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Development and validation of a predictive model for pneumonia risk in ICU patients with stroke: A retrospective cohort study using the MIMIC-IV 3.0 database

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Abstract

Background: Stroke is a leading cause of death and disability worldwide, with poststroke complications such as pneumonia significantly increasing mortality and healthcare burden. Existing models for predicting pneumonia risk in stroke patients have limitations, particularly in ICU settings. *Methods:* This retrospective study utilized the Medical Information Mart for Intensive Care IV (MIMIC-IV) database to construct a nomogram predicting pneumonia risk in stroke patients within the ICU. The nomogram integrated multiple risk factors identified through univariate and multivariate logistic regression analyses. *Results:* The study included 6542 stroke patients, with 11.5% developing pneumonia. Key predictive factors included breath rate, white blood cell, calcium, mean corpuscular hemoglobin concentration (MCHC), mechanical ventilation, antibiotics, pulmonary circulation disorders, metastatic cancer, and weight loss. The nomogram demonstrated good discrimination ability and calibration, with an AUC of 0.821 in the training set and 0.809 in the test set.
Conclusions: The nomogram provides a valuable tool for clinicians to assess pneumonia risk in stroke patients in the ICU, potentially improving patient outcomes and reducing the burden of pneumonia. Further research is needed for external validation and to incorporate additional variables.

Keywords: Stroke, pneumonia, nomogram; MIMIC-IV, predictive model

INTRODUCTION

Stroke is commonly described as a neurological deficit caused by an acute focal injury to the central nervous system (CNS), typically of vascular origin, including cerebral infarction, intracerebral hemorrhage (ICH), and subarachnoid hemorrhage (SAH).[1] The survey indicates that the absolute incidence and mortality of stroke have significantly increased, making it the second leading cause of death worldwide, and also the third leading cause of death and disability.[2,3] Due to its high prevalence, long-term impact, and loss of workforce, it imposes a significant burden on individuals, families, and the healthcare system.[4,5] Following a stroke, various complications may arise, including paralysis, speech or swallowing difficulties, sensory deficits, and infections such as pneumonia and urinary tract infections. These secondary conditions significantly impair the patient's daily life and are the leading causes of mortality following a stroke.[6] The gravity of stroke's impact on global health underscores the urgent need for comprehensive prevention strategies, improved acute care, and robust rehabilitation programs.

Stroke patients frequently encounter complications such as cerebral edema and pneumonia during their hospitalization, which

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can significantly increase in-hospital mortality rates.[7,8] Among these complications, post-stroke pneumonia, which is pneumonia that occurs in individuals following a stroke, is particularly concerning. It is often a result of the weakened immune system and reduced cough reflex in these patients, with incidence rates varying from 5% to 26%.[9] This complication not only raises mortality rates but also increases the risk of readmission, extends hospital stays, and negatively affects functional outcomes.[10] Moreover, post-stroke pneumonia disrupts the recovery process, making it more difficult for stroke patients to undergo rehabilitation.[11] Recent studies have highlighted that elderly stroke patients with pre-existing conditions such as heart failure, chronic obstructive pulmonary disease (COPD), and extensive atherosclerosis are at a significantly higher risk of developing pneumonia in the early stages after a stroke.[12] Given these findings, it is crucial to identify early those stroke patients who are at a higher risk of developing pneumonia and to implement targeted medical interventions.

Currently, the models for predicting pneumonia following stroke primarily consist of the A2DS2 score and the ISAN score. The A2DS2 score is specific to patients with ischemic stroke, while the ISAN score is not applicable to ICU patients.[13,14] This highlights a gap in the literature regarding the systematic prediction of pneumonia risk in critically ill stroke patients within the ICU environment. To address this, we turn to nomograms, which are graphical representations of statistical predictive models that allow for the calculation of precise probabilities for specific endpoints, such as disease progression or mortality, on an individual patient basis. These models are particularly valuable in the clinical setting for their ability to personalize risk assessments and guide medical decision-making processes.[15] In this study, our objective is to construct a nomogram based on the Medical Information Mart for Intensive Care IV (MIMIC-IMIIV) database, integrating multiple independent risk factors to more accurately predict the risk of pneumonia in stroke patients within the Intensive Care Unit (ICU). This endeavor is crucial for further personalizing patient treatment and providing support for the development of evidence-based, effective prevention and intervention strategies.

METHODS

Medical Information Mart for Intensive Care IV

This retrospective observational study leveraged extensive data from the MIMIC-IV database, which was compiled between 2008 and 2019 at the Beth Israel Deaconess Medical Center's (BIDMC) Intensive Care Unit (ICU). The MIMIC-IV database is a rich repository of multifaceted clinical data from ICU patients, encompassing physiological metrics, lab results, clinical interventions, pharmaceutical records, and more, as detailed on their official website (https://physionet.org/content/mimiciv/3.0/). The data contributed by BIDMC were anonymized, processed, and disseminated to researchers who had completed human subjects research training and executed data use agreements. The Institutional Review Board at BIDMC waived the requirement for informed consent and sanctioned the distribution of these research materials. To access this database, individuals were required to undertake designated training courses, submit applications, pass specific examinations, and secure the necessary data access authorizations.

Patient and public involvement

The MIMIC-IV data utilized in this retrospective analysis are precise and freely accessible medical records. All personal identifiers within the database have been meticulously deidentified, with patient-specific details replaced by anonymizing random codes, thereby safeguarding patient privacy. Consequently, the use of such publicly accessible databases is exempt from the need for patient-informed consent and does not necessitate ethical approval, aligning with the standards for deidentified data in research.

Patient selection

Patients with intracranial injuries were identified in the MIMIC-IV (version 3.0) database using International Classification of Diseases (ICD) codes: ICD-9: I60-63 and ICD-10: 430-432, 43301, 43311, 43321, 43331, 43381, 43391, 43401, 43411. 7614 patients with stroke admitted to the ICU were screened. Patients who met any of the following criteria were excluded: (1) age <18 or >90 years old; (2) not the first admission to the ICU; (3) ICU stay less than 1 day and (4) death within 3 days after ICU admission. 6542 eligible patients were included in this study and randomly assigned to training set and development

set in a 7:3 ratio. The patient selection process is plotted in Figure 1.

Data collection

We extracted a comprehensive set of variables from the MIMIC-IV database, including demographic information, vital signs, severity scores, laboratory indicators, treatment information, and comorbidities. Demographic details encompassed age, gender, race, and marital status. Vital signs comprised heart rate (HR), mean systolic blood pressure, respiratory rate, temperature, and peripheral oxygen saturation (SpO2). Severity scores included the Sequential Organ Failure Assessment (SOFA) score, Simplified Acute Physiology Score-II (SAPS-II), and Glasgow Coma Scale (GCS). Laboratory indicators consisted of blood glucose concentration, anion gap, hematocrit, hemoglobin, sodium, chloride, calcium concentrations, platelet count, potassium, bicarbonate, prothrombin time, partial thromboplastin time, international normalized ratio (INR), blood urea nitrogen, white blood cell count (WBC), red blood cell count, red blood cell distribution width (RDW), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), and creatinine level. Treatment information detailed the use of antibiotics and vasopressors—norepinephrine, epinephrine, phenylephrine, dopamine, and vasopressin—within 24 hours of ICU admission, lasting over 48 hours, mechanical ventilation, and renal replacement therapy. Comorbidities included congestive heart failure, valvular disease, pulmonary circulation disorders, peripheral vascular disorders, hypertension, chronic pulmonary disease, diabetes with and without complications, hypothyroidism, renal failure, liver disease, metastatic cancer, solid tumor without metastasis, rheumatoid arthritis/collagen vascular diseases, obesity, weight loss, deficiency anemia, alcohol abuse, drug abuse, and depression, identified through ICD codes.[16] Vital signs and laboratory data were collected within 24 hours post-ICU admission. F For indicators that had multiple measurements, the value that corresponded to the most severe condition was selected for the recorded data, following the principle of prioritizing higher scores as seen in the APACHE II scoring system.

Clinical outcomes

The primary clinical outcomes we observed in our study were hospital length of stay (LOS) and hospital mortality rate.

Pneumonia

Patients with pneumonia were identified in the MIMIC-IV database using ICD codes: ICD-10: J12-18 and ICD-9: 480-486.[17]

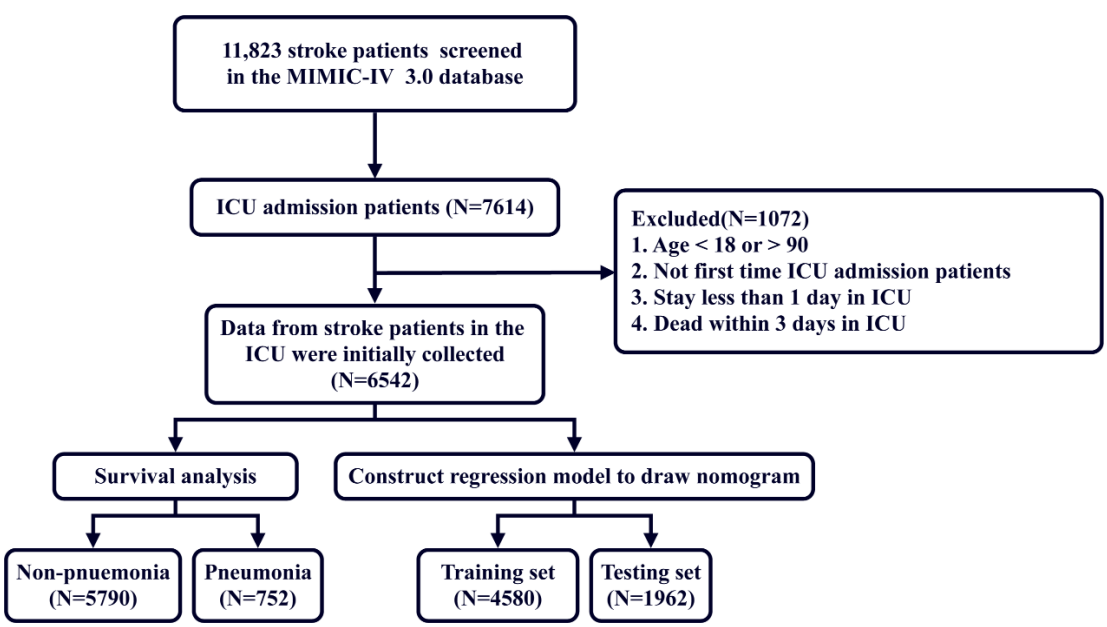

Figure 1. Flow chart of selection. ICU, intensive care unit. MIMIC-IV, Medical Information Mart for Intensive Care IV

Statistical analysis

The median and IQR were used to represent continuous variables, while categorical data were expressed as percentages (%). The differences between continuous variables were tested using Wilcoxon-Mann-Whitney test, and comparison of categorical variables was done using $\chi 2$ test. A two-sided $p<0.05$ is considered statistically significant. The samples were randomly allocated to training set and development set in a 7:3 ratio. A univariate logistic regression model was built in training set to identify potential factors associated with adverse outcomes. Further, a multivariate logistic regression model was built using Akaike information criterion for stepwise regression to select independent predictive factors. Variables with $p<0.05$ were included in the final model. The Kaplan-Meier curve was utilized to illustrate the evolving trends in survival probability across various time intervals. Additionally, Landmark analysis was applied to evaluate the disparities in survival rates between distinct groups, both prior to and subsequent to these critical time points. The nomogram model was constructed based on multivariate logistic regression analysis results, and the model was validated in training set and development set. Receiver operating characteristic (ROC) curve and calibration curve were plotted using 1000 resamples to evaluate predictive performance of model. Hosmer-Lemeshow test was implemented to assess the goodness of fit of the model, and decision curve analysis (DCA) was to evaluate the clinical value of nomogram. Statistical analysis was done on R (V.4.4.1) software. The R packages used included missForest[18] (https://stat.ethz.ch/CRAN/web/packages/missForest/index.html), tableone[19], scitb (https://stat.ethz.ch/CRAN/web/packages/scitb/index.html), caret (https://stat.ethz.ch/CRAN/web/packages/caret/index.html), tidyverse (https://stat.ethz.ch/CRAN/web/packages/tidyverse/index.html), plyr (https://stat.ethz.ch/CRAN/web/packages/plyr/index.html), +leaps (https://stat.ethz.ch/CRAN/web/packages/leaps/index.html), MASS (https://stat.ethz.ch/CRAN/web/packages/MASS/index.html), ResourceSelection (https://stat.ethz.ch/CRAN/web/packages/ResourceSelection/index.html), regplot (https://cran.r-project.org/web/packages/regplot/index.html), rms (https://cran.r- project.org/web/packages/rms/index.html), pROC (https://cran.r- project.org/web/packages/pROC/index.html), rmda (https://cran.r- project.org/web/packages/rmda/index.html), survival (https://stat.ethz.ch/CRAN/web/packages/survival/index.html), survminer (https://stat.ethz.ch/CRAN/web/packages/survminer/index.html) and jskm (https://stat.ethz.ch/CRAN/web/packages/jskm/index.html). In this study, variables with missing values accounting for more than 20% of the total sample were excluded from vital signs and biochemical indicators. Other missing variables were handled using the Random Forest method in the 'missForest' package. The 'regplot' package was applied to plot nomogram and output the risk scores of predictive factors.

RESULTS

Baseline characteristics

Differences in baseline characteristics of samples between the pneumonia group and the non- pneumonia group were shown in Table 1. Among 6542 patients with stroke, approximately 11.5% (n=752) had secondary pneumonia. The median age of the total sample was 69.57 years (IQR: 57.95-80.57), and most patients were white (61.3%) and male (52.0%). The hospital LOS and mortality rate in the pneumonia group were 16.6 days (IQR: 13.85-27.44)) and 28.3%, respectively, significantly higher than those in the nonpneumonia group, which were 7.78 days (IQR: 4.43-13.85) and 10.1% ($p<0.05$). HR, breath rate, temperature and blood glucose of pneumonia group were higher, and they were more prone to CHF, Cardiac arrhythmias, Pulmonary circulation, Chronic pulmonary disease, Diabetes complicated, Renal Failure, Liver Disease, Metastatic Cancer, Weight loss and Alcohol abuse (all $p<0.05$). MBP is lower in the pneumonia group ($p<0.05$). Patients with pneumonia exhibit higher SOFA ($p<0.001$) and SAPS II scores (($p<0.001$)), but a lower GCS score($p<0.05$).

The impact of pneumonia on patient survival

The Kaplan-Meier curve revealed that pneumonia exerts a detrimental effect on the survival of stroke patients (log-rank $p<0.001$) (Figure 2A). Subsequently, time points at 7 days, 14 days, and 30 days post-admission were selected for analysis. Among pneumonia patients, there was no significant difference in survival curves between the two groups within the first 7 days (log-rank

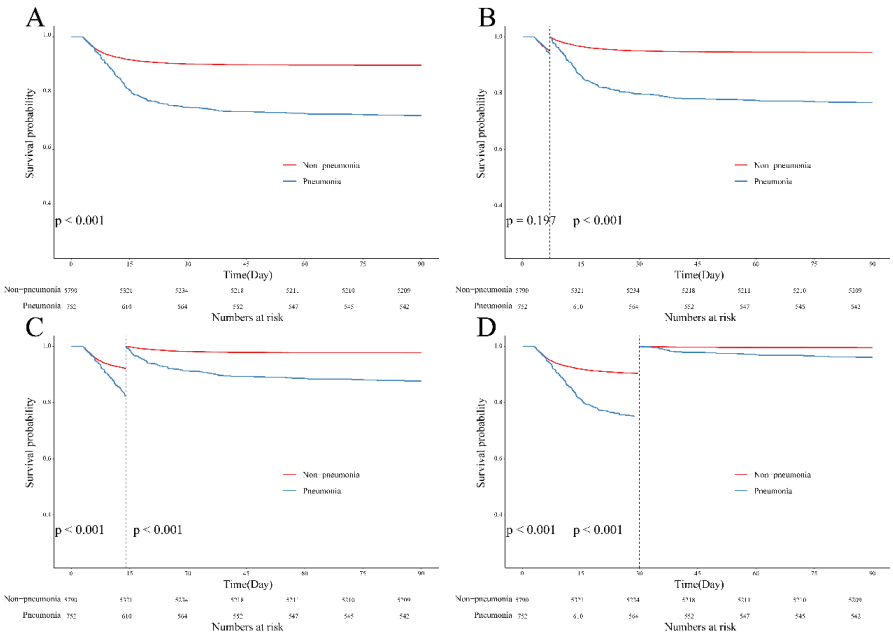

Figure 2. Kaplan-Meier survival probability curves, stratified by pneumonia status, are depicted before and after the landmark time. (A) Illustrates the Kaplan-Meier survival curves prior to the landmark time. (B-D) Present the Kaplan-Meier survival curves post-landmark time, with the landmark time set at 7, 14, and 30 days, respectively. The p-values denoted on the left and right correspond to the log-rank test results for the Kaplan-Meier curves before and after the landmark time, respectively.

p > 0.05) (Figure 2B). However, after the 7th, 14th, and 30th days, a pronounced survival disadvantage was observed (log-rank p<0.001) (Figures 2C and 2D). In conclusion, the development of secondary pneumonia in stroke patients significantly impacts patient survival.

Logistic regression variable screening results and nomogram establishment

Risk factors for pneumonia were studied through training set and development set, and there was no significant intergroup difference (all p>0.05, Table 2). In training set, results of univariate logistic regression analysis and potential risk factors for pneumonia in multivariate logistic model were listed in Table 3. Multivariate logistic analysis revealed that breath rate (OR: 1.023, 95% CI 1.013 to 1.033, p<0.001), WBC (OR: 1.009, 95% CI 1.001 to 1.019, p=0.026), Calcium (OR: 0.825, 95% CI 0.731 to 0.932, p=0.002), MCHC (OR: 0.922, 95% CI 0.867 to 0.980, p=0.009), mechanical ventilation (OR: 2.250, 95% CI 1.799 to 2.824, p<0.001), antibiotics (OR: 7.975, 95% CI 5.770 to 11.273, p<0.001), pulmonary circulation disorders (OR: 1.624, 95% CI 1.188 to 2.201 p=0.002), metastatic cancer (OR: 1.563, 95% CI 1.022 to 2.342, p=0.034) and weight loss (OR: 1.659, 95% CI 1.265 to 2.164, p<0.001) were independent risk factors for pneumonia in patients with stroke. In conclusion, based on variables such as breath rate, WBC, Calcium, MCHC, mechanical ventilation, antibiotics, pulmonary circulation disorders, metastatic cancer and weight loss, the nomogram model was built to predict risk of pneumonia in patients with stroke (Figure 3A).

Validation of the nomogram model

Area under the ROC curve of nomogram in training set was 0.821 (95% CI 0.804 to 0.837) (Figure 3B), and it was 0.809 (95% CI 0.782 to 0.836) in test set, indicating that nomogram had favourable discrimination ability (Figure 3C). HosmerLemeshow test showed that p values in training set and test set were 0.099 and 0.612, respectively, indicating a high goodness of fit for model. Calibration curve depicted that predictions of nomogram model in training set (Figure 3D) and test set (Figure 3E) were consistent with actual results. DCA results presented that in training set (Figure 4A) and test set (Figure 4B), intervention strategy guided by the nomogram model generated higher clinical utility. In addition, based on the results of DCA, we further plotted clinical impact curves to evaluate the clinical utility of

Table 1: Participants characteristics of included patients stratified by pneumonia

Characteristics	Total (n=6542)	Non pneumonia (n=5790)	Pneumonia (n=752)	P value
Gender				0.019
Female	3138(48.0)	2808(48.5)	330(43.9)	
Male	3404(52.0)	2982(51.5)	422(56.1)	
Age (years)	69.57(57.95-80.57)	69.73(57.91-80.62)	68.38(58.41-79.87)	0.391
Race				<0.001
White	4011(61.3)	3605(62.3)	406(54.0)	
Black	661(10.1)	577(10.0)	84(11.2)	
Other race	1870(28.6)	1608(27.8)	262(34.8)	
Marital status				0.002
Married	2964(45.3)	2664(46.0)	300(39.9)	
Unmarried	3578(54.7)	3126(54.0)	452(60.1)	
LOS	8.46(4.72-15.52)	7.78(4.43-13.85)	16.6(13.85-27.44)	<0.001
Hospital mortality	797(12.2)	584(10.1)	213(28.3)	<0.001
Vital signs				
Heart rate (times/min)	65.00(57.00-108.00)	65.00 (57.00-106.00)	93.00 (60.00-117.00)	<0.001
MBP (mmHg)	67.00(58.50-112.00)	67.00 (59.00-113.00)	63.00 (56.00-74.00)	<0.001
Breathrate(times/min)	25.00(11.00-29.00)	25.00 (11.00-29.00)	27.00(22.00-32.25.00)	<0.001
Temperature (°C)	37.22(36.94-37.61)	37.17(36.94-37.56)	37.5 (37-38.11)	<0.001
SpO2	93.00(91.00-95.00)	93.00 (91.00-95.00)	93.00 (91.00-96.00)	0.739
Severity score				
GCS	14.00(12.00-15.00)	14.00(12.00-15.00)	15.00(11.00-15.00)	0.006
SAPSII	31.00(25.00-40.00)	31.00 (24.00-39.00)	37.00 (30.00-47.00)	<0.001
SOFA	3.00(1.00-5.00)	2.00 (1.00-4.00)	4.00 (2.00-7.00)	<0.001
Laboratory tests				
Haematocrit (%)	38.20(33.10-41.90)	38.40(33.70-42.00)	36.60 (27.90-41.30)	<0.001
Haemoglobin (g/dL)	11.80(10.10-13.10)	11.90 (10.30-13.20)	10.85 (8.83-12.50)	<0.001
Platelet (K/μL)	200.00(156.00-250.00)	201.00 (158.00-250.00)	185.00 (134.00-249.25)	<0.001
WBC (K/μL)	10.90(8.30-14.50)	10.70(8.20-14.00)	13.30(10.10-17.30)	<0.001
RBC(m/uL)	3.94(3.38-4.38)	3.96(3.43-4.39)	3.64(3.02-14.5)	<0.001
RDW(%)	13.80(13.10-15.00)	13.80(13.10-14.9)	14.50(13.50-15.88)	<0.001
MCH (pg)	30.00(28.50-31.30)	30.00(28.60-31.30)	29.80(28.00-31.20)	0.004
MCHC (g/L)	32.80(31.80-33.70)	32.80(31.80-33.70)	32.40(31.30-33.40)	<0.001
MCV (fL)	90.00(87.00-94.00)	90.00(87.00-94.00)	90.00(86.00-95.00)	0.768
Anion gap (mmol/L)	13.00(11.00-15.00)	13.00 (11.00-15.00)	13.00 (11.00-15.00)	0.826
BUN (mg/dL)	18.00(13.00-15.00)	17.00(13.00-24.00)	21.00(15.00-34.00)	<0.001
Creatinine (mg/dL)	0.90(0.70-1.20)	0.90(0.70-1.20)	1.10(0.80-1.68)	<0.001
Glucose (mg/dL)	135.00(110.00-171.00)	133.00(109.00-168.00)	150.00(121.00-191.25)	<0.001
Calcium (mg/dL)	8.60(8.10-9.00)	8.70(8.20-9.10)	8.30(7.70-8.70)	<0.001
Chloride (mmol/L)	105.00(102.00-108.00)	105.00(102.00-108.00)	106.00(102.00-110.00)	<0.001
Sodium (mEq/L)	140.00(138.00-143.00)	140.00(138.00-143.00)	141.00(138.00-144.00)	<0.001
Potassium (K/μL)	4.10(3.70-.60)	4.10(3.70-4.60)	4.20(3.50-4.70)	0.244
INR	1.20(1.10-1.30)	1.20(1.10-1.30)	1.20(1.10-1.50)	<0.001
PT (s)	12.80(11.80-14.5)	12.70(11.80-14.30)	13.70(12.30-16.70)	<0.001
PTT (s)	29.50(26.70-34.3)	29.40(26.70-34.00)	30.0(26.75-36.50)	0.008

Treatment measures				
Mechanical ventilation				<0.001
No	4262(65.1)	4048(69.9)	214(28.5)	
Yes	2280(34.9)	1742(30.1)	538(71.5)	
RRT				<0.001
No	6280(96.0)	5614(97.0)	666(88.6)	
Yes	262(4.0)	176(3.0)	86(11.4)	
Antibiotic				<0.001
No	3424(52.3)	3351(57.9)	73(9.7)	
Yes	3118(47.7)	2439(42.1)	679(90.3)	
Vasopressor				<0.001
No	6119(93.5)	5493(94.9)	626(83.2)	
Yes	423(6.5)	297(5.1)	126(16.8)	
Comorbidity				
Congestive heart failure				<0.001
No	5360(81.9)	4799(82.9)	561(74.6)	
Yes	1182(18.1)	991(17.1)	191(25.4)	
Cardiac arrhythmias				<0.001
No	3946(60.3)	3560(61.5)	386(51.3)	
Yes	2596(39.7)	2230(38.5)	366(48.7)	
Valvular disease				0.061
No	5833(89.2)	5178(89.4)	655(87.1)	
Yes	709(10.8)	512(10.6)	97(12.9)	
Pulmonary circulation disorders				<0.001
No	6070(92.8)	5423(93.7)	647(86.0)	
Yes	472(7.2)	367(6.3)	105(14.0)	
Peripheral vascular disorders				0.092
No	5924(92.8)	5258(90.8)	647(86.0)	
Yes	616(7.2)	532(9.2)	105(14.0)	
Hypertension				0.483
No	1709(26.1)	1521(26.3)	188(25.0)	
Yes	4833(73.9)	4259(73.7)	564(75.0)	
Chronic pulmonary disease				<0.001
No	5548(84.8)	4947(85.4)	601(79.9)	
Yes	994(15.2)	843(14.6)	151(20.1)	
Diabetes uncomplicated				0.249
No	5576(85.2)	4924(85.0)	652(86.7)	
Yes	966(14.8)	866(15.0)	100(13.3)	
Diabetes complicated				0.016
No	5741(87.8)	5102(88.1)	639(85.0)	
Yes	801(12.2)	688(11.9)	113(15.0)	
Hypothyroidism				0.819
No	5773(88.2)	5107(88.2)	666(88.6)	
Yes	769(11.8)	683(11.8)	86(11.4)	
Renal Failure				<0.001
No	5534(84.6)	4941(85.3)	593(78.9)	
Yes	1008(15.4)	849(14.7)	159(21.1)	

Liver Disease				
No	6110(93.4)	5456(94.2)	654(87.0)	<0.001
Yes	432(6.6)	334(5.8)	98(13.0)	
Metastatic Cancer				0.02
No	6224(95.1)	5522(95.4)	702(93.4)	
Yes	318(4.9)	268(4.6)	50(6.6)	
Solid tumor without metastasis				1.00
No	6317(96.6)	5591(96.6)	726(96.5)	
Yes	225(3.4)	199(3.4)	26(3.5)	
Rheumatoid arthritis/ collagen vascular diseases				0.088
No	6335(96.8)	5615(97.0)	720(95.7)	
Yes	207(3.2)	175(3.0)	32(4.3)	
Obesity				0.546
No	6417(98.1)	5682(98.1)	735(97.7)	
Yes	125(1.9)	108(1.9)	17(2.3)	
Weight loss				<0.001
No	5990(91.6)	5385(93.0)	605(80.5)	
Yes	552(8.4)	405(7.0)	147(19.5)	
Deficiency anemias				0.065
No	6391(97.7)	5664(97.8)	727(96.7)	
Yes	151(2.3)	126(2.2)	25(3.3)	
Alcohol abuse				<0.001
No	6048(92.4)	5380(92.9)	668(88.8)	
Yes	494(7.6)	410(7.1)	84(11.2)	
Drug abuse				0.001
No	6273(95.9)	5569(96.2)	704(93.6)	
Yes	269(4.1)	221(3.8)	48(6.4)	
Depression				0.048
No	5719(87.4)	5079(87.7)	640(85.1)	
Yes	823(12.6)	711(12.3)	112(14.9)	

GCS, Glasgow Coma Scale; SAPSII, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment; MBP, mean blood pressure; WBC, white blood cell; RBC, red blood cell; RDW, red cell distribution width; MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration; MCV, mean corpuscular volume; BUN, blood urea nitrogen; INR, international normalised ratio; PT, prothrombin time; PTT, partial thromboplastin time; RRT, renal replacement therapy;

the nomograms. The clinical impact curves of nomogram showed that the predicted probability coincided well with the actual probability in the training sets, respectively (Figure 4C). Consistent findings were observed in the test set (Figure 4D).

DISCUSSIONS

In this retrospective cohort study, we constructed a predictive model based on nomogram to assess risk of pneumonia in patients with stoke in ICU during ICU admission. Research findings revealed that in this population, breathing rate, WBC, Calcium, MCHC, mechanical ventilation, antibiotics, pulmonary circulation disorders, metastatic cancer and weight loss were key predictive factors for pneumonia.

This study identified mechanical ventilation as a significant risk factor for pneumonia in stroke patients within the ICU. This risk is multifaceted: mechanical ventilation bypasses the upper airway's natural defenses, increasing susceptibility to pulmonary infections.[20] Endotracheal intubation, often required for ventilation, can cause airway trauma and further raise the risk.[21] Stroke patients with dysphagia are particularly at risk due to a higher chance of aspiration, which is exacerbated by ventilation's suppression of protective airway reflexes, including coughing.[22,23] Subclinical

Table 2: Participants characteristics of included patients of training set and test set

Characteristics	Total (n=6542)	Training set (n=4580)	Test set (n=1952)	P value
Gender				0.058
Female	3138 (48.0)	2232 (48.73)	906 (46.18)	
Male	3404 (52.0)	2348 (51.27)	1056 (53.82)	
Age (years)	69.57 (57.95-80.57)			
Race				0.629
White	4011 (61.3)	2815 (61.46)	1196 (60.96)	
Black	661 (10.1)	452 (9.87)	209 (10.65)	
Other race	1870 (28.6)	1313 (28.67)	557 (28.39)	
Marital status				0.057
Married	2964 (45.3)	2040 (44.54)	924 (47.09)	
Unmarried	3578 (54.7)	2540 (55.46)	1038 (52.91)	
LOS	8.46 (4.72-15.52)	8.45 (4.72-15.66)	8.57 (4.73-15.14)	0.597
Hospital mortality	797 (12.2)	581 (12.69)	216 (11.01)	0.057
Vital signs				
Heart rate (times/min)	65.00 (57.00-108.00)	65.00 (57.00-108.00)	66.00 (57.00-107.00)	0.552
MBP (mmHg)	67.00 (58.50-112.00)	67.00 (58.00-112.00)	67.00 (59.00-112.38)	0.442
Breath rate (times/min)	25.00 (11.00-29.00)	25.00 (11.00-29.00)	25.00 (11.00-30.00)	0.808
Temperature (°C)	37.22 (36.94-37.61)	37.17 (36.94-37.61)	37.22 (36.94-37.61)	0.747
SpO2	93.00 (91.00-95.00)	93.00 (91.00-95.00)	93.00 (91.00-95.00)	0.815
Severity score				
GCS	14.00 (12.00-15.00)	14.00 (12.00-15.00)	14.00 (12.00-15.00)	0.221
SAPSII	31.00 (25.00-40.00)	32.00 (25.00-40.00)	31.00 (24.00-40.00)	0.252
SOFA	3.00 (1.00-5.00)	3.00 (1.00-5.00)	3.00 (1.00-4.00)	0.266
Laboratory tests				
Haematocrit (%)	38.20 (33.10-41.90)	38.20 (33.48-41.90)	38.40 (32.90-41.80)	0.912
Haemoglobin (g/dL)	11.80 (10.10-13.10)	11.80 (10.10-13.10)	11.90 (10.10-13.20)	0.631
Platelet (K/μL)	200.00 (156.00-250.00)	201.00 (157.00-248.00)	199.49 (156.00-250.00)	0.723
WBC (K/μL)	10.90 (8.30-14.50)	10.90 (8.38-14.40)	10.90 (8.50-14.60)	0.317
RBC(m/uL)	3.94 (3.38-4.38)	3.94 (3.38-4.38)	3.95 (3.40-4.37)	0.766
RDW()	13.80 (13.10-15.00)	13.80 (13.10-15.00)	13.80 (13.20-14.80)	0.408
MCH (pg)	30.00 (28.50-31.30)	30.00 (28.60-31.30)	30.00 (28.60-31.30)	0.693
MCHC (g/L)	32.80 (31.80-33.70)	32.80 (31.78-33.70)	32.80 (31.90-33.70)	0.065
MCV (fL)	90.00 (87.00-94.00)	90.00 (87.00-94.00)	90.92 (87.00-94.00)	0.974
Anion gap (mmol/L)	13.00 (11.00-15.00)	13.00 (11.00-15.00)	13.00 (11.00-15.00)	0.786
BUN (mg/dL)	18.00 (13.00-15.00)	18.00 (13.00-25.00)	17.00 (13.00-24.94)	0.374
Creatinine (mg/dL)	0.90 (0.70-1.20)	0.90 (0.70-1.20)	0.90 (0.70-1.20)	0.616
Glucose (mg/dL)	135.0 0(110.00-171.00)	135.00 (110.00-172.00)	134.00 (112.00-166.00)	0.526
Calcium (mg/dL)	8.60 (8.10-9.00)	8.60 (8.20-9.00)	8.60 (8.16-9.00)	0.868
Chloride (mmol/L)	105.00 (102.00-108.00)	105.00 (102.00-108.00)	105.00 (102.00-108.00)	0.889
Sodium (mEq/L)	140.00 (138.00-143.00)	140.00 (138.00-143.00)	140.00 (138.00-142.00)	0.128
Potassium (K/μL)	4.10 (3.70-.60)	4.10 (3.70-4.51)	4.20 (3.70-4.60)	0.079
INR	1.20 (1.10-1.30)	1.20 (1.10-1.30)	1.20 (1.10-1.30)	0.800
PT (s)	12.80 (11.80-14.5)	12.90 (11.90-14.70)	12.90 (11.90-14.70)	0.930
PTT (s)	29.50 (26.70-34.3)	29.80 (26.90-35.10)	29.70 (26.70-35.01)	0.520

Treatment measures				
Mechanical ventilation				0.619
No	4262 (65.1)	2975 (64.96)	1287 (65.60)	
Yes	2280 (34.9)	1605 (35.04)	675 (34.40)	
RRT				0.739
No	6280 (96.0)	4399 (96.05)	1881 (95.87)	
Yes	262 (4.0)	181 (3.95)	81 (4.13)	
Antibiotic				0.548
No	3424 (52.3)	2386 (52.10)	1038 (52.91)	
Yes	3118 (47.7)	2194 (47.90)	924 (47.09)	
Vasopressor				0.064
No	6119 (93.5)	4267 (93.17)	1852 (94.39)	
Yes	423 (6.5)	313 (6.83)	110 (5.61)	
Comorbidity				
Congestive heart failure				0.752
No	5360 (81.9)	3757 (82.03)	1603 (81.70)	
Yes	1182 (18.1)	823 (17.97)	359 (18.30)	
Cardiac arrhythmias				0.306
No	3946 (60.3)	2744 (59.91)	1202 (61.26)	
Yes	2596 (39.7)	1836 (40.09)	760 (38.74)	
Valvular disease				0.819
No	5833 (89.2)	4081 (89.10)	1752 (89.30)	
Yes	709(10.8)	499 (10.90)	210 (10.70)	
Pulmonary circulation disorders				0.963
No	6070 (92.8)	4250 (92.79)	1820 (92.76)	
Yes	472 (7.2)	330 (7.21)	142 (7.24)	
Peripheral vascular disorders				0.257
No	5924 (92.8)	4161 (90.85)	1765 (89.96)	
Yes	616 (7.2)	419 (9.15)	197 (10.04)	
Hypertension				0.978
No	1709 (26.1)	1196 (26.11)	513 (26.15)	
Yes	4833 (73.9)	3384 (73.89)	1449 (73.85)	
Chronic pulmonary disease				0.413
No	5548 (84.8)	3895 (85.04)	1653 (84.25)	
Yes	994 (15.2)	685 (14.96)	309 (15.75)	
Diabetes uncomplicated				0.922
No	5576 (85.2)	3905 (85.26)	1671 (85.17)	
Yes	966 (14.8)	675 (14.74)	291 (14.83)	
Diabetes complicated				0.114
No	5741 (87.8)	4000 (87.34)	1741 (88.74)	
Yes	801 (12.2)	580 (12.66)	221 (11.26)	
Hypothyroidism				0.579
No	5773 (88.2)	4035 (88.10)	1738 (88.58)	
Yes	769 (11.8)	545 (11.90)	224 (11.42)	
Renal Failure				0.306
No	5534 (84.6)	3888 (84.89)	1646 (83.89)	
Yes	1008 (15.4)	692 (15.11)	316 (16.11)	

Liver Disease				0.962
No	6110 (93.4)	4278 (93.41)	1832 (93.37)	
Yes	432 (6.6)	302 (6.59)	130 (6.63)	
Metastatic Cancer				0.863
No	6224 (95.1)	4356 (95.11)	1868 (95.21)	
Yes	318 (4.9)	224 (4.89)	94 (4.79)	
Solid tumor without metastasis				0.207
No	6317 (96.6)	4431 (96.75)	1886 (96.13)	
Yes	225 (3.4)	149 (3.25)	76 (3.87)	
Rheumatoid arthritis/collagen vascular diseases				0.213
No	6335 (96.8)	4427 (96.66)	1908 (97.25)	
Yes	207 (3.2)	153 (3.34)	54 (2.75)	
Obesity				0.92
No	6417 (98.1)	4493 (98.10)	1924 (98.06)	
Yes	125 (1.9)	87 (1.90)	38 (1.94)	
Weight loss				0.965
No	5990 (91.6)	4194 (91.57)	1796 (91.54)	
Yes	552 (8.4)	386 (8.43)	166 (8.46)	
Deficiency anemias				0.959
No	6391 (97.7)	4474 (97.69)	1917 (97.71)	
Yes	151 (2.3)	106 (2.31)	45 (2.29)	
Alcohol abuse				0.747
No	6048 (92.4)	4231 (92.38)	1817 (92.61)	
Yes	494 (7.6)	349 (7.62)	145 (7.39)	
Drug abuse				0.857
No	6273 (95.9)	4393 (95.92)	1880 (95.82)	
Yes	269 (4.1)	187 (4.08)	82 (4.18)	
Depression				0.228
No	5719 (87.4)	3989 (87.10)	1730 (88.18)	
Yes	823 (12.6)	591 (12.90)	232 (11.82)	

GCS, Glasgow Coma Scale; SAPSII, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment; MBP, mean blood pressure; WBC, white blood cell; RBC, red blood cell; RDW, red cell distribution width; MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration; MCV, mean corpuscular volume; BUN, blood urea nitrogen; INR, international normalised ratio; PT, prothrombin time; PTT, partial thromboplastin time; RRT, renal replacement therapy;

aspiration in these patients can lead to pathogen colonization and pneumonia.[24] Immobilization from mechanical ventilation can decrease functional residual capacity and cause atelectasis, fostering bacterial growth.[25] As previously discussed, stroke can induce immunosuppression, a condition that is exacerbated by mechanical ventilation, rendering patients more prone to infections.[26] Additionally, mechanical ventilation can induce immunosuppression, making patients more prone to infections, and high tidal volumes or positive pressure ventilation may lead to ventilator-induced lung injury, further increasing pneumonia risk.[27] Antibiotic use is also implicated; it can cause gut dysbiosis, disrupt the microbiota's symbiotic balance, and lead to translocation, increasing reflux and aspiration risks.[28,29]

In terms of comorbidities, conditions that impact pulmonary circulation can result in a dampened immune response, hindering the body's natural defense against infections.[30] Disorders affecting pulmonary circulation may precipitate vascular complications, notably pulmonary hypertension, which can trigger right-sided heart failure and further diminish the lungs' capacity to effectively oxygenate blood. Consequently, these conditions can create hypoxemic environments that encourage pathogen growth and heighten

Table 3: Univariate and multivariate logistic regression analyses in the training set

Characteristics	Univariate analysis		P value	Multivariate analysis		P value
	β	OR (95% CI)		β	OR (95% CI)	
Gender						
Female	Ref.					
Male	0.185	1.203(1.002-1.445)	0.047			
Marital status						
Unmarried	Ref.					
Married	-0.197	0.821(0.682-0.988)	0.037			
Race						
Black	Ref.					
White	-0.279	0.756(0.559-1.023)	0.070			
Other	0.102	1.107(0.807-1.520)	0.529			
Age	-0.003	0.997(0.992-1.003)	0.358			
Vital signs						
Heart rate (times/min)	0.011	1.011(1.008-1.014)	<0.001			
MBP (mmHg)	-0.007	0.993(0.990-0.996)	<0.001			
Breath rate (times/min)	0.035	1.036(1.026-1.045)	<0.001	0.023	1.023(1.013~1.033)	<0.001
Temperature (°C)	0.229	1.257(1.126-1.403)	<0.001			
SpO2	-0.010	0.990(0.976-1.004)	0.156			
Severity score						
GCS	-0.057	0.945(0.918-0.972)	<0.001			
SAPSII	0.042	1.043(1.036-1.050)	<0.001			
SOFA	0.189	1.208(1.176-1.242)	<0.001			
Laboratory tests						
Haematocrit (%)	-0.036	0.964(0.953-0.976)	<0.001			
Haemoglobin (g/dL)	-0.165	0.848(0.816-0.882)	<0.001			
latelet (K/μL)	-0.002	0.998(0.997-1.000)	0.008			
WBC (K/μL)	0.051	1.053(1.039-1.066)	<0.001	0.009	1.009(1.001~1.019)	0.026
Anion gap (mmol/L)	-0.003	0.997(0.968-1.027)	0.839			
BUN (mg/dL)	0.016	1.017(1.012-1.021)	<0.001			
Calcium (mg/dL)	-0.640	0.527(0.471-0.590)	<0.001	-0.192	0.825(0.731~0.932)	0.002
Chloride (mmol/L)	0.042	1.043(1.026-1.059)	<0.001			
Creatinine (mg/dL)	0.169	1.185(1.122-1.250)	<0.001			
Glucose (mg/dL)	0.003	1.003(1.002-1.003)	<0.001			
Sodium (mEq/L)	0.028	1.028(1.010-1.046)	0.002			
Potassium (K/μL)	0.065	1.068(0.967-1.179)	0.194			
INR	0.208	1.231(1.127-1.344)	<0.001			
PT (s)	0.021	1.021(1.012-1.029)	<0.001			
PTT (s)	0.004	1.004(1.001-1.008)	0.016			
MCH (pg)	-0.053	0.948(0.916-0.981)	0.002			
MCHC (g/L)	-0.205	0.815(0.770-0.863)	<0.001	-0.081	0.922(0.867~0.980)	0.009
MCV (fL)	-0.003	0.997(0.984-1.011)	0.706			
RBC (m/uL)	-0.423	0.655(0.583-0.736)	<0.001			
RDW (%)	0.136	1.146(1.103-1.190)	<0.001			
Treatment measures						
Mechanical ventilation	1.703	5.488(4.495-6.700)	<0.001	0.811	2.250(1.799~2.824)	<0.001
RRT	1.436	4.205(3.041-5.815)	<0.001			
Antibiotics	2.702	14.906(10.879-20.424)	<0.001	2.076	7.975(5.770~11.273)	<0.001
Vasopressor	1.396	4.039(3.115-5.235)	<0.001			

Comorbidity						
Congestive heart failure	0.518	1.679(1.357-2.077)	<0.001			
Cardiac arrhythmias	0.412	1.510(1.258-1.812)	<0.001			
Valvular disease	0.322	1.379(1.056-1.801)	0.018			
Pulmonary circulation disorders	0.912	2.490(1.890-3.279)	<0.001	0.485	1.624(1.188~2.201)	0.002
Peripheral vascular disorders	0.102	1.107(0.816-1.504)	0.513			
Hypertension	-0.013	0.987(0.803-1.214)	0.902			
Chronic pulmonary disease	0.448	1.565(1.245-1.969)	<0.001			
Diabetes uncomplicated	-0.056	0.945(0.728-1.227)	0.673			
Diabetes complicated	0.298	1.348(1.047-1.735)	0.021			
Hypothyroidism	-0.070	0.932(0.700-1.242)	0.631			
Renal Failure	0.461	1.586(1.263-1.992)	<0.001			
Liver Disease	0.689	1.991(1.474-2.688)	<0.001			
Metastatic Cancer	0.452	1.572(1.091-2.264)	0.015	0.447	1.563(1.022~2.342)	0.034
Solid tumor without metastasis	-0.148	0.863(0.502-1.482)	0.593			
Rheumatoid arthritis/collagen vascular diseases	0.379	1.461(0.936-2.281)	0.095			
Obesity	0.314	1.369(0.754-2.486)	0.302			
Weight loss	1.166	3.210(2.506-4.112)	<0.001	0.506	1.659(1.265~2.164)	<0.001
Deficiency anemias	0.668	1.95(1.199-3.173)	0.007			
Alcohol abuse	0.406	1.501(1.108-2.033)	0.009			
Drug abuse	0.532	1.703(1.156-2.509)	0.007			
Depression	0.339	1.403(1.095-1.799)	0.008			

GCS, Glasgow Coma Scale; SAPSII, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment; MBP, mean blood pressure; WBC, white blood cell; RBC, red blood cell; RDW, red cell distribution width; MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration; MCV, mean corpuscular volume; BUN, blood urea nitrogen; INR, international normalised ratio; PT, prothrombin time; PTT, partial thromboplastin time; RRT, renal replacement therapy;

the susceptibility to pneumonia.[31] Moreover, pulmonary circulation disorders are often linked to a hypercoagulable state, precipitating thrombosis within the pulmonary vasculature. Such obstructions to blood flow and oxygenation foster an environment that is ripe for pneumonia to develop.[32] In patients with metastatic cancer, an immunosuppressed state is indeed very common, which can lead to an increased risk of pneumonia.[33] Weight loss in patients is often accompanied by a reduction in muscle mass, which can affect the diaphragm and other respiratory muscles, leading to a decrease in the ability to produce a forceful cough to clear respiratory tract secretions, thereby increasing the risk of pneumonia.[34,35] Consequently, clinicians must pay close attention to the pulmonary circulation of patients, avoid fluid overload, and actively enhance nutritional support and early rehabilitation exercises to minimize muscle loss.

In this nomogram, WBC, Calcium, MCHC were also served as predictors to assess a patient's risk of developing pneumonia. Current research indicates that patients with acute ischemic stroke who have high WBC at admission are at a significantly higher risk of in-hospital mortality and pneumonia, and they tend to have poorer functional outcomes at discharge.[36,37] Inflammation and stress responses may be potential pathogenic factors contributing to elevated WBC levels after stroke.[38] Chen *et al.*'s study has identified a correlation between serum calcium levels and the risk of stroke-associated

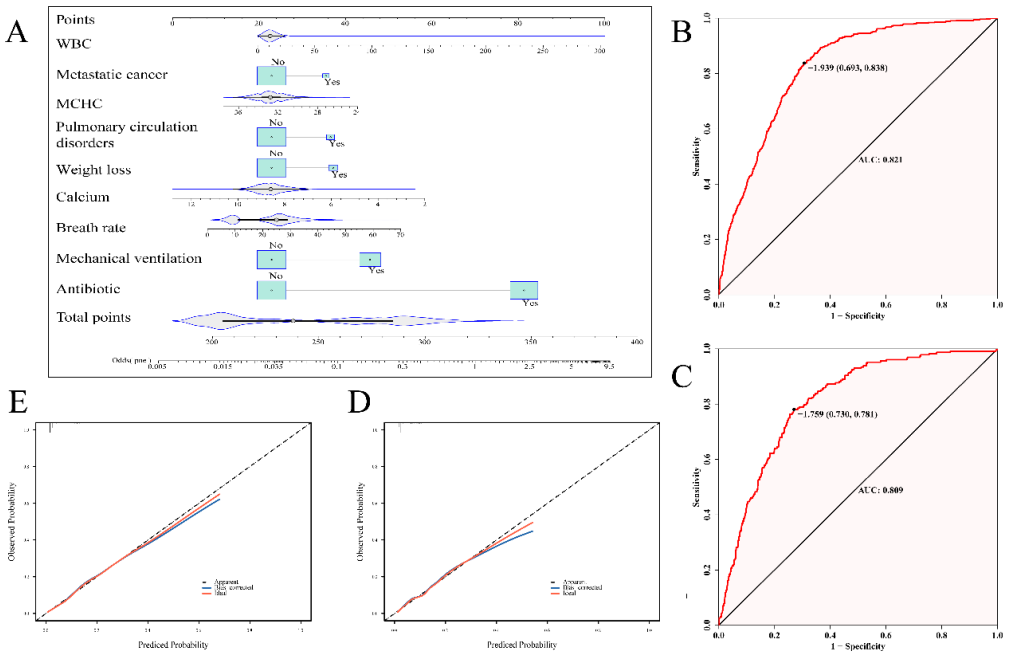

Figure 3. Nomogram for predicting probability of pneumonia in participants (A), The receiver operating characteristic (ROC) curve of the nomogram for both training (B) and test(C) sets, Calibration curves for nomograms in the training set (E) and test set (D). WBC, white blood cell count, MCHC, mean corpuscular hemoglobin concentration

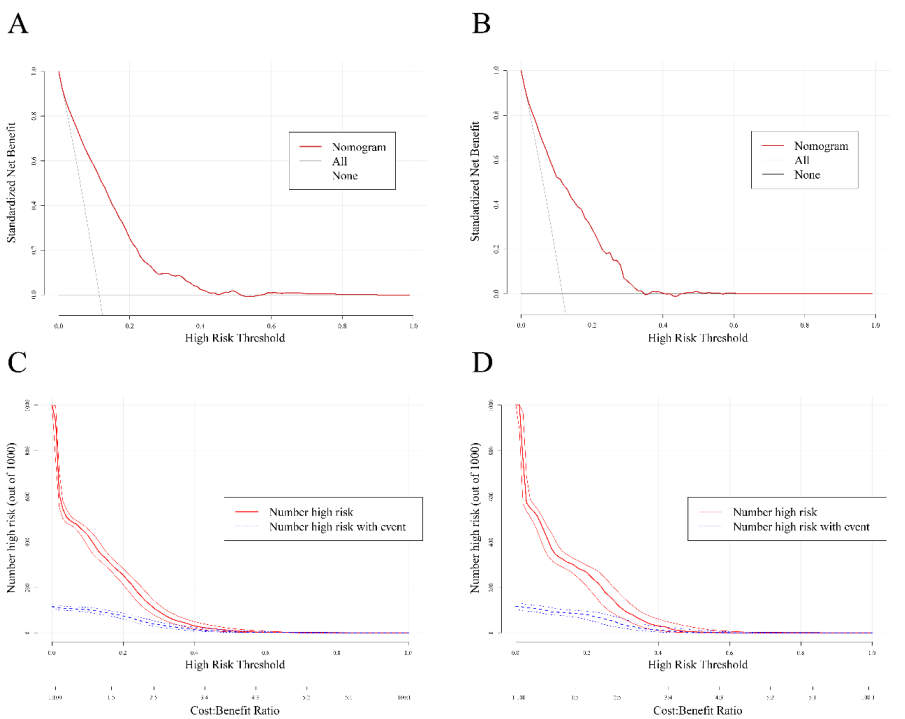

Figure 4. Evaluation of clinical utility of nomogram prediction models in the training and test set. (A) Decision curve analysis (DCA) of nomogram in training set. (B) DCA of nomogram in test set. (C)Clinical impact curves of nomogram prediction in the training set. (D) Clinical impact curves of nomogram prediction in the test set

infections (SAI), with a decrease in serum calcium levels being associated with an increased risk of SAI, a finding that aligns with our study.[39] As a second messenger, calcium ions play a crucial role in a variety of physiological functions of immune cells, including proliferation, receptor-induced activation, secretion, phagocytosis, chemotaxis, and programmed cell death.[40] We hypothesize that the concentration of extracellular calcium ions may influence key calcium signaling pathways within immune cells, thereby affecting the body's immune function and predisposing stroke patients to secondary infections. This intricate relationship underscores the importance of calcium homeostasis in maintaining immune competence and preventing post-stroke infections. MCHC is a critical measure of hemoglobin concentration within red blood cells and serves as an essential parameter in diagnosing anemia and other hematological disorders.[41] The inflammatory response triggered by pneumonia can result in damage to the alveolar-capillary membrane, increasing vascular permeability and potentially causing hemoglobin to leak into the alveolar spaces, thereby affecting the MCHC. Additionally, pneumonia can precipitate hypoxemia, a state of diminished oxygen levels in the blood. In response to hypoxemia, the body may produce additional red blood cells as a compensatory mechanism to enhance oxygen delivery to tissues, an adaptation that could influence MCHC levels.[42] In summary, for stroke patients, it is essential that the clinicians monitor key indicators such as WBC, calcium levels, and MCHC. When these parameters deviate from normal ranges, proactive intervention may significantly reduce the incidence of post-stroke pneumonia.

Nonetheless, there are certain limitations in this study. As this is a retrospective cohort study, the exclusion of variables in vital signs and biochemical indicators when the percentage of missing values exceeds 20% of the total sample size may affect the study results. In the MIMIC database, sedated patients are assigned a GCS score of 15, which affects the assessment of consciousness in stroke patients and may impact the study results. Furthermore, since we only performed internal validation using this database, future studies based on our own data will require external validation to confirm the robustness and validity of the nomogram. Lastly, due to the limited types of variables in the public database, certain important factors, such as cytokine levels, were excluded from the analysis.

In summary, the predictive nomogram developed in this study fills a significant gap in clinical practice, offering clinicians an effective tool for assessing the risk of secondary pneumonia in stroke patients within the ICU. The early identification of high-risk patients and implementation of targeted interventions can improve patient prognoses and reduce the burden of pneumonia in vulnerable populations. Nonetheless, additional research and validation are necessary to confirm the practicality and generalizability of this nomogram.

DISCLOSURE

Ethics**:** This study is approved by the Ethics Committee of Taizhou Municipal Hospital (Taizhou University Affiliated Municipal Hospital), School of Medicine, Taizhou University (LWSL202400222).

Availability of data: We declare that the data supporting the conclusions of this article are fully described within the article, and the database is available from the first author (dr.chenyangshi@hotmail.com) upon reasonable request.

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Conflict of interest: None

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