curve Evaluation for Hyponatremia Prediction

To evaluate the predictive strength of the model, Receiver Operating Characteristic (ROC) curves were generated using several variables: duration of medication (DOM), linezolid concentration, baseline serum sodium (BSS), estimated glomerular filtration rate (eGFR), total bilirubin (TBIL), and the composite Z-score. The area under the curve (AUC) values, as shown in Table 4, demonstrated statistically significant discrimination power ($P < 0.05$ across all variables).

Among these, the Z-score yielded the highest diagnostic performance, with the optimal cutoff point identified at -3.24, based on the maximum Youden index. The model resulted in 29 misclassified cases and achieved an overall predictive accuracy of 85.5% for identifying hyponatremia.

Calibration of the Predictive Nomogram

Calibration analysis was conducted to evaluate the agreement between the nomogram's predicted probabilities and the actual observed outcomes. As shown in Figure 3, the calibration curve illustrates the model's performance.

In this plot, the green solid line reflects the observed calibration, the green dashed line denotes the ideal reference line (perfect prediction), and the red dashed line represents the theoretical best-fit line under ideal conditions. The close proximity between the model's calibration line and the ideal reference line indicates that the nomogram demonstrates strong alignment with real-world clinical data, affirming its good predictive accuracy.

Table 2. SFA results on risk factors for linezolid-induced hyponatremia

Item	CI patients group (n = 79)	Non-CI patients group (n = 121)	χ2/t/Z	P
Cases	79	121		
Gender (males/females)	34/45	84/37	0.163	0.091
Age (years old)	64.9 ± 4.5	62.4 ± 5.7	0.455	0.083
DOM (days)	9.19 ± 4.53	7.4 ± 3.06	-4.729	**< 0.001**
BSS (mmol/L)	158.2 ± 4.67	148.2 ± 4.51	-6.638	**< 0.001**
ALB (g/L)	69.86 ± 16.63	62.31 ± 9.32	-1.065	0.294
ALT (g/L)	37.83 ± 5.51	34.54 ± 4.47	-3.659	0.004
Linezolid concentration (mg/L)	11.4 (6.03,17.31)	4.78 (1.79,8.38)	-1.823	< 0.001
eGFR (mL/min)	62.82 (35.42,97.65)	46.43 (29.14,41.36)	-5.122	< 0.001
Glucose (mmol-1)	9.52 ± 3.12	8.14 ± 2.03	0.675	0.275
CRP (mg/L)	61.32 (57.38,134.8)	41.2 (7.89,51.49)	-1.957	0.053
PCT (ng/mL)	0.78 (0.18,5.31)	0.31 (0.09,1.46)	-1.876	0.062
Baseline serum chlorine (mmol/L)	104 (101,107	103 (101,108)	-0.934	0.316
WBC count (109/L)	8.52 (5.98,12.84)	6.34 (4.52,8.16)	-4.86	0.001
Creatinine (μmol)	71 (54,132)	73 (60,123)	-0.051	0.974
eGFR	87 (49,123)	101 (53,118)	-0.715	0.452
TBIL (/μmol)	35.8 (13.8,319.4)	9.1 (6.3,29.1)	-4.715	**0.005**
Combined diseases (cases (%))				
NGAL(ng/mL)	250.6±42.3	179.3± 36.1		< 0.001
suPAR (ng/mL)	5.8 ± 1.7	3.9 ± 1.2		< 0.001
Cystatin C (mg/L)	1.52 ± 0.26	1.23 ± 0.22		< 0.01
Hypertension	9 (11.39%)	87 (71.90%)	0.343	0.713
Diabetes	25 (31.65%)	49 (40.505)	3.455	0.073
Malignant tumor	5 (6.33%)	41 (33.88%)	0.167	0.845
Drug combination				
Albumin preparation	19 (24.05%)	39 (32.23%)	0.206	0.06
Spirolactone	21 (26.58%)	41 (33.88%)	1.819	0.01
Carbapenems	22 (27.85%)	38 (31.40%)	0.568	0.63
Fat milk injection	11 (13.92%)	29 (23.97%)	2.754	0.41
Glucocorticoid	9 (11.39%)	31 (25.62%)	3.068	0.13
Combined with more than 3 antibacterial drugs	15 (18.99%)	26 (21.49%)	0.269	0.83

Table 3. LRA results for risk factors of linezolid-induced hyponatremia

Item	β	S.E	Wald	OR	95% CI	P
DOM	0.413	0.105	8.863	1.505	1.012 ~ 1.821	0.004
Linezolid concentration	0.167	0.086	5.325	1.139	0.543 ~ 0.917	0.019
BSS	-0.404		15.321	0.893	0.618 ~ 0.942	< 0.001
eGFR	-0.452	0.193	7.593	0.864	0.812 ~ 0.985	0.013
TBIL	0.008	0.003	10.436	2.634	1.083 ~ 1.374	0.002
NGAL	0.319	0.082	15.124	1.376	1.189–1.593	< 0.001
suPAR	0.512	0.097	17.211	1.669	1.352–2.057	< 0.001
Cystatin C	0.287	0.077	13.995	1.333	1.183–1.608	< 0.001

Figure 2 illustrates the ROC curve, along with sensitivity and specificity distributions, confirming the model's effectiveness in risk stratification and early detection of linezolid-associated hyponatremia.

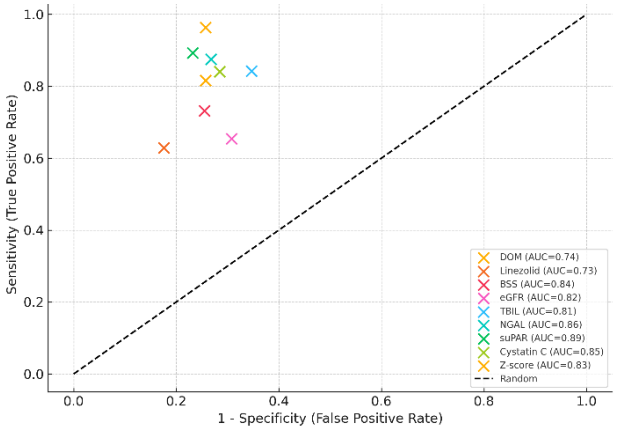

Figure 2. ROC curve to predict hyponatremia

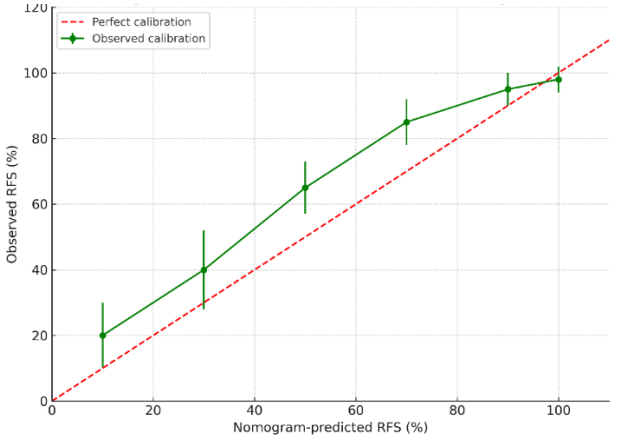

Figure 3. Calibration results of nomogram model

Development of the Nomogram for Predicting Linezolid-Associated Hyponatremia

A predictive nomogram was developed utilizing the independent risk factors identified through multivariate logistic regression analysis. To assess the model's calibration and reliability, the Hosmer-Lemeshow goodness-of-fit test was applied.

As illustrated in Figure 4, the calibration results demonstrated strong concordance between predicted and observed probabilities, indicating that the model exhibited high consistency and satisfactory predictive performance. These findings validate the utility of the nomogram as a practical clinical tool for estimating the risk of hyponatremia in patients undergoing linezolid therapy.

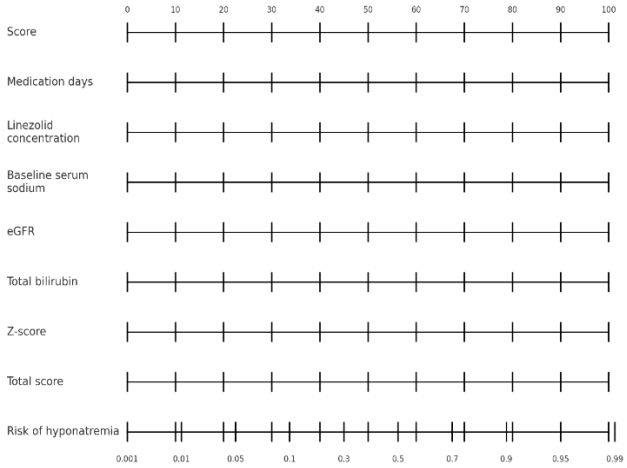

Figure 4. Linezolid correlation low-risk nomogram model

Patient Outcomes

Among the 121 patients in the non-critically ill (non-CI) group, a variety of clinical responses to hyponatremia management were observed:

- 32 patients achieved normalization of serum sodium levels following sodium chloride supplementation.
- 12 patients recovered normal sodium levels after discontinuation or dose reduction of linezolid.
- 9 patients were discharged voluntarily before sodium levels had returned to normal.
- Interestingly, 15 patients experienced normalization of serum sodium while continuing linezolid therapy, suggesting spontaneous or treatment-mediated resolution.

These varied outcomes highlight the heterogeneity of treatment responses and the importance of individualized management strategies in non-CI patients undergoing linezolid treatment.

Table 4. Predictive values of various risk factors of hyponatremia

Risk factors	Critical value	Sensitivity	Specificity	Youden index	AUC
DOM	9.31	0.816	0.743	0.483	0.745 (0.612 ~ 0.891)
Linezolid concentration	7.32	0.629	0.824	0.582	0.729 (0.433 ~ 0.945)
BSS	2.05	0.732	0.745	0.432	0.836 (0.713 ~ 0.974)
eGFR	63.24	0.654	0.692	0.794	0.824 (0.853 ~ 0.852)
TBIL	5.04	0.842	0.653	0.864	0.813 (0.662 ~ 0.754)
NGAL	221.5	0.875	0.732	0.607	0.861
suPAR	4.8	0.893	0.768	0.661	0.887
Cystatin C	1.38	0.841	0.715	0.556	0.849
Z-score	-3.24	0.964	0.743	0.892	0.835 (0.534 ~ 0.975)

Discussion

Hyponatremia, characterized by reduced serum sodium concentration—typically below 135 mmol/L—is a multifactorial electrolyte disturbance commonly encountered in clinical practice. Its etiology spans a broad spectrum, including excessive fluid intake, impaired renal function, endocrine abnormalities, medication effects, heart failure, hepatic disease, and metabolic disorders such as diabetes (15,16). Several studies have reported that linezolid, although therapeutically valuable, can be linked to hyponatremia, with incidence rates ranging from 17.5% to 23.6% (17,18). Notably, Tanaka et al. (19) observed a rate of 18.0%. Our findings demonstrated a higher prevalence of 39.5% among critically ill (CI) patients, underscoring the amplified vulnerability of this subgroup.

The heightened incidence among CI patients highlights the imperative need for vigilant monitoring of sodium levels, especially during prolonged or high-dose linezolid administration. This agent, although bearing structural and pharmacodynamic similarities to somatostatin, is primarily employed in antimicrobial therapy and in managing neuroendocrine tumor manifestations. Its prolonged use may precipitate various adverse events, including gastrointestinal distress, hepatobiliary disturbances, arrhythmias, and metabolic disruptions such as hyponatremia. In our study, 47 patients experienced adverse events, yielding an overall adverse reaction rate of 23.5%. These were predominantly gastrointestinal or hepatic in nature.

The pathophysiological mechanisms underpinning linezolid-induced hyponatremia remain incompletely understood. However, it is hypothesized that certain pharmacologic agents, including linezolid, may exacerbate inappropriate secretion of antidiuretic hormone (SIADH), thereby promoting water retention and dilutional hyponatremia (20,21).

Several external investigations have also explored predictive factors for hyponatremia. For example, Hatakeyama et al. (22) identified advanced age, certain malignancies (e.g., small cell lung or esophageal cancer), and marginal baseline sodium levels as significant risk variables. Ye et al. (23) found that hyponatremia in tuberculous meningitis patients was associated with worse outcomes, particularly when correction was delayed. Similarly, Cao et al. (24) utilized logistic regression to establish that prior diuretic use, distant metastases, and pre-treatment sodium levels significantly influenced hyponatremia risk. Moreover, Cao et al. (25) further documented the relationship between white blood cell count, albumin levels, anesthesia type, and hyponatremia in elderly fracture patients. Other population studies have emphasized the role of age, gender, BMI, and intensive systolic blood pressure control as influential variables (26–28).

Our study reinforces and expands upon these findings through the use of multivariate logistic regression analysis (LRA), which pinpointed duration of medication (DOM), serum linezolid levels, baseline sodium (BSS), estimated glomerular filtration rate (eGFR), and total bilirubin (TBIL) as independent predictors of hyponatremia ($P < 0.05$). Prolonged exposure to linezolid may lead to drug accumulation, elevating serum concentrations and potentially exacerbating sodium imbalances. Likewise, diminished BSS levels represent a pre-existing susceptibility, whereas reduced eGFR reflects impaired renal clearance, a known amplifier of adverse drug reactions (29). TBIL, a marker of liver function, may indicate hepatic insufficiency, which can alter drug metabolism and exacerbate electrolyte disturbances.

Beyond these conventional risk parameters, our model incorporated biomarkers—namely NGAL, suPAR, and Cystatin C—which were statistically significant contributors to model accuracy. NGAL is a well-established indicator of renal tubular damage and may reflect early nephrotoxic responses to pharmacologic exposure. suPAR, a circulating marker of systemic inflammation and immune activation, emerged as the most potent predictor among the trio. Cystatin C, which offers a refined gauge of glomerular function, complements eGFR by capturing renal function independent of creatinine fluctuations.

The inclusion of these biomarker variables not only enhanced the model's discriminative performance but also strengthened its clinical applicability in early identification and individualized risk management. With this enhanced predictive tool, clinicians can proactively adjust therapy or introduce monitoring protocols tailored to patient-specific risk profiles, ultimately improving outcomes for critically ill individuals vulnerable to drug-induced hyponatremia.

Conclusion

This study highlights the necessity of incorporating a multifactorial approach when managing linezolid therapy in critically ill patients. Key clinical parameters—such as duration of treatment, serum drug levels, baseline sodium concentration, renal filtration metrics, and liver function indicators—were identified as significant contributors to the development of hyponatremia. The predictive nomogram constructed herein exhibited strong diagnostic utility, offering clinicians a practical tool for early identification of at-risk individuals.

Importantly, the integration of emerging biomarker data—namely NGAL, suPAR, and Cystatin C—further enhanced the model's predictive precision. These biomarkers provide valuable insights into renal stress, systemic immune response, and filtration dynamics,

complementing traditional variables and enabling more nuanced risk stratification.

With proactive surveillance and timely clinical intervention based on these findings, the likelihood and severity of linezolid-induced hyponatremia may be significantly mitigated. Moving forward, further investigation into the underlying mechanisms of hyponatremia—including drug effects on electrolyte regulation and fluid homeostasis—will be essential. Such work will not only refine predictive capabilities but also support optimized therapeutic strategies, thereby improving outcomes and quality of life for patients requiring intensive pharmacologic support.

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Conflicts of Interest

The authors declare no conflicts of interest related to this research.

Authors' Contributions

Saeedeh Chalaki conceived and designed the study. Vahideh Chalaki and Mona Foghani Ahangari were responsible for data collection and clinical validation. Seyyed Ghodsiyeh Esmaeilnejad and Seyyed Mohammad Hosseinnejad performed the statistical analysis and model development. Saeedeh Chalaki drafted the manuscript. All authors contributed to manuscript revision and approved the final version.

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