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Prediction Model and Decision Analysis for Early Recognition of SDNS/FRNS in Children

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Purpose: This study identified factors that identification of progression-predicting utility from steroid-sensitive nephrotic syndrome (SSNS) to steroid-dependent or frequently relapsing nephrotic syndrome (SDNS/FRNS) in patients and developed a corresponding predictive model.

Patients and Methods: This retrospective study analyzed clinical data from 756 patients aged 1 to 18 years, diagnosed with SSNS, who received treatment at the Department of Nephrology, Children's Hospital of Chongqing Medical University, between November 2007 and May 2023. We developed a shrinkage and selection operator (LASSO) - logistic regression model, which was visualized using a nomogram. The model's performance, validity, and clinical utility were evaluated through receiver operating characteristic curve analysis, confusion matrix, calibration plot, and decision curve analysis.

Results: The platelet-to-lymphocyte ratio (PLR) was identified as an independent risk factor for progression, with an odds ratio (OR) of 1.01 (95% confidence interval (CI) = 1.01–1.01, p = 0.009). Additionally, other significant factors included the time for urinary protein turned negative (OR = 1.17, 95% CI = 1.12–1.23, p < 0.001), estimated glomerular filtration rate(eGFR) (OR = 0.99, 95% CI = 0.98–0.99, p < 0.001), low-density lipoprotein (OR = 0.90, 95% CI = 0.83–0.97, p = 0.006), thrombin time (OR = 1.22, 95% CI = 1.07–1.39, p = 0.003), and neutrophil absolute counts (OR = 1.10, 95% CI = 1.02–1.18, p = 0.009). The model's performance was assessed through internal validation, yielding an area under the curve of 0.78 (0.73–0.82) for the training set and 0.81 (0.75–0.87) for the validation set.

Conclusion: PLR, eGFR, the time for urinary protein turned negative, low-density lipoprotein, thrombin time, and neutrophil absolute counts may be effective predictors for identifying SSNS patients at risk of progressing to SDNS/FRNS. These findings offer valuable insights for early detection and support the use of precision medicine strategies in managing SDNS/FRNS.

Keywords: PLR, LASSO, SSNS, SDNS/FRNS, nomogram, prediction

Introduction

Idiopathic nephrotic syndrome (INS) is a prevalent glomerular disorder in children, with an annual global incidence of 1.15 to 16.90 cases per 100,000.[1] It is marked by heavy proteinuria, hypoalbuminemia, hyperlipidemia, and edema. The initial treatment involves oral prednisone (PDN), and patients are classified as either steroid-sensitive nephrotic syndrome (SSNS) or steroid-resistant nephrotic syndrome based on their response to the first four weeks of PDN therapy.[2] Approximately 80% to 90% of INS cases are SSNS.[3] However, around 50% of SSNS cases progress to steroid-dependent or frequently relapsing nephrotic syndrome (SDNS/FRNS). Patients are diagnosed with SDNS/FRNS if they relapse within 14 days of stopping PDN, require continuous PDN to stay in remission, or experience at least two relapses in six months or three relapses in a year.[4]

While SDNS/FRNS generally does not impair kidney function,[3,5,6] frequent relapses often require prolonged PDN therapy, which increases the risk of adverse effects such as behavioral changes, sleep disturbances, obesity, and comorbidities like

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diabetes.[6] Studies following these patients into adulthood show a high prevalence of hypertension, osteoporosis, and cataracts, all linked to chronic glucocorticoid exposure during childhood.[7–9] Although non-corticosteroid immunosuppressive medications can help reduce relapse frequency, their use is typically limited to SDNS/FRNS due to the potential for significant side effects.[10–12] This underscores the importance of early identification of SSNS patients who are at risk of progressing to SDNS/FRNS.

Currently, patient response to steroid therapy remains the primary standard for clinicians diagnosing SDNS/FRNS. However, diagnosing based on recurrence frequency during PDN therapy results in PDN accumulation, which severely impacts children's quality of life. Although some research has explored factors influencing disease progression, reliably identifying these factors remains challenging due to limitations such as small sample sizes, inconsistent follow-up, and variability in reported outcomes.[13–19] Additionally, the few identified factors are often inconsistent. The absence of a predictive model to facilitate early identification of SDNS/FRNS represents a significant unmet clinical need.

Several studies have explored the potential risk factors associated with SDNS/FRNS, analyzing various demographic and clinical data. However, most of these analyses rely on univariate and multivariate methods, which have limitations in addressing multicollinearity among variables.[13–20] least absolute shrinkage and selection operator (LASSO) regression offers a solution to this limitation by constructing penalty functions to create more refined models and has been widely utilized in various disease modeling efforts.[21–27] However, few studies have applied this method specifically to SSNS. In this study, we combine LASSO regression with logistic regression. The former effectively screens variables, while the latter enables straightforward modeling and visualization for easier interpretation.

Materials and Methods

Patient Enrollment

This retrospective study used data from the Big Data Management Centre at the Children's Hospital of Chongqing Medical University. It included patients aged 1 to 18 years, diagnosed with SSNS, defined as achieving negative urinary protein levels within 4 weeks of oral PDN treatment. A total of 756 patients, admitted to the Department of Nephrology between November 2007 and May 2023, met the inclusion criteria for analysis. Patients were excluded if they met any of the following criteria: The exclusion criteria for this study were as follows: (1) age below 1 year, (2) resistance or intolerance to PDN, (2) secondary nephrotic syndrome caused by infections (such as hepatitis B, hepatitis C, or human immunodeficiency virus), systemic diseases (such as systemic lupus erythematosus, Henoch-Schonlein Purpura or diabetes), hematologic and oncologic disorders, medication use, obesity, or other identifiable causes, (3) clinically suspected or confirmed cases of Alport syndrome, IgA nephropathy, C3 glomerulopathy, hemolytic uremic syndrome, or other non-podocytopathic renal diseases, (4) congenital nephrotic syndrome; (5) loss to follow-up.

To develop and validate a predictive model, the cohort was randomly divided into two groups: 70% (529 cases) were designated as the training cohort, while the remaining 30% (227 cases) comprised the validation cohort. The model was constructed using the training cohort and its performance was assessed with the validation cohort. This study received approval from the ethics committee of the Children's Hospital of Chongqing Medical University. Informed consent was waived due to the retrospective nature of the data, which were de-identified.

Clinicopathological Data Collection

This study collected demographic and clinical data from SSNS patients, with laboratory data limited to results obtained before starting PDN treatment. Demographic information included age at onset, gender, weight, height, history of allergic diseases, and details related to birth.

The clinicopathological data were categorized into several key areas. (1) Trigger Events: This included coinfections such as respiratory, urinary tract, or gastrointestinal infections. (2) Complications: We documented conditions such as coagulation dysfunction and acute kidney injury. (3) Routine Blood Tests and Organ Function Assessments: This encompassed various blood parameters, including white blood cell counts, neutrophil and lymphocyte counts, eosinophil counts, platelet counts, hemoglobin levels, red blood cell counts, C-reactive protein, total protein, serum albumin, albumin-to-globulin ratio, blood urea nitrogen, creatinine, and uric acid levels. (4) Serum Electrolyte Levels: Measurements included potassium, sodium, chloride, and calcium. (5) Lipid Profiles: We analyzed total cholesterol, triglycerides, high-density lipoprotein, and low-

density lipoprotein (LDL). (6) Immune Complex Levels: This involved assessing levels of immunoglobulins G, M, and E, as well as complement components 3, and 4. (7) Coagulation Markers: We evaluated prothrombin time, international normalized ratio, activated partial thromboplastin time, fibrinogen, thrombin time (TT), and D-dimer levels. (8) Renal function markers include retinol-binding protein, urinary cystatin C, and urinary N-acetyl-β-D-glucosaminidase, among others. (9) Treatment-Related Factors: Key data included the duration until urinary protein turned negative after the first full dose of PDN.

In this study, platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), and estimated glomerular filtration rate (eGFR) were examined for their predictive significance. The PLR was calculated by dividing the platelet counts by the lymphocyte counts, and the SII was determined by multiplying the platelet counts by the neutrophil counts and dividing by the lymphocyte counts. The eGFR was calculated as 0.413 times height (cm) divided by blood creatinine (mg/dL).

Grouping and Treatment

Due to variability in clinical outcomes, accurately classifying children with SDNS/FRNS based on recurrence frequency can be challenging. Research shows that patients who remain relapse-free during the first year have a significantly lower risk of subsequent relapses compared to those with frequent recurrences. Specifically, the risk of relapse for patients with frequent recurrences during the first year is 1.72 to 2.12 times higher than for those who remain relapse-free.[18] To minimize the risk of misclassification, the control group was defined as steroid-sensitive nephrotic syndrome without relapse (SSNSWR). The groups are defined as follows: (1) SSNS: Adequate treatment with 2 mg/(kg·d) or 60 mg/(m2·d) PDN results in proteinuria remission after 4 weeks of treatment, (2) SSNSWR: SSNS patients withdraw from steroid treatment and without relapse during the follow-up. The length of follow-up time should be set to at least 12 months individually; SDNS: SSNS patients who experience two consecutive relapses either during the recommended PDN therapy for the initial presentation or within 14 days after stopping treatment; FRNS: SSNS patients who experience two or more relapses within the first six months following remission of the initial episode, or three or more relapses within any 12-month period. The grouping is based on data collected up to May 2024.

Follow-Up

All patients were monitored through regular outpatient clinic visits. Initially, follow-up appointments were scheduled every 1 to 2 months. As the patients' conditions stabilized and hormone tapering was successfully achieved without complications, the intervals between follow-ups were gradually extended to 2 to 3 months. After discontinuation of treatment, follow-ups were conducted every 6 months. During these visits, routine blood tests, biochemical assessments, and urinary ultrasonography were performed to monitor the patients' conditions and provide timely interventions when necessary.

Statistical Analysis

For categorical variables, the chi-square test was used. Measurement data were first tested for normality and homogeneity of variance. When data followed a normal distribution with equal variances, they were reported as mean ± standard deviation, and an independent sample *t*-test was applied. For non-normally distributed data and/or unequal variances, values were expressed as medians [lower quartile - upper quartile], and a non-parametric rank-sum test (Wilcoxon test) was used. Missing data, accounting for less than 20% of the dataset, were imputed using the multivariate imputation by chained equations method. Univariate analysis identified 21 significant disease predictors, while univariate regression analysis further filtered out 4 variables.

We compared the performance of LASSO regression, Elastic Net, and Ridge regression model using ten-fold cross-validation, root mean square error (RMSE), R-squared (R^2), and the receiver operating characteristic (ROC) curve. Based on the results, we selected LASSO regression for variable screening. The LASSO algorithm was employed to identify and rank statistically significant clinical features. We conducted tenfold cross-validation on the training set to determine the optimal weight for the LASSO penalty, referred to as lambda. The maximum lambda value within one standard deviation of the minimum mean squared error was chosen for feature selection. After removing features with non-zero coefficients, we applied multifactor logistic regression and stepwise regression to ensure that all variables in the final

model had P-values below 0.05. Following this, we performed multifactor logistic regression to develop the model and utilized a nomogram for visualization. Data processing and analysis were carried out using R version 4.4.0 (released April 24, 2024) and Zstats 1.0 (www.zstats.net). The methodology for sample size calculation followed the approach outlined by Riley R D et al[28] with the results detailed in Supplementary Table 1.

Results

Baseline Characteristics and Clinical Characteristics of Patients

A total of 756 children with SSNS were eligible for inclusion in the study. Of these, 384 children (275 males and 109 females) did not experience a relapse and were categorized into the SSNSWR group, while 372 children (263 males and 109 females) progressed to SDNS/FRNS group. The median age at first onset was 4 years. The selection process is detailed in Figure 1.

To ensure balanced data distribution, the dataset was randomly divided into 70% for model training and 30% for internal validation. No significant differences in SDNS/FRNS prevalence were observed between the two groups (P = 0.366, Supplementary Table 2). Clinical characteristics were also comparable across the training and validation cohorts, supporting their suitability for model development and validation (see Supplementary Tables 2–5).

Univariate analysis identified 21 potential risk factors associated with the progression from SSNS to SDNS/FRNS. These factors include neutrophil, lymphocyte, and eosinophil counts, total protein, blood urea nitrogen, creatinine, potassium, chloride, high-density lipoprotein cholesterol, low-density lipoprotein, fibrinogen, complement components 4, TT, D-dimer, urinary creatinine/albumin ratio, eGFR, SII, and PLR. Additionally, concurrent respiratory infections, concurrent gastrointestinal infection, and the time it took for urinary protein to turn negative were also considered potential risk factors (Supplementary Tables 6–9). 4 variables were excluded following univariate analysis (Table 1)

Comparison of Elastic Network, Ridge Regression, and LASSO Regression Models

We compared the performance of elastic network, Ridge regression, and LASSO regression models using RMSE, R^2, and the ROC curve. Among these models, LASSO regression exhibited the lowest RMSE (0.468), the highest R^2 (0.124) (see Table 2), and the highest area under curve (AUC = 0.7) (see Figure 2), indicating it as the most effective model for variable selection in predicting the progression from SSNS to SDNS/FRNS.

LASSO -Logistic Model Development and Visualization

To optimize the LASSO-logistic model, tenfold cross-validation was performed on the training set to identify the optimal penalty parameter (lambda), defined as the maximum lambda value within one standard deviation of the minimum mean squared error. At the best lambda, 10 variables with non-zero coefficients were selected: time for urinary protein to turn negative, neutrophil counts, TT, PLR, eGFR, complement components 4, LDL, total protein, concurrent respiratory infections, and concurrent gastrointestinal infection (Figure 3). Stepwise regression was then applied to select variables with a P-value < 0.05 for inclusion in the final predictive model. Multifactor logistic regression identified six factors significantly associated with the progression from SSNS to SDNS/FRNS: PLR (odds ratio (OR) = 1.01, 95% CI = 1.01–1.01, p = 0.009), time to urinary protein normalization (OR = 1.17, 95% CI = 1.12–1.23, p < 0.001), eGFR (OR = 0.99, 95% CI = 0.98–0.99, p < 0.001), LDL (OR = 0.90, 95% CI = 0.83–0.97, p = 0.006), TT (OR = 1.22, 95% CI = 1.07–1.39, p = 0.003), and absolute neutrophil count (OR = 1.10, 95% CI = 1.02–1.18, p = 0.009) (Table 3), and a nomogram was constructed to represent the predictive model (Figure 4).

Prediction Model Construction, Evaluation, and Validation

In this study, internal validation was used to assess three aspects of the model: discrimination, calibration, and clinical utility. The confusion matrix (Table 4) and the ROC curve (Figure 5) were used to evaluate the accuracy and discrimination of the prediction model for SSNS recurrence. The predictive accuracy, sensitivity, specificity, positive predictive value, and negative predictive value of both the training and validation sets were favorable. The AUC for the training set was 0.78 (0.73–0.82), and for the validation set, it was 0.81 (0.75–0.87), indicating that the model has good predictive value. R software was used to resample the original data 1000 times to validate the recurrence prediction

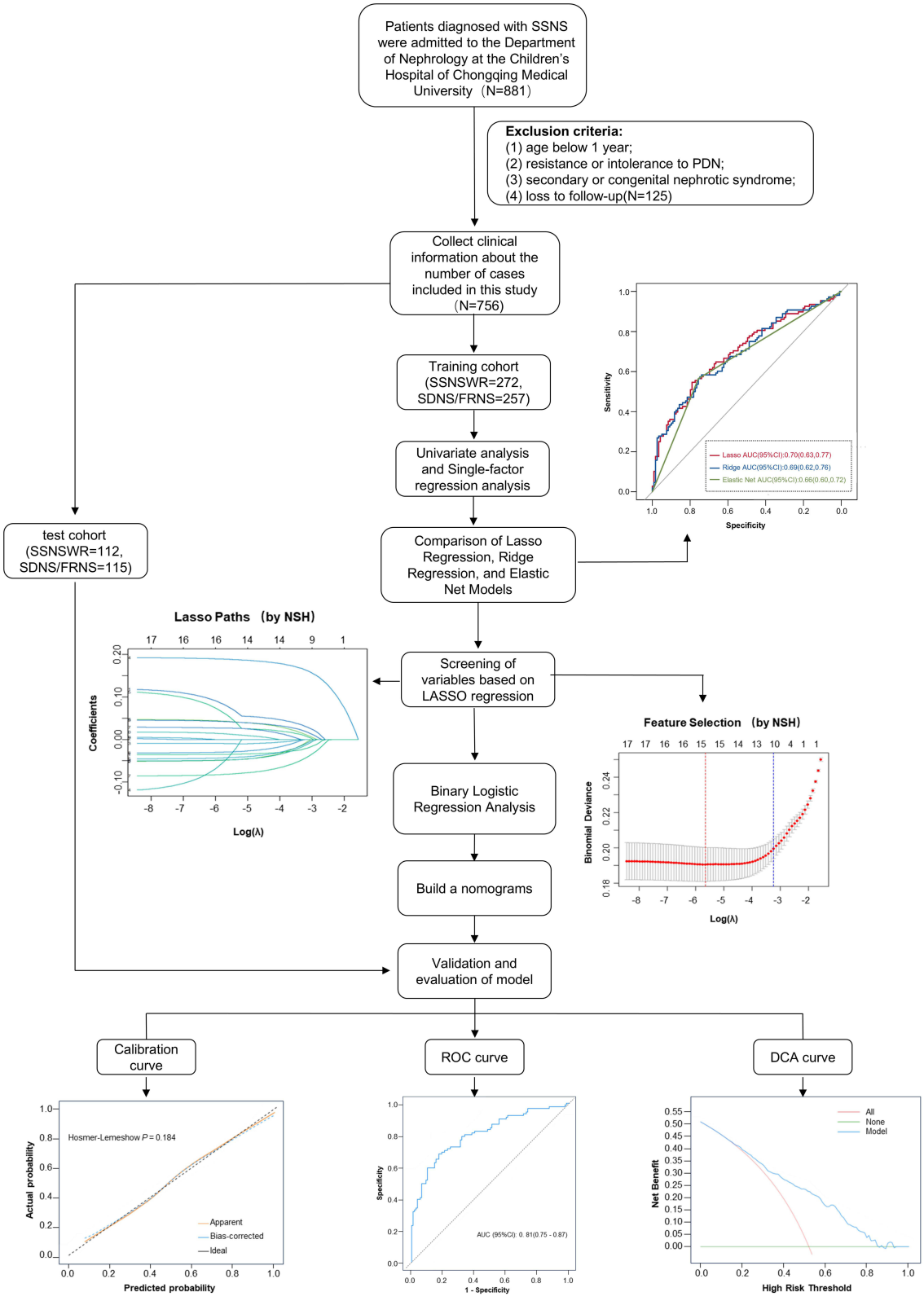

Figure 1 Flow chart of the study process. This flow chart outlines the key steps involved in the study process, detailing the progression from participant recruitment to data analysis.

model, and the calibration curve was plotted (Figure 5). The results showed that the predictive accuracy of the nomogram was validated through random split resampling of the original sample, and the calibration curve fluctuated closely around the 45° line, indicating that the nomogram had good performance and accuracy in predicting SSNS recurrence.

Table 1 Univariate Logistic Regression Results

Variables	B	S.E	Z	*P*	OR (95% CI)
Time for urinary protein turned negative (day), M (Q_1, Q_3)	0.15	0.02	7.60	<0.001**	1.17 (1.12 ~ 1.21)
Neutrophil counts, (×10^9/L), M (Q_1, Q_3)	0.09	0.03	3.25	0.001**	1.10 (1.04 ~ 1.16)
Lymphocyte counts, (×10^9/L), M (Q_1, Q_3)	−0.12	0.04	−3.02	0.003**	0.88 (0.82 ~ 0.96)
Eosinophil counts, (×10^9/L), M (Q_1, Q_3)	−0.96	0.36	−2.63	0.009**	0.38 (0.19 ~ 0.78)
SII, M (Q_1, Q_3)	0.01	0.00	2.75	0.006**	1.01 (1.01 ~ 1.01)
PLR, M (Q_1, Q_3)	0.01	0.00	2.37	0.018*	1.01 (1.01 ~ 1.01)
Total protein, (g/L), M (Q_1, Q_3)	0.04	0.01	3.32	<0.001**	1.04 (1.02 ~ 1.06)
BUN, (mmol/L), M (Q_1, Q_3)	0.08	0.03	2.69	0.007**	1.08 (1.02 ~ 1.14)
Creatinine, (umol/L), M (Q_1, Q_3)	0.01	0.00	1.68	0.092	1.01 (1.00 ~ 1.01)
HDL, (mmol/L), M (Q_1, Q_3)	0.39	0.12	3.18	0.001*	1.48 (1.16 ~ 1.89)
LDL, (mmol/L), M (Q_1, Q_3)	−0.11	0.03	−3.42	<0.001*	0.90 (0.84 ~ 0.95)
eGFR, mL/min·1.73m^2, M (Q_1, Q_3)	−0.01	0.00	−4.09	<0.001*	0.99 (0.99 ~ 0.99)
Potassium levels, (mmol/L), M (Q_1, Q_3)	−0.51	0.17	−2.92	0.004*	0.60 (0.43 ~ 0.85)
Chloride levels, (mmol/L), M (Q_1, Q_3)	−0.05	0.02	−1.99	0.047*	0.95 (0.91 ~ 0.99)
C4, (g/L), M (Q_1, Q_3)	−2.00	0.97	−2.06	0.040*	0.14 (0.02 ~ 0.91)
Thrombin time, (sec), M (Q_1, Q_3)	0.10	0.04	2.38	0.018*	1.10 (1.02 ~ 1.20)
Fibrinogen, (g/L), M (Q_1, Q_3)	−0.08	0.04	−1.88	0.060	0.92 (0.85 ~ 1.00)
D- dimer, (mg/L), M (Q_1, Q_3)	−0.01	0.03	−0.21	0.831	0.99 (0.93 ~ 1.06)
Urinary creatinine/albumin ratio, M (Q_1, Q_3)	−0.00	0.00	−1.08	0.281	1.00 (1.00 ~ 1.00)
Concurrent respiratory infection, n (%)					
NO					1.00 (Reference)
Yes	−0.70	0.27	−2.55	0.011*	0.50 (0.29 ~ 0.85)
Combined gastrointestinal infection, n (%)					
NO					1.00 (Reference)
Yes	−0.72	0.28	−2.56	0.010*	0.49 (0.28 ~ 0.85)

Notes: *:*P*≤0.05, **:*P*≤0.01.

Abbreviations: PLR, platelet-to-lymphocyte ratio, NLR, Neutrophil-to-Lymphocyte Ratio, BUN, blood urea nitrogen, HDL, high-density lipoprotein, LDL, low-density lipoprotein, eGFR, estimated glomerular filtration rate, C4, complement components 4, M, Median, Q_1, 1st Quartile, Q_3, 3st Quartile.

Table 2 Comparison of Model Performance

Model	RMSE	R^2
Lasso regression	0.469	0.124
Ridge Regression model	0.470	0.118
Elastic Network Model	1.084	0.107

Abbreviations: RMSE, root mean square error, R^2, R-squared, Lasso, least absolute shrinkage and selection operator.

A decision curve analysis (DCA) was conducted to evaluate the potential benefit to patients. As shown in Figure 6, the decision curve consistently remained above the "None" and "All" lines, confirming the clinical applicability of the model.

Discussion

As one of the most prevalent glomerular diseases in children, SDNS/FRNS pose significant health risks. Studies indicate that the initial SSNS episode requires approximately 115 mg/kg of PDN, with each subsequent relapse necessitating an

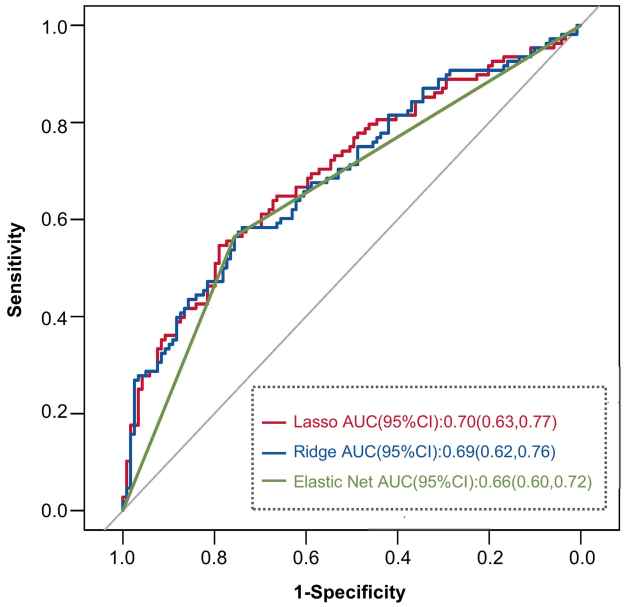

Figure 2 ROC curve analyses to compare the predictive performance of different models: (1) Lasso model (red), (2) Ridge model (blue), and (3) Elastic Net model (green). The ROC curve demonstrates the model's performance at various classification thresholds. The x-axis represents the false positive rate (1-specificity), while the y-axis indicates the true positive rate (sensitivity). The AUC measures the model's ability to differentiate between outcomes, with a higher AUC signifying better predictive accuracy.

additional 40–45 mg/kg. In cases of frequent relapses, cumulative PDN exposure can reach 0.5 mg/kg per day, substantially increasing toxicity risks.[2] Long-term research shows that over half of affected children suffer severe side effects from prolonged glucocorticoid use, including growth failure, obesity, and low bone density.[26] Early identification of SDNS/FRNS is an effective approach to reducing recurrence frequency. Few studies have previously addressed this area, and the accuracy of existing models has been limited. This gap is precisely what our study aims to fill.

Unlike previous studies, we first compared Ridge regression, LASSO regression, and elastic network models to select the best-performing model. We then combined LASSO regression with logistic regression analysis to build the final model, improving both its stability and predictive efficiency. The model's strong predictive accuracy and clinical utility were validated through multiple methods, including ROC curve analysis, confusion matrix, calibration plot, and DCA, confirming its applicability in clinical practice.

Infection is a key factor in the recurrence of SDNS/FRNS,[27] prompting our focus on PLR, a novel biomarker of inflammation that reflects platelet activation and systemic inflammation. PLR is both accessible and cost-effective, as it can be derived from routine blood tests.[28,29] Compared to single indicators, PLR reduces the impact of physiological variations and specimen processing on blood cell values, and it has recently been recognized as an important inflammatory marker in nephrology.[30–32] Inflammation, a well-known driver of kidney disease progression through oxidative and carbonyl stress,[33] is closely linked to PLR. Emerging evidence suggests that platelets play a role in both innate and adaptive immune responses,[34] with lymphocytes, particularly T and B cells, being central to the development of SSNS.[35]

Turkmen et al found that in patients with end-stage chronic kidney disease, PLR level was elevated and positively correlated with acute-phase reactants like C-reactive protein, interleukin-6, and tumor necrosis factor-alpha.[36] In primary membranous nephropathy, patients with a poor response to treatment tend to have a higher PLR, which is associated with unfavorable renal outcomes.[37] Overall, systemic inflammation and renal function throughout the disease course are linked to poor prognosis.[38] Proteinuria is a crucial marker for assessing treatment outcomes in SSNS. Its association with the PLR highlights the potential of PLR as a predictor of renal damage.[39] However, the role of PLR in the early identification of SDNS/FRNS has not been extensively studied. Our research addresses this gap by identifying PLR as an important risk factor for the progression of SSNS to SDNS/FRNS.

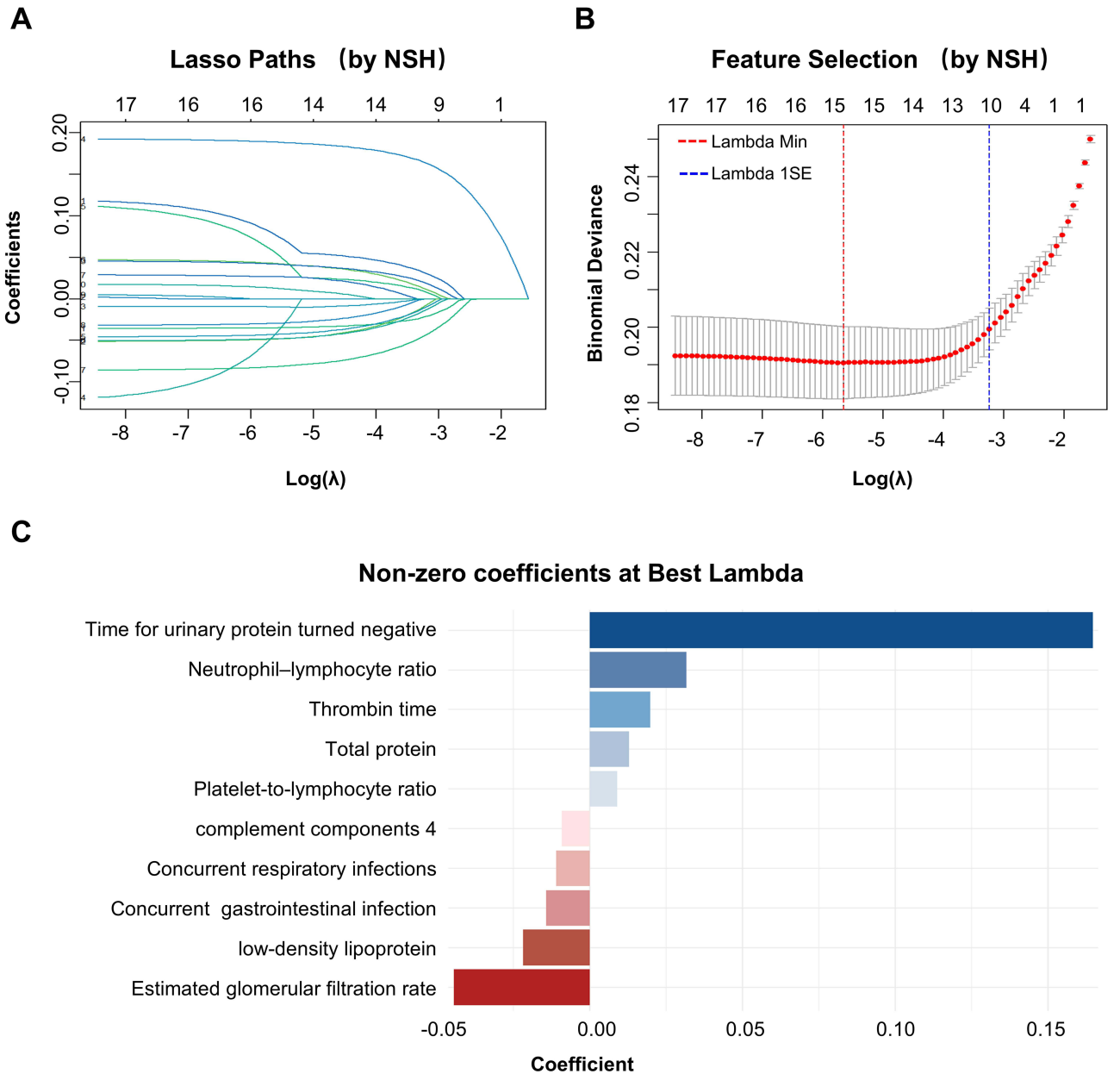

Figure 3 Screening of variables based on LASSO regression. (**A**) The variation characteristics of the coefficient of variables. As the value of λ decreased, the degree of model compression increased and the function of the model to select important variables increased. (**B**) Selection of the Optimal Lambda Value in LASSO Regression Using Cross-Validation. In the LASSO regression model, the optimal value of the regularization parameter, λ, was chosen through cross-validation. The X-axis represents the log-transformed lambda penalty coefficient, while the Y-axis shows the model's deviation. A dotted red line on the left marks the log (λ) value where the model error reaches its minimum, selecting 15 variables at log (λ) = 0.003. The dotted blue line on the right marks the "lambda 1se" value, representing the smallest deviation with a more simplified model. At this point, with log (λ) = 0.039, only 10 variable is selected, providing a balance between model simplicity and performance. (**C**) Non-zero Coefficients Plot at Best Lambda.

Recent advancements in lipidomics and proteomics have brought significant attention to lipid interconversion's role in SSNS. Studies indicate a positive correlation between proteinuria severity and lipid metabolism disturbances, suggesting that lipid dysregulation may play a central role in SSNS progression.[40–43]Prior research highlights significant lipid alterations and a range of abnormalities in SSNS patients,[44] with key metabolic differences between children with SSNS and healthy controls primarily linked to amino acid metabolism and the tricarboxylic acid cycle.[45,46] These findings underscore the importance of lipid transformation processes in the disease's pathophysiology.

Table 3 Multivariate Logistic Regression Results

Variables	β	S.E	Z	*P*	OR (95% CI)
Intercept	−3.62	1.36	−2.67	0.008**	0.03 (0.00 ~ 0.38)
Neu	0.09	0.04	2.62	0.009**	1.10 (1.02 ~ 1.18)
PLR	0.01	0.00	2.63	0.009**	1.01 (1.01 ~ 1.01)
LDL	−0.11	0.04	−2.73	0.006**	0.90 (0.83 ~ 0.97)
TT	0.20	0.07	2.95	0.003**	1.22 (1.07 ~ 1.39)
Time for urinar protein turned negative	0.16	0.02	7.27	<0.001**	1.17 (1.12 ~ 1.23)
eGFR	−0.01	0.00	−4.79	<0.001**	0.99 (0.98 ~ 0.99)

Notes: *:P≤0.05, **:P≤0.01.
Abbreviations: PLR, platelet-to-lymphocyte ratio, LDL-C, low-density lipoprotein, eGFR, estimated glomerular filtration rate, OR, Odds Ratio, CI, Confidence Interval.

Li W et al demonstrated that in SSNS, adiponectin levels are significantly lower in patients with infrequent relapses compared to those with frequent relapses.[47] Additionally, previous research has established an inverse relationship between adiponectin and LDL levels[48,49]. This relationship supports our findings that LDL levels are lower in patients with SDNS or FRNS. However, this finding contradicts previous studies, highlighting the complexity of the underlying lipid dysregulation mechanisms of the disease. It emphasizes the need for larger, prospective studies to validate these results and clarify the role of LDL in disease progression.

The duration of proteinuria resolution following the initiation of steroid therapy is closely linked to the risk of progression from SSNS to SDNS/FRNS, serving as a marker for steroid responsiveness. This correlation is well-supported by existing research.[1,2,6,27] Serum creatinine is a renal biomarker used to calculate the eGFR, a common measure for assessing the severity of kidney damage.[50,51] Our study found that lower eGFR was linked to SDNS/FRNS, underscoring the importance of monitoring renal function. Moreover, we identified TT as an independent risk factor for the progression from SSNS to SDNS/FRNS, suggesting that abnormal coagulation may play a significant role in this transition. Therefore, regular monitoring of coagulation parameters in SSNS patients is crucial.

LASSO regression offers key advantages over univariate analysis by reducing the risk of overfitting. It addresses multicollinearity and handles numerous covariates, helping to pinpoint a set of variables with the strongest predictive value. As a result, the nomogram developed from the LASSO-logistic regression model provides an effective tool for clinicians to identify SDNS/FRNS early. This tool supports the creation of personalized follow-up and treatment strategies, helping to reduce recurrence, minimize adverse drug reactions, and improve outcomes for affected children.

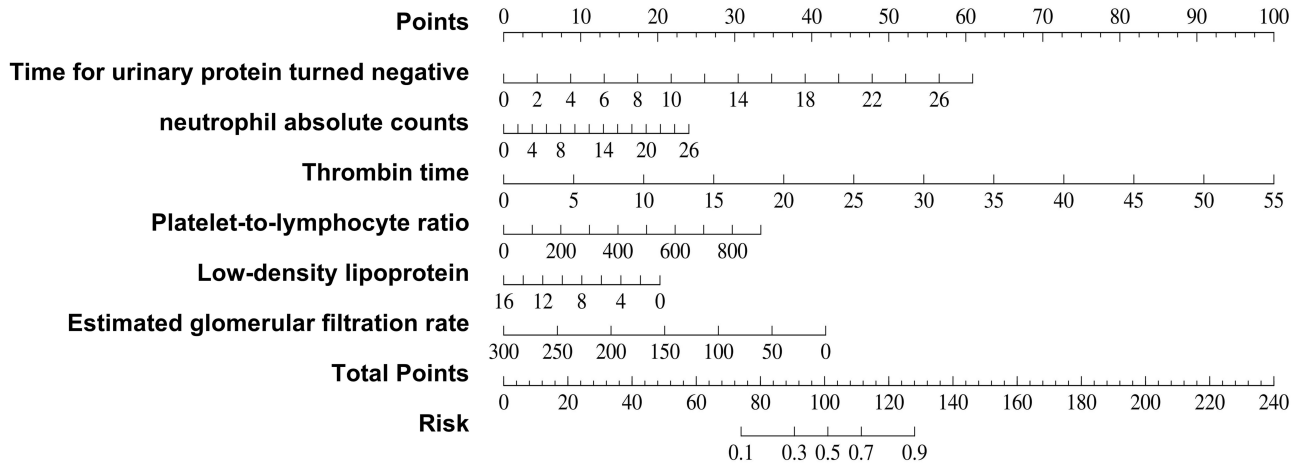

Figure 4 Nomogram used to predict the likelihood of SSNS progressing to SDNS/FRNS. Each variable's score reflects its contribution to the risk of SSNS progressing to SDNS/FRNS. By summing the scores of all variables, the model estimates the probability of progression from SSNS to SDNS/FRNS.

Table 4 Confusion Matrix: Training Cohort + Validation Cohort

Data	Accuracy (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Cut Off
Train sets	0.78 (0.73–0.82)	0.72 (0.68–0.76)	0.75 (0.69–0.80)	0.70 (0.64–0.76)	0.70 (0.65–0.76)	0.75 (0.69–0.80)
Test sets	0.81 (0.75–0.87)	0.73 (0.66–0.79)	0.73 (0.64–0.81)	0.73 (0.63–0.82)	0.76 (0.68–0.84)	0.69 (0.59–0.78)

Abbreviations: PPV, Positive predictive values, NPV, negative predictive value.

Although our study involved a moderate sample size with internal validation, its generalizability may be constrained by the single-hospital data source. To further validate and enhance the model, future studies across multiple centers with larger sample sizes will be essential.

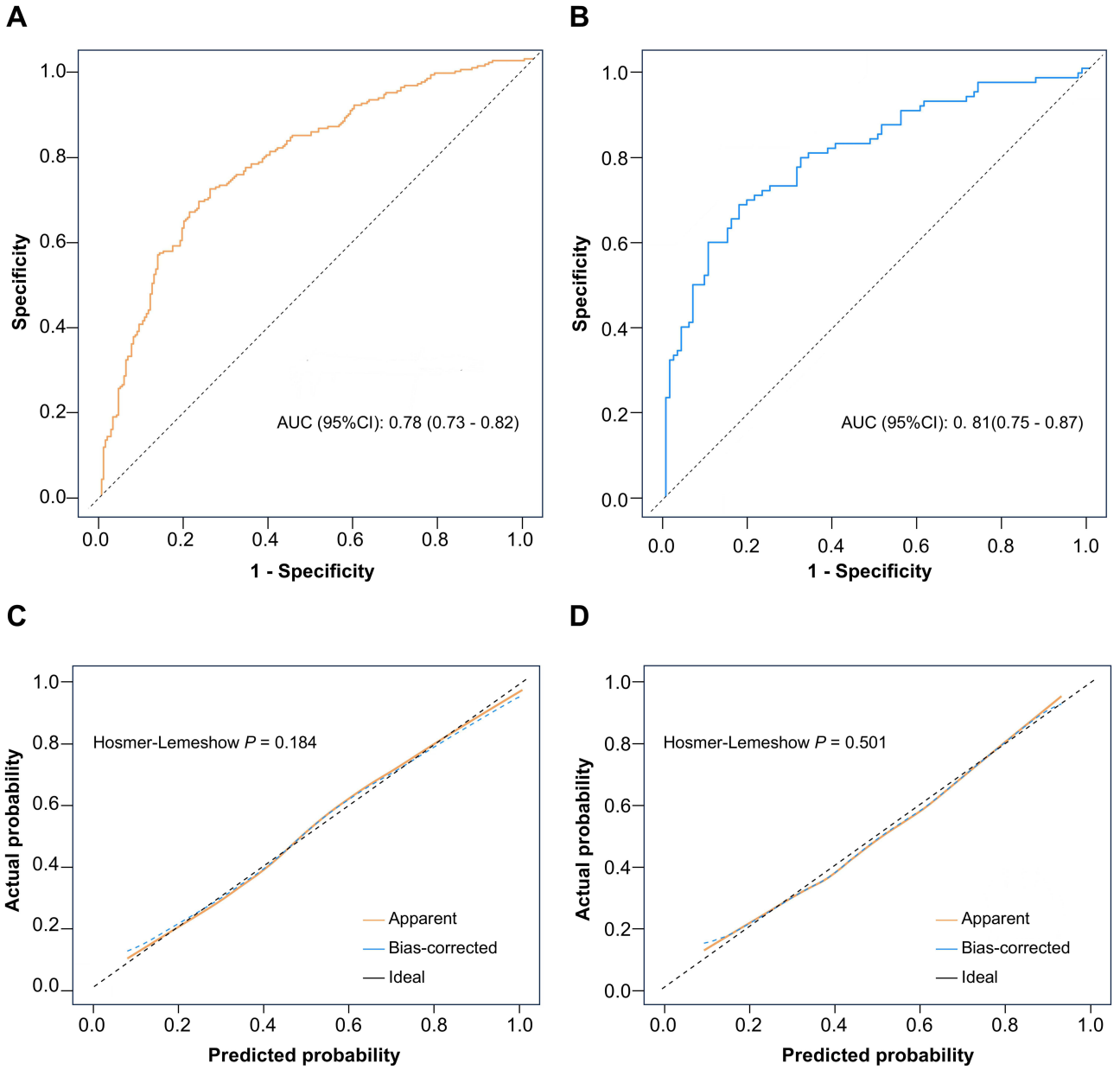

Figure 5 Evaluation of validity and reliability of the model. (**A**) ROC curves of the nomogram prediction model in the training cohort. (**B**) ROC curves of the nomogram prediction model in the validation cohort. (**C**) Calibration curves of the nomogram prediction model for the training cohort. (**D**) Calibration curves of the nomogram prediction model for the validation cohort. The calibration curve assesses the agreement between the model's predicted probabilities and the actual observed outcomes. The x-axis represents the predicted probabilities, while the y-axis shows the actual event frequencies. When the calibration curve closely aligns with the diagonal (45° line), it indicates better calibration, meaning the predicted probabilities closely match the observed outcomes. Deviation from the diagonal suggests miscalibration, where the model either overestimates or underestimates the probabilities.

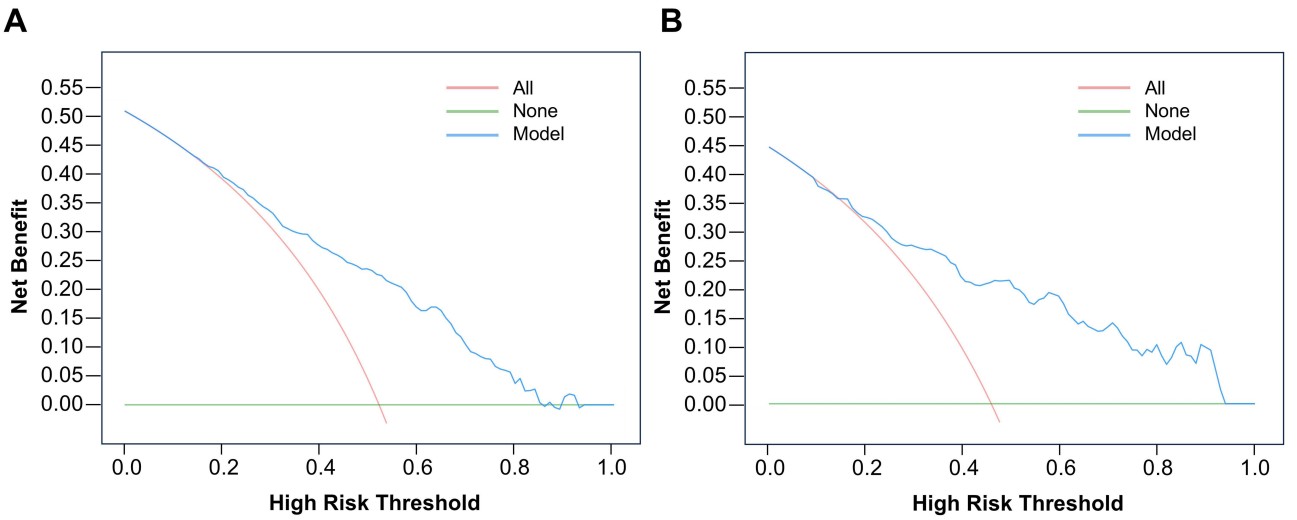

Figure 6 Decision curve analysis of the nomogram. (**A**) Decision curve analysis of the nomogram for the training cohort. (**B**) Decision curve analysis of the nomogram for the validation cohort The green horizontal lines represent the scenario where no patients progress to SDNS/FRNS, while the red lines indicate that all children progress to SDNS/FRNS. The blue line, which represents the model's predictions, consistently remains above both the "None" and "All" lines, showing that the model offers a better net benefit than these extreme clinical strategies across a range of decision thresholds.

Conclusion

This study employed a model combining LASSO regression and logistic regression to early identify SDNS/FRNS, resulting in six key predictors: time to proteinuria remission, PLR, LDL, TT, eGFR, and neutrophil absolute count. Together, these indicators help assess an individual's risk of progressing from SSNS to SDNS/FRNS. This approach may facilitate more accurate, personalized treatment, offering valuable insights to improve hormone-related adverse outcomes and enhance the quality of life for children with SDNS/FRNS.

Abbreviations

INS, idiopathic nephrotic syndrome; PDN, prednisone; SSNS, steroid-sensitive nephrotic syndrome; SDNS, steroid-dependent nephrotic syndrome; FRNS, frequently relapsing nephrotic syndrome; LASSO, least absolute shrinkage and selection operator; LDL, low-density lipoprotein, TT, thrombin time, PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; eGFR, estimated glomerular filtration rate; SSNSWR, steroid-sensitive nephrotic syndrome without relapse; RMSE, root mean square error; R^2: R-squared; ROC, receiver operating characteristic; AUC, area under curve; CI, confidence interval; DCA, decision curve analysis; OR, odds ratio.

Data Sharing Statement

The datasets generated or analyzed in this study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

This study was approved by the ethics committee of Children's Hospital of Chongqing Medical University. Informed consent was waived due to the retrospective nature of the data, which were de-identified. This study was conducted in accordance with the Declaration of Helsinki.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors confirm that this research was carried out without any commercial or financial relationships that could be perceived as potential conflicts of interest.

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