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Combined Fibrinogen and Urinary α1-Microglobulin as Predictors of Respiratory Tract Infection in Children with Nephrotic Syndrome

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

BCEFG 1 Hu Lijuan
BC 2 Liu Yuxin
AEG 1 Wang Kangying
BCD 3 Wu Fan
AE 3 Lin Yuanjie

1 Department of Clinical Laboratory, Affiliated Hospital of Putian University, Putian, Fujian, PR China
2 Provincial Clinical Medical College, Fujian Medical University, Fuzhou, Fujian, PR China
3 Department of Nephrology, Affiliated Hospital of Putian University, Putian, Fujian, PR China

Corresponding Author: Wang Kangying, e-mail: kangyingw@163.com
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Background: Respiratory tract infections (RTIs) are a major complication and prognostic determinant in children with nephrotic syndrome (NS), yet reliable predictors for infection risk remain lacking. Although fibrinogen (FIB) and urinary α1-microglobulin (α1-MG) have been individually linked to inflammation and renal injury, their combined prognostic value in pediatric NS has not been established. This study investigated the correlation between FIB, urinary α1-MG, and RTI occurrence in children with NS and evaluated whether their combined measurement improves early RTI risk prediction and prognosis assessment.

Material/Methods: Eighty children with NS and 70 age-matched healthy controls were enrolled. Serum FIB and urinary α1-MG levels were compared between groups. NS patients were stratified retrospectively into a good-prognosis group (n=50; no RTI during follow-up) and a poor-prognosis group (n=30; RTI occurrence), based on clinical outcomes rather than randomization. Clinical characteristics were assessed, and multivariate logistic regression identified independent risk factors for RTI. Correlation analysis and combined biomarker predictive modeling were performed.

Results: FIB and urinary α1-MG levels were significantly elevated in NS patients compared to controls. RTI risk was independently associated with younger age, longer hospital stay, lower albumin, and lack of vitamin A/D supplementation. Both FIB and urinary α1-MG were positively correlated with RTI occurrence, with higher levels in the poor-prognosis group ($P<0.05$). The combination of FIB and urinary α1-MG demonstrated superior predictive accuracy for RTI compared with either marker alone (AUC >0.917).

Conclusions: This study is the first to identify the combined measurement of FIB and urinary α1-MG as a possible independent predictor of RTI in children with NS. These findings provide a promising biomarker-based approach for early risk assessment, enabling targeted interventions to reduce RTI occurrence, shorten hospitalization, and ultimately improve prognosis in pediatric NS.

Keywords: Nephrotic Syndrome • Fibrinogen • Respiratory Tract Infections

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Introduction

Nephrotic syndrome (NS) is a common primary kidney disorder in children, characterized by hypoproteinemia, massive proteinuria, severe edema, and hyperlipidemia, resulting from increased glomerular capillary wall permeability [1]. Although its etiology remains unclear, factors such as allergies, genetic predisposition, and infections are implicated. Delayed diagnosis and treatment can lead to severe complications, including respiratory tract infections (RTIs), sepsis, lung infections, and other systemic infections, which can be life-threatening [2,3].

NS is the most common glomerular disorder in children, and the annual incidence is approximately 2 to 7 cases per 100 000 population, while the prevalence is 12 to 16 cases per 100 000 population. The disease occurs most frequently between 2 and 6 years of age, with boys affected nearly twice as often as girls. Minimal change disease accounts for most pediatric cases, while focal segmental glomerulosclerosis is more common in older children. Although corticosteroids induce remission in most patients, relapses are frequent and complications such as infections remain a major cause of morbidity and adverse outcomes.

Among pediatric patients with NS, RTIs are a frequent and clinically significant complication. Children with NS are particularly susceptible due to urinary loss of immunoglobulins and complement factors, contributing to impaired humoral immunity and increased infection risk [4]. The use of corticosteroids and other immunosuppressive therapies further compromises immune function [5]. RTIs not only prolong hospital stays and elevate healthcare costs, but also frequently contribute to relapse, delay recovery, and in severe cases lead to life-threatening complications such as pneumonia or sepsis [6]. Hence, early identification of high-risk NS children is critical for implementing timely preventive strategies and interventions.

While most pediatric NS cases respond well to corticosteroids, approximately 10% develop steroid resistance, referred to as hormone-resistant nephrotic syndrome [7]. Children with this disease can develop some level of resistance to immunosuppressants and gradually develop end-stage renal disease in the next 5 to 10 years [8,9]. Early renal injury in NS can go undetected because standard renal function tests often remain within normal ranges in the initial stages[10], contributing to missed or delayed risk assessment for complications. Fibrinogen (FIB) and urinary α1-microglobulin (α1-MG) are increasingly recognized as sensitive biomarkers reflecting both renal injury and systemic inflammatory status [11]. Elevated FIB levels indicate an acute-phase response to infection and inflammation, while α1-MG, a low-molecular-weight protein, serves as an early indicator of proximal tubular injury and systemic immune activation. In children with NS, these biomarkers may not only reflect the severity of kidney dysfunction but could also signal a heightened susceptibility to RTIs, given that systemic inflammation and impaired renal handling of immune mediators create a permissive environment for recurrent infections [12]. Establishing this link provides a strong rationale for investigating whether the FIB and urinary α1-MG combination can serve as predictive markers for RTI risk in pediatric NS patients.

However, studies directly evaluating these markers in the context of RTIs in NS remain limited, representing a critical gap that the present study seeks to address. Reliable predictors could enable risk stratification, guide targeted prophylactic strategies, inform therapeutic decision-making, and improve long-term outcomes. Therefore, investigating the clinical and laboratory markers associated with RTI in NS is essential to reduce complications, optimize patient management, and lessen the overall healthcare burden. Consequently, this study aimed to assess, for the first time, the relationship between FIB and urinary α1-MG levels and RTI risk in children with NS, and to evaluate whether their combined measurement improves early prediction and prognosis assessment.

Material and Methods

Research Subjects

This prospective study was conducted in the Department of Nephrology at the Affiliated Hospital of Putian University. Participants were recruited prospectively between July 2021 and July 2022. During the recruitment period, a total of 112 children attending our hospital with suspected nephrotic syndrome were screened. We excluded the following: patients with secondary nephrotic (lupus nephritis, IgA vasculitis, hepatitis-associated nephropathy syndrome) (n=10), histopathology inconsistent with primary nephrotic syndrome (n=7), recent (<3 months) immunosuppressive therapy other than corticosteroids (n=6), active infection at baseline before sample collection (n=5), and incomplete baseline laboratory data (n=4). Eventually, 80 patients with confirmed primary nephrotic syndrome were enrolled. Additionally, 70 age- and sex-matched healthy children were recruited from the Pediatric Health Examination Clinic of the same hospital during the same period to serve as the control group, as shown in the flow diagram in **Figure 1**. Clinical and laboratory data were extracted from standardized medical records. No missing data were present for variables included in the analysis, as data collection relied on routinely recorded parameters required for clinical management of nephrotic syndrome. All participants completed baseline laboratory testing, and informed consent was obtained from their parents or legal guardians before enrollment.

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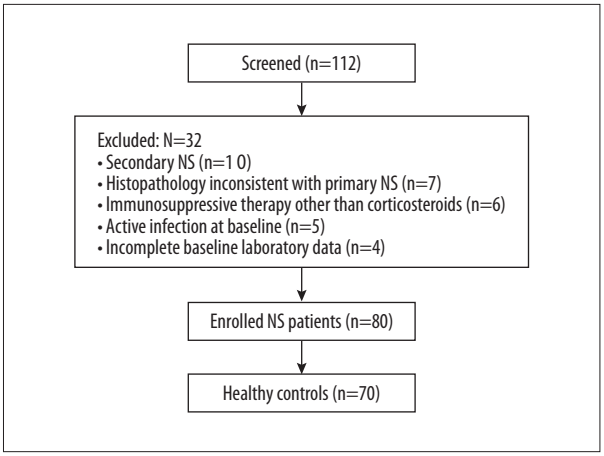

Figure 1. Flow diagram.

The study was approved by the Ethics Committee of the Affiliated Hospital of Putian University on January 20, 2021 (approval code Puyi Fuxilun 202411). The approval specifically covered the study population, objectives, and all clinical and laboratory data analyzed in this manuscript. The study was conducted in accordance with the Declaration of Helsinki and relevant national regulations. Where applicable, age-appropriate consent was obtained from participating children.

Participant confidentiality was safeguarded by assigning unique identification codes, with personal identifiers removed from the dataset before analysis. Access to data was restricted to the research team and stored on password-protected computers. The study involved minimal risk, limited to standard blood and urine collection procedures, which were performed by trained staff using sterile techniques to ensure participant safety.

For outcome analysis, NS patients were not randomized but were stratified into 2 groups according to their clinical course during hospitalization and follow-up: a good-prognosis group (n=50; no RTI occurrence) and a poor-prognosis group (n=30; RTI occurrence). Grouping was therefore based on observed outcomes rather than prospective random allocation. The control group consisted of age- and sex-matched healthy children recruited from routine health check-ups at the same hospital during the study period. Controls had no history of chronic kidney disease, nephrotic syndrome, acute or chronic infections, autoimmune disorders, or recent use of anti-inflammatory or immunosuppressive medications. Children with abnormal findings on physical examination or laboratory screening (including serum creatinine or urinalysis) were excluded.

The sample size was determined based on the availability of consecutive eligible patients admitted to the Affiliated Hospital of Putian University during the study period, along with matched healthy controls. Although no formal a priori power calculation was performed, all eligible patients who met the inclusion criteria were enrolled to maximize statistical robustness. A post hoc power analysis indicated that the sample size provided >80% power to detect significant differences in FIB and urinary α1-MG levels between groups at a significance level of 0.05. This was a prospective observational cohort study, in which pediatric patients with nephrotic syndrome were enrolled at presentation and followed longitudinally. Although data collection occurred prospectively, prognostic subgroups were assigned retrospectively based on clinical outcomes observed during the follow-up period, making this a prospective cohort with retrospective outcome-based classification.

Respiratory Tract Infection classifications

Respiratory tract infections (RTIs) were diagnosed according to standard pediatric clinical criteria and classified as upper respiratory tract infections (URTIs) or lower respiratory tract infections (LRTIs). The URTIs included acute pharyngitis, tonsillitis, rhinitis, sinusitis, otitis media, and nonspecific viral upper respiratory infections. The URTI diagnoses were based on symptoms (eg, fever, sore throat, nasal congestion, ear pain), physical examination, and, when required, supportive testing (throat swabs, rapid antigen tests). On the other hand, LRTIs included acute bronchitis, bronchiolitis, and pneumonia (viral, bacterial, or atypical). Diagnosis was based on clinical signs (cough, tachypnea, respiratory distress), auscultatory findings, and chest radiography or laboratory markers when indicated. All RTIs were diagnosed by attending pediatricians or pediatric infectious disease specialists.

Inclusion Criteria

All children with NS met the diagnostic requirements of the Evidence-Based Guidelines for the Diagnosis and Treatment of Hormone-Sensitive, Relapsing/Dependent Nephrotic Syndrome in Children (2016) [13]. Participants were eligible if they met and fulfilled 1 of the following categories**:** (1) Primary nephrotic syndrome**:** diagnosed clinically, with or without supportive histopathology. When biopsy was performed, histological patterns consistent with primary NS were accepted, including minimal change disease (MCD), Focal segmental glomerulosclerosis (FSGS), and Mesangial proliferative glomerulonephritis (MesPGN), (2) Treatment-based eligibility**:** Newly diagnosed, steroid-naïve patients; or steroid-sensitive patients (infrequent relapsers, frequent relapsers, or steroid-dependent); or steroid-resistant patients with prior biopsy confirming a primary nephrotic syndrome histologic pattern. All the study subjects were first-time patients with serum ALB <20 g/L; proteinuria >3.5 g/24 h, had not received any treatment before enrollment, and had normal liver function. Only patients with complete clinical data were included in this study.

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Exclusion Criteria

Children were excluded if any of the following were present: (1) Secondary nephrotic syndrome, including systemic lupus erythematosus, Henoch–Schönlein purpura/IgA vasculitis, hepatitis B/C–associated nephropathy, diabetes, infections, or known genetic/metabolic causes; (2) Histopathology indicating secondary or non-idiopathic disease, such as membranous nephropathy, membranoproliferative glomerulonephritis (MPGN) or chronic sclerotic changes inconsistent with active primary NS; (3) Ongoing or recent (<3 months) immunosuppressive therapy other than corticosteroids, unless part of stable maintenance treatment for steroid-resistant disease; (4) Active infection at baseline before sampling, comorbidities that impair immune function (eg, HIV, congenital immunodeficiency, malignancy) or prior kidney transplantation. We also excluded children with severe blood system infection, severe cardiovascular and cerebrovascular diseases, malignant tumors, congenital genetic diseases, poor treatment compliance, constant crying, or severe heart, liver, and lung function abnormalities.

Diagnostic Framework for Nephrotic Syndrome

Nephrotic syndrome was defined using established pediatric criteria and required nephrotic-range proteinuria with hypoalbuminemia, with supportive clinical and biochemical features outlined as follows: (1) Proteinuria (required): Patients were required to meet at least one of the following thresholds: 24-hour urinary protein excretion ≥40 mg/m^2/hour, or spot urine protein-to-creatinine ratio (UPCR) ≥2.0 mg/mg (≥200 mg/mmol), or urine dipstick protein ≥3+ on at least 2 consecutive samples when quantitative testing was not available; (2) Hypoalbuminemia (required): Serum albumin ≤2.5 g/dL (25 g/L) measured at presentation or during the same clinical episode as documented nephrotic-range proteinuria; (3) Edema (supportive but not mandatory): Presence of clinically apparent edema (periorbital, peripheral, genital, or generalized) was recorded but was not required for diagnosis if both nephrotic-range proteinuria and hypoalbuminemia were present; (4) Hyperlipidemia (supportive): hyperlipidemia was defined as total serum cholesterol ≥200 mg/dL (5.2 mmol/L) and/or triglycerides ≥200 mg/dL (2.3 mmol/L) when measured. Absence of lipid measurements did not preclude diagnosis.

All patients included in the study met the above core diagnostic criteria of nephrotic-range proteinuria and hypoalbuminemia. Supportive features (edema and hyperlipidemia) were documented when available but were not required for inclusion. If diagnostic practices evolved over the study period, such as increased use of spot UPCR in place of timed urine collections, thresholds were harmonized retrospectively to ensure a consistent case definition across the cohort. No patients were included based solely on clinical edema or dipstick proteinuria without confirmatory biochemical evidence of NS.

FIB and Urine α1-MG Detection

For prediction analyses, FIB and urine α1-MG biomarker measurements were obtained at predefined time points before the occurrence of respiratory tract infection (RTI). Specifically, urine and blood samples used in predictive models were collected during periods of clinical stability (baseline) or at NS presentation/relapse before any documented RTI episode. Only biomarker values measured in advance of the subsequent RTI event were included as predictors to ensure appropriate temporal sequencing. RTI outcomes were ascertained prospectively during follow-up, and biomarker measurements collected after RTI onset were not used in prediction analyses.

About 3 to 5 mL of venous blood was collected in anticoagulant-free and EDTA-K_2- or sodium citrate containing vacutainer tubes (Becton Dickinson, MountainView, CA, USA), under standardized conditions, from the patients and healthy controls in a fasting state at 8: 00 AM, after an overnight fast, before admission, 1 month after admission, and on the day of the physical examination of healthy children in our hospital. To obtain sera and plasma, blood samples were processed within 2 h of collection by centrifuging at 3000×g for 10 min at 4°C using a swing-bucket rotor (radius 10 cm). The serum and plasma were extracted and stored at -20°C for experimental assessment.

Plasma fibrinogen (FIB) in the patients and the healthy groups was measured using the Clauss clotting method on an automated Sysmex CS-5100 coagulation analyzer (Sysmex Corporation, Kobe, Japan), following the manufacturer's protocol. Calibration was performed with reference plasma from the manufacturer, and 2 levels of internal quality controls were included in each run to ensure assay reliability. The FIB detection limit was 50 mg/dL.

Urinary α1-microglobulin (α1-MG) was quantified by nephelometry on the BN™ II System Analyzer (Siemens Healthineers AG, Forchheim, Germany), with the corresponding N Latex α1-Microglobulin Kit (Siemens, Cat. No. 10466113). The normal reference range provided by the manufacturer was 0.0 to 1.2 mg/dL. Calibration was done using the manufacturer-provided standards and routine inclusion of low- and high-level internal controls. All assays were conducted in accordance with the manufacturer's instructions to maintain reproducibility. Three clean test tubes were recorded as blank, standard, and sample tubes. Next, 300 µL of buffer was added to each tube, 25 µL of distilled water was added to the blank tube, 25 µL of urinary α1-MG standard solution was added to the standard tube, and 25 µL of the sample to be tested was added to the test tube. The mixture was shaken well and placed at 27°C for

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15 min. The colorimetry was performed using a spectrophotometer. The turbidity of the immune complex was measured at a wavelength of 560 nm, and the absorbance was recorded to calculate the urinary α1-MG level of each group. The detection limit was 0.5 mg/L. The concentrations of urinary α1-MG were normalized to urinary creatinine to correct for urine dilution, and results were expressed as mg/g creatinine.

Serum albumin and lipid profile were assessed using Cobas c702 analyzer (Roche Diagnostics, Mannheim, Germany), while the renal function (creatinine, urea) was determined using Cobas c702 analyzer (Roche Diagnostics). Finally, complete blood cell counts were measured using the fluorescent dyeing flow cytometry method with the XN3000 analyzer (Sysmex, Japan). Reference ranges were those provided by the manufacturer and standardized for pediatric age groups at the study institution.

All assays were performed in duplicate for each study subject, and the mean values of the replicate measurements were used for statistical analysis. Outcome data on RTIs were obtained from medical records and confirmed by attending physicians based on standardized clinical criteria (fever, respiratory symptoms, and radiological or microbiological evidence where applicable). To ensure accuracy, outcome classification was independently verified by 2 investigators blinded to exposure status. All clinical and laboratory data were recorded using standardized case report forms and entered into a secure electronic database with double-entry verification to minimize errors.

To minimize bias, laboratory staff measuring serum FIB and urinary α1-MG were blinded to participants' clinical status and group allocation. Statistical analyses were performed on de-identified datasets, ensuring assessor blinding during data processing and interpretation. Participant blinding was not applicable due to the observational nature of the study, but objective biomarker measurements and assessor blinding strengthened the validity of the findings.

Patients' Clinical Data

General data included age (<2 years, ≥2 years), course of disease, sex (male, female), infection site (upper respiratory tract, lower respiratory tract), clinical classification (simple nephropathy, nephritic nephropathy), hospital stay (<30 days, ≥30 days), use of antimicrobial drugs before hospitalization (no, yes), and vitamin A/D supplementation (yes, no). The laboratory indicators analyzed included were IgA (≥3 g/L, <3 g/L), IgG (≥9 g/L, <9 g/L), and ALB (≥20 g/L, <20 g/L). Potential confounding factors, including age, sex, disease duration, serum albumin levels, length of hospital stay, and vitamin A/D supplementation, were systematically recorded. These variables were first analyzed using univariate tests, and those with significant associations were incorporated into multivariate logistic regression models to adjust for their influence. This approach allowed us to control for confounding effects and identify FIB and urinary α1-MG as independent predictors of RTI.

Study Outcomes

The primary outcome of this study was the occurrence of RTIs in children with NS. The secondary outcomes were: (1) Serum fibrinogen (FIB) and urinary α1-microglobulin (α1-MG) levels compared between NS patients and healthy controls, (2) The correlation between FIB/urinary α1-MG levels and RTI occurrence, (3) The predictive performance of FIB, urinary α1-MG, and their combination for RTI risk (measured using ROC curve analysis and AUC values), and (4) Identification of independent clinical risk factors for RTI (including age, sex, albumin level, hospital stay, and vitamin A/D supplementation) using multivariate logistic regression.

Statistical Analysis

Data were analyzed using SPSS 19.0 (IBM Corp, Armonk, NY, USA). Normality was assessed with the Kolmogorov–Smirnov test. Normally distributed variables were expressed as mean±standard deviation and compared between groups using independent-sample *t* tests; categorical variables were compared with the χ^2 test. Variables with $P<0.05$ in univariate analyses or considered clinically relevant were entered into multivariate logistic regression to identify independent predictors of respiratory tract infection (RTI), using stepwise forward selection. Odds ratios (ORs) with 95% confidence intervals (CIs) were reported, with OR >1 indicating increased RTI risk.

Receiver operating characteristic (ROC) analyses were also conducted with SPSS 19.0. ROC curves were generated to evaluate the discriminative ability of fibrinogen, urinary α1-microglobulin, and the combined predictive model for identifying respiratory tract infection in children with nephrotic syndrome. In SPSS, ROC curves were produced using the *Analyze* → *Classify* → *ROC Curve* function. The binary outcome variable (RTI: yes/no) was specified as the state variable, with "1" coded as the positive state. Each biomarker (fibrinogen and urinary α1-microglobulin) or model-predicted probability was assigned as the test variable. Discrimination of the predictive model combining plasma fibrinogen and urinary α1-microglobulin was assessed using the area under the receiver operating characteristic curve (AUC). Point estimates and 95% confidence intervals (CIs) for the AUC were computed using DeLong's method. We performed 10-fold cross-validation to estimate out-of-sample discrimination. Sensitivity, specificity, and corresponding coordinates across thresholds were also computed. The optimal cutoff was determined using the Youden index (maximum value of sensitivity + specificity – 1). A two-sided $P<0.05$ was considered statistically significant. Given the limited number

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Table 1. Comparison of FIB and urinary α1-MG levels between the 2 groups ($\bar{\chi}\pm s$).

Groups	Cases (n)	FIB (g/L)	Urine α1-MG (mg/g Cr)
Control group	70	2.32±1.05	15.7±2.21
Test group	80	3.89±1.30[a]	30.72±4.18[a]
t	/	8.061	10.206
P	/	0.0001	0.0001

Compared with the control group (*P*<0.05).

of RTI events, the number of predictors included in each multivariable model was restricted to reduce the risk of overfitting. Each model included 5 predictors for 25 RTI events, corresponding to an events-per-variable ratio of approximately 25/5. Model results should therefore be interpreted as exploratory and hypothesis-generating rather than definitive evidence of superior predictive performance.

Results

FIB and Urinary α1-MG Levels Are Elevated in Children With Nephrotic Syndrome

The research group included 46 males and 34 females aged 2 to 12 years. The average age of the participants in the experimental group was 3.75 (0.26) years. Another 70 children who underwent health examinations at our hospital during the same period were selected as the control group, comprising 40 males and 30 females, aged 2 to 11 years, with an average age of 3.37 (0.22) years. There was no significant difference in the overall data between the 2 groups (*P*>0.05), and they were comparable. We assessed the serum FIB and urinary α1-MG levels in the patients (test group) and the healthy controls. FIB expression was significantly elevated in the test compared to the control group (3.89 [1.30][a] vs 2.32 [1.05], *P*=0.0001). Similarly, the urine α1-MG levels were significantly increased in the test compared to the control group (30.72 [4.18][a] vs 15.7 [2.21]) (*P*=0.0001), as shown in **Table 1** (*P*<0.05). Our findings suggest that both FIB and urinary α1-MG levels are increased in children with Nephrotic syndrome. All participants completed the planned follow-up, and no attrition occurred.

Clinical Factors Associated With Respiratory Tract Infections in Children With Nephrotic Syndrome

Univariate analysis revealed that the occurrence of respiratory tract infection in children with nephrotic syndrome was not related to the course of disease, sex, location of infection, clinical classification, IgA, IgG, and pre-hospital use of antimicrobial drugs, with no statistical difference (*P*>0.05), as shown in **Table 2**. However, several clinical variables were significantly associated with the occurrence of RTIs in children with nephrotic syndrome. Younger age was correlated with higher RTI risk, reflecting greater immunologic immaturity in this group. Serum albumin (ALB) levels were inversely associated with RTI, with lower ALB values indicating increased susceptibility to infection. Length of hospital stay was also positively correlated to RTI occurrence, suggesting that prolonged hospitalization can increase exposure to nosocomial pathogens. Lack of vitamin A and D supplementation was also significantly associated with higher RTI rates (*P*<0.05), highlighting the role of nutritional support and immune regulation in infection prevention. These findings indicate that both host-related and treatment-related factors contribute to infection vulnerability in pediatric NS.

Multivariate Analysis of Independent Risk Factors For Respiratory Tract Infection in Children With Nephrotic Syndrome

To determine the risk factors for respiratory tract infection in children with NS, the incidence of respiratory tract infection in children with nephrotic syndrome was used as the dependent variable, and the variables with *P*<0.05 in the basic clinical data were selected as independent variables for multivariate logistic regression analysis (**Tables 3, 4**). Age, ALB, hospitalization time, supplementation of vitamins A, D, FIB, and urine α1-MG were the main risk factors for respiratory tract infection in children with nephrotic syndrome (*P*<0.05). Regression analysis results indicated that the factors that significantly affect respiratory tract infection in children with nephrotic syndrome include age (OR=3.050, 95%CI: 1.938-4.162, *P*=0.003), ALB (OR=3.068, 95%CI: 1.910-4.226, *P*=0.004), Length of hospital stay (OR=3.031, 95%CI: 1.909-4.153, *P*=0.004), Supplementing with A, D (OR=3.337, 95%CI: 2.003-4.671, *P*=0.007), FIB (OR=3.111, 95%CI: 1.895-4.327, *P*=0.001) and urine α1-MG (OR=3.597, 95%CI: 2.255-4.939, *P*=0.001) (**Table 4**).

Correlation Between FIB, Urinary α1-MG, and Respiratory Tract Infection

We further aimed to determine the correlation between FIB, urinary α1-MG, and the occurrence of respiratory tract infection. As shown in **Table 5**, FIB and urinary α1-MG are strongly

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Table 2. Assessment of factors associated with respiratory tract infections in children with nephrotic syndrome.

Factor		Good prognosis (n=50)	Poor prognosis (n=30)	χ^2/t	*P*
Age (years)	3≤12	33 (66.00)	11 (36.67)	6.519	0.011
	2-<3	17 (34.00)	19 (63.33)		
Disease duration (months)	/	9.20±1.59	9.43±1.67	0.615	0.541
Sex	Male	30 (60.00)	16 (53.33)	0.341	0.559
	Female	20 (40.00)	14 (46.67)		
Infection location	Upper respiratory tract	27 (54.00)	17 (56.67)	0.054	0.817
	Lower respiratory tract	23 (46.00)	13 (43.33)		
Clinical classification	Simple kidney disease	28 (56.00)	18 (43.33)	1.204	0.273
	Nephritis type nephropathy	22 (44.33)	12 (56.67)		
IgA (g/L)	≥3	26 (52.00)	14 (46.67)	0.213	0.644
	<3	24 (48.00)	16 (53.33)		
IgG (g/L)	≥9	28 (56.00)	12 (40.00)	1.920	0.166
	<9	22 (44.00)	18 (60.00)		
ALB (g/L)	≥20	33 (66.00)	10 (33.33)	8.049	0.005
	<20	17 (34.00)	20 (66.67)		
Hospitalization time (d)	<30	32 (64.00)	11 (36.67)	5.635	0.018
	≥30	18 (36.00)	19 (63.33)		
Pre-hospitalization use of antibiotics (example)	Nothing	27 (28.33)	14 (70.00)	0.404	0.525
	Have	23 (71.67)	16 (30.00)		
Supplementing with vitamin A, D	Have	32 (28.33)	9 (30.00)	8.675	0.003
	Nothing	18 (71.67)	21 (70.00)		

Table 3. Independent variable assignment.

Independent variables	Assignment
Age	2-<3 years old=0; 3 ≤12 years old=1
ALB	≥20 g/L=0; <20 g/L=1
Duration of hospital stay	<30 days=0; ≥30 days=1
Supplementing with Vit. A, D	Yes=0; No=1

correlated with the occurrence of respiratory tract infection (R-values: 0.595 vs 0.585, *P*=0.001).

Relationship Between FIB, Urinary α1-MG, and the Prognosis of Respiratory Tract Infection in Children With Nephrotic Syndrome

Next, we aimed to investigate the relationship between the FIB, urinary α1-MG, and the respiratory tract infection prognosis. We compared the FIB and urinary α1-MG expression levels in the good- and poor-prognosis groups. Our findings indicated that FIB levels in the poor-prognosis group were significantly elevated compared to the good-prognosis group (4.92 [1.35] [a] vs 3.26 [1.02]) (*P*=0.0001). Similarly, urinary α1-MG levels in the poor-prognosis group were significantly higher than in

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Table 4. Analysis of risk factors for respiratory tract infection in children with nephrotic syndrome.

Factor	β value	S. E	Wald χ^2	*P* value	OR value	95% CI
Age	1.115	0.556	4.022	0.003	3.050	1.938-4.162
ALB	1.121	0.579	3.748	0.001	3.068	1.910-4.226
Length of hospital stay	1.109	0.561	3.908	0.004	3.031	1.909-4.153
Supplementing with A, D	1.205	0.667	3.263	0.007	3.337	2.003-4.671
FIB	1.135	0.608	3.485	0.001	3.111	1.895-4.327
Urine α1-MG	1.280	0.671	3.639	0.001	3.597	2.255-4.939

Table 5. Correlation between FIB, α1-MG, and the RTI incidence and association between FIB, urinary α1-MG, and the prognosis of RTI in NS children.

Index	Incidence of respiratory tract infections	
	R-value	*P* value
FIB	0.595	0.001
Urine α1-MG	0.580	0.001

Groups	No of cases (n)	FIB (g/L)	Urine α1-MG (mg/g.Cr)
Good-prognosis group	50	3.26±1.02	25±2.5
Poor-prognosis group	30	4.92±1.35[a]	35.1±3.6[a]
t	/	6.230	14.8
P	/	0.0001	0.0001

Compared with the good-prognosis group, [a] P<0.05; FIB-Fibrinogen; respiratory tract infection; RTI, α1-MG – α1-microglobulin.

the good-prognosis group (35.1 [3.6][a] vs 25 [2.5]), (*P*=0.0001) (**Table 5**).

The Possible Use of FIB and Urine α1-MG Markers For Predicting Respiratory Tract Infection in Children With Nephrotic Syndrome

Finally, we aimed to assess the accuracy of FIB and urine α1-MG in diagnosing respiratory tract infection in children with nephrotic syndrome. To this effect, ROC curve analysis was done to propose the possible use of FIB and urine α1-MG levels for screening respiratory tract infections in children with nephrotic syndrome. The FIB demonstrated a lower separation (AUC=0.795, 95%CI: [0.691-0.898], *P*=0.001), with a sensitivity of 63.33% and a specificity of 72%, while urine α1-MG demonstrated slightly higher separation (AUC=0.811, 95%CI: [0.709-0.912], *P*=0.001), with a sensitivity of 56.67% and a specificity of 80%. The apparent AUC for the combined fibrinogen + urinary α1-microglobulin model was 0.917(95% CI: [0.846-0.988] (**Table 6, Figure 2**). At the pre-specified threshold, sensitivity was 90% and specificity was 94%. The 10-fold cross-validated AUC (mean of 10 repetitions) was 0.920 (95% CI: [0.847-0.993], *P*=0.001) (data not shown).

Discussion

In this study, we found that children with NS had significantly higher levels of fibrinogen (FIB) and urinary α1-microglobulin (α1-MG) compared with healthy controls, and these elevations were closely associated with the occurrence of RTIs. Multivariate analysis further identified younger age, prolonged hospitalization, lower serum albumin, and lack of vitamin A/D supplementation as independent risk factors for RTI. Notably, both FIB and urinary α1-MG were significantly elevated in the poor-prognosis group, and their combined measurement provided superior predictive accuracy for RTI compared with either biomarker alone, with an AUC exceeding 0.80. These findings suggest that the integration of clinical risk factors with biomarker assessment can enhance the early identification of NS children at high risk of infection.

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Table 6. ROC curve analysis of the prognostic value of FIB and urine α1-MG in predicting respiratory tract infection in children with nephrotic syndrome.

Factor	AUC	*P* value	Sensitivity |(%)	Specificity |(%)	Accuracy |(%)	95% CI
FIB	0.795	0.001	19/30 (63.33)	46/50 (92.00)	65/80 (81.25)	0.683-0.907
Urine α1-MG	0.811	0.001	23/30 (76.67)	45/50 (90.00)	68/80 (85.00)	0.714-0.909
FIB+Urine α1-MG	0.917	0.001	268/30 (93.33)	44/50 (88.00)	72/80 (90.00)	0.846-0.988

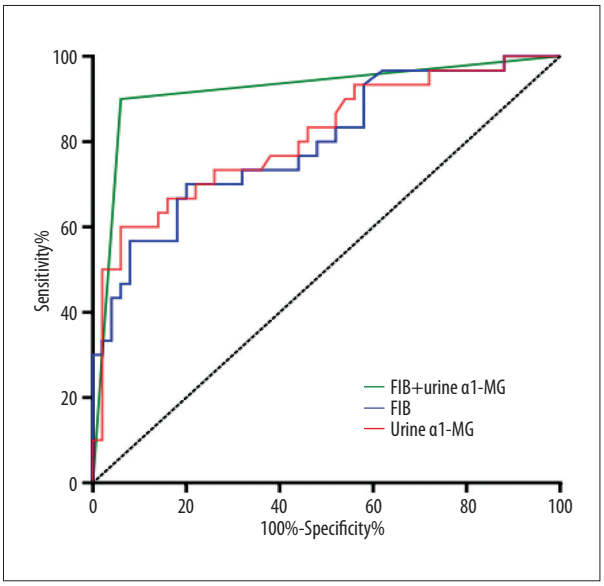

Figure 2. ROC curve of FIB and urinary α1-MG in predicting respiratory tract infection in children with nephrotic syndrome.

The association between elevated FIB and urinary α1-MG with RTI risk in children with NS may be explained by their roles in systemic inflammation and renal tubular injury. Fibrinogen is an acute-phase reactant that reflects heightened inflammatory activity and a prothrombotic state, both of which can impair host defense and predispose patients to infection [14]. Similarly, urinary α1-MG serves as a sensitive marker of tubular dysfunction and proteinuria-related renal injury, conditions that can exacerbate immune dysregulation in NS [15]. The synergistic predictive value observed when combining these biomarkers suggests that systemic inflammation and renal impairment contribute additively to infection susceptibility. Together with traditional risk factors, such as younger age, hypoalbuminemia, prolonged hospitalization, and inadequate vitamin supplementation, these findings underscore the multifactorial nature of RTI vulnerability in pediatric NS and highlight the potential of biomarker-based models to improve individualized risk stratification.

Our results are consistent with previous reports showing that children with NS are highly prone to infections due to impaired immune function, loss of protective proteins in the urine, and the frequent use of immunosuppressive therapy [16]. Prior studies have emphasized hypoalbuminemia and malnutrition as key contributors to infection risk, while others have noted the protective role of adequate vitamin A and D supplementation in maintaining mucosal and immune defenses [17,18]. However, few investigations have focused on objective biomarkers for early RTI risk prediction. By demonstrating that the combined measurement of FIB and urinary α1-MG provides superior predictive accuracy compared to traditional clinical factors alone, our study adds to the growing evidence supporting biomarker-driven approaches in pediatric nephrology. Clinically, incorporating these biomarkers into routine monitoring may enable earlier identification of high-risk children, guide preventive interventions, and ultimately reduce RTI-related morbidity and hospitalization in NS patients.

FIB is a plasma glycoprotein involved in the coagulation process and is an acute-phase reactant protein. When the coagulation system in the body is activated, the body can produce a large amount of FIB in response to stress to meet the supply needs of the coagulation system [19]. This study found that the FIB level in children with nephrotic syndrome was higher than that in healthy children, indicating that the hypercoagulable state in children with NS was higher than that in healthy children, thereby increasing the incidence of symptoms, causing respiratory infections, and threatening the life and health of children. Our finding is similar to the results of other previous research [20]. Our results show that observing the expression changes of FIB in children with nephrotic syndrome provides a basis for clinical prediction and treatment of the disease.

Urinary α1-MG is a small-molecule protein mainly produced by the liver [21]. It can pass freely in the glomerulus and is almost completely decomposed and taken up by epithelial cells in the renal tubules. Therefore, the physiological concentration in urine is relatively low. When the renal tubules are diseased, the urinary α1-MG in urine increases significantly. Thus,

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changes in urinary α1-MG levels can be used as an important indicator for clinical evaluation and prediction of kidney diseases, and play an important clinical role in primary kidney diseases [22].

The changes in urinary α1-MG levels in acidic urine are relatively stable, and the expression in urine is significantly higher than that of urinary β2-microglobulin (β2-MG) [23]. Therefore, urinary α1-MG has a high sensitivity and specificity in the early clinical assessment of renal tubular damage [24]. This study found that the urinary α1-MG level in the study group was higher than that in the control group, and the urinary α1-MG level in the poor-prognosis group was higher than that in the good-prognosis group.

Urinary α1-MG level was positively correlated with the occurrence of respiratory tract infections in children. This finding indicates that determining urinary α1-MG levels can be effectively used to assess the severity of NS in children. These results are consistent with the previous observations, which reported that urinary excretion of α1-MG had high diagnostic accuracy in identifying patients developing AKI following cardiac surgery in children [25]. The possible reason is that the lipoprotein synthesized by the liver increases, but the decomposition ability decreases, resulting in lipid metabolism disorders, hence hyperlipidemia, aggravating glomerular damage, and causing proteinuria leakage. Monitoring the urinary α1-MG expression changes can effectively reduce the degree of glomerular damage and alleviate the condition, showing that urinary α1-MG can effectively evaluate the urinary tract infection progression and the degree of renal function damage in children with nephrotic syndrome. Consequently, urinary α1-MG might be an important marker for improving the diagnosis and alleviating respiratory tract infections.

However, previous research examining fibrinogen levels in nephrotic syndrome has produced mixed results. While many studies report elevated fibrinogen in active nephrotic syndrome due to hepatic overproduction and the prothrombotic milieu, several investigations have found that fibrinogen increases are not consistently associated with clinical outcomes such as infection risk. Some reports have shown only modest or non-significant correlations between fibrinogen and markers of disease activity [26], and others have suggested that fibrinogen behaves primarily as a nonspecific acute-phase reactant rather than a disease-specific biomarker [27]. These discrepancies may reflect differences in patient demographics, disease stage, concurrent inflammation, lipid abnormalities, or steroid exposure. As a result, the role of fibrinogen as a predictive biomarker – especially for respiratory tract infection—remains incompletely defined. Our findings, showing higher fibrinogen levels in children who developed infection, strengthen the biological plausibility of this association but should be interpreted within the broader context of these inconsistent data.

Similarly, the literature on urinary α1-microglobulin (α1-MG) in NS demonstrates substantial variability. Although α1-MG is widely recognized as a marker of tubular protein handling and is often elevated in nephrotic patients due to increased tubular load, several studies have reported weak or absent associations between α1-MG and infection susceptibility [28]. In some cohorts, α1-MG appeared to reflect generalized tubular stress or proteinuria severity rather than serving as an indicator of immune vulnerability. Other research has shown that α1-MG rises in a variety of non-infectious conditions, including febrile illnesses and transient reductions in renal perfusion, further limiting its specificity [29]. These null or contradictory findings highlight that α1-MG alone may not reliably distinguish infection-related complications from other nephrotic syndrome–related physiological changes. In light of this heterogeneity, the strong discriminatory performance observed in our cohort requires cautious interpretation and underscores the need for replication in larger, diverse populations to determine whether the combined use of fibrinogen and α1-MG offers robust, generalizable predictive value.

We found that respiratory tract infections in NS patients are mainly related to age, hospitalization time, and supplementation of vitamins A/D, and ALB. These observations agree with the conclusions made by previous reports, which also affirmed the direct correlation of these factors with increased respiratory tract infection [30,31]. Several factors might support this observation. First, since the immune system of young children is not yet mature, their ability to resist these infections is relatively low. Therefore, clinical attention should be paid to the progression of the disease in young children, and appropriate immunomodulators should be used for treatment to avoid respiratory tract infections. Second, hospitals are areas where pathogens are relatively concentrated. Hospital pathogens are mainly drug-resistant bacteria and pathogenic bacteria. The longer the hospital stay, the more pathogens the child is exposed to, and the higher the chance of respiratory tract infection. Therefore, clinicians should pay special attention to children with longer hospital stays to reduce the occurrence of respiratory tract infections.

On the role of nutrition, our findings suggest that vitamin A and D deficiencies contribute to increased susceptibility to respiratory tract infections. This aligns with previous studies demonstrating that inadequate vitamin A and D status impairs immune defense mechanisms [32]. Vitamin A deficiency can cause nonspecific and specific immune damage, destroy the integrity of the digestive tract mucosa and respiratory tract, and be extremely susceptible to invasion by pathogenic microorganisms. The more severe the vitamin A deficiency, the

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higher the incidence rate, with severe symptoms. Lack of vitamin D leads to compromised immunity in children. Finally, the RTI risk in NS patients whose serum ALB is lower than normal is about 4.69 times that of children with normal serum ALB. Therefore, NS treatment in children include providing sufficient calories and high-quality proteins.

Although NS is generally reported to affect male children more frequently than females, at a ratio of approximately 2: 1, our study did not demonstrate a significant sex-related difference. This discrepancy may be attributed to several factors. First, the relatively small sample size may have limited the statistical power to detect sex-related differences. Second, our cohort consisted of hospitalized children within a defined age range (2-12 years), which may have attenuated the typical male predominance. Third, regional and ethnic variations have been shown to influence the epidemiology of NS, and such population-specific factors may partly explain our findings.

In summary, the occurrence of RTIs in children with NS was influenced by several interrelated clinical factors. Younger age was associated with a higher risk of RTI, likely due to the immaturity of the immune system and increased susceptibility to viral and bacterial pathogens. Lower serum albumin (ALB) levels reflected both protein loss and impaired immune defense, predisposing children to infections through reduced synthesis of immunoglobulins and complement proteins. Longer hospital stays increase exposure to nosocomial pathogens and invasive procedures, further elevating infection risk. Finally, lack of vitamin A and D supplementation contributed to impaired mucosal integrity and dysregulated immune function, weakening resistance to respiratory pathogens. Collectively, these factors interact with the underlying immune dysfunction of NS, amplifying vulnerability to RTIs and underscoring the need for integrated clinical and nutritional management strategies.

This study has some limitations. It was conducted at a single center with a relatively small sample size, which may limit the generalizability of the findings. Although we enrolled all consecutive eligible patients during the study period, the sample size was determined by feasibility rather than a prospective power calculation. Despite internal validation, the study has challenges that might affect conclusions about the high apparent predictive performance. The sample was relatively small and drawn from a single tertiary-care center, increasing the risk of sample-specific effects and optimistic estimates. Although cross-validation reduced overfitting and yielded similar, but somewhat lower, estimates of discrimination, external validation in larger, geographically diverse cohorts is required before clinical implementation of the biomarker panel. Similarly, the study had a relatively low events-per-variable ratio in the prediction models, which increases the potential for overfitting and optimistic estimates of predictive performance. While the observed associations suggest potential prognostic value, the models should not be considered clinically definitive, and external validation in larger datasets is necessary before implementation.

The study also lacked an independent validation cohort, which prevents firm conclusions about the robustness and reproducibility of the predictive model across different settings, case-mix distributions, or clinical practices. Next, variability in fibrinogen and urinary α1-microglobulin biomarker measurements may have introduced measurement error despite adherence to standardized protocols. Residual confounding cannot be excluded, since not all potential RTI risk factors (such as vaccination history or environmental exposures) were accounted for in the analysis.

The observational design precludes causal inference, and multicenter studies are needed to validate these results. Unmeasured confounding variables, including variability in infection severity, clinical management, and background immunosuppression, may have influenced biomarker levels and diagnostic performance. Finally, while laboratory staff and statisticians were blinded to group allocation, the observational design means that some degree of observer bias and residual confounding cannot be completely excluded. Multicenter studies with larger samples and external validation cohorts are needed to confirm these findings and support the clinical application of the combined biomarker model. Despite these limitations, our results consistently demonstrate that the combined measurement of fibrinogen and urinary α1-microglobulin provides a promising predictive value, and multicenter, prospective studies with larger cohorts are warranted to validate these findings.

Conclusions

Analysis of a combination of both urinary α1-MG and FIB can enhance the predictive value of RTI in children with NS. This study is the first to demonstrate that combining fibrinogen (FIB) and urinary α1-microglobulin (α1-MG) enhances the prediction of RTI in children with nephrotic syndrome. Unlike either marker alone, the dual-marker approach captures both systemic inflammation and renal tubular injury, providing a more comprehensive assessment of infection risk. This novel strategy offers a promising tool for early risk stratification and targeted intervention in pediatric NS.

The findings of this study have several potential clinical applications. First, routine measurement of FIB and urinary α1-MG in children with NS could serve as a practical tool for early identification of patients at high risk for RTIs, allowing clinicians to initiate closer monitoring and timely preventive measures. Second, these biomarkers may help guide individualized

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treatment strategies, such as optimizing albumin correction, nutritional supplementation, or immunomodulatory therapy in high-risk children. Third, incorporating FIB and urinary α1-MG into predictive models alongside traditional risk factors (eg, age, hospitalization duration, and vitamin status) could improve the accuracy of risk stratification, enabling a shift toward more personalized infection prevention. Finally, from a research perspective, these markers may provide valuable endpoints for evaluating the efficacy of future interventions aimed at reducing infection-related morbidity in pediatric NS.

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Ethics Statement

This study observed the 1964 Helsinki Declaration and subsequent amendments, and was approved by the ethical committee of the Affiliated Hospital of Putian University under approval number (Puyi Fuxilun 202411). The privacy and personal identity information of the subjects have been strictly protected and are not shown in the data.

Informed Consent

The participants were included in the study after providing written informed consent.

Data Availability

All pertinent data and analysis documentation have been fully incorporated within the submitted materials. If the review process would benefit from any further detail or supplementary explanation, we would be pleased to provide it upon request.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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