

Effect of voriconazole combined with glucocorticoid on nephrotic syndrome in children

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Abstract. – OBJECTIVE: To explore the efficacy of voriconazole combined with glucocorticoid on the nephrotic syndrome in children.

PATIENTS AND METHODS: A total of 62 children with nephrotic syndrome were enrolled in this study. They were treated in our hospital from February 2016 to August 2019, including 35 children treated with voriconazole in a control group, and 27 children treated with glucocorticoid combined with voriconazole in a research group. The efficacy was evaluated, and a logistic regression analysis was carried out to find out the risk factors affecting the efficacy. The enzyme-linked immunosorbent assay (ELISA) was used to determine the serum creatinine and urine protein expression before and after treatment. In addition, receiver operating characteristic (ROC) curves were drawn to analyze the predictive value of serum creatinine and urine protein expression.

RESULTS: The marked efficacy and total effective rate in the research group were significantly higher than those in the control group, while the non-efficacy in the research group was significantly lower than that in the control group ($p < 0.05$). After treatment, the expression of serum creatinine and urine protein in the research group was significantly lower than that in the control group ($p < 0.05$). The area under the curve (AUC) of urine protein was 0.798. The AUC of serum creatinine was 0.724. Multivariate logistic regression analysis revealed that serum albumin, high edema, infection, serum creatinine, and urine protein were independent risk factors.

CONCLUSIONS: Glucocorticoid can improve clinical efficacy. Serum creatinine and urine protein can be adopted as predictive factors for efficacy on children with nephrotic syndrome. Serum albumin, high edema, infection, serum creatinine, and urine protein were independent risk factors for the efficacy on children with nephrotic syndrome.

Key Words:

Nephrotic syndrome in children, Voriconazole, Glucocorticoid, Efficacy, Risk factor, Urine protein, Serum creatinine.

Introduction

Nephrotic syndrome is one of the most common kidney diseases in pediatric population mainly characterized by edema, massive proteinuria, and hypoproteinemia¹. Its annual prevalence rate is 16/0.1 million². The male and female prevalence ratio was 2:1³. Children with nephrotic syndrome would experience declined life quality⁴ and sufferings from various complications, with a mortality rate as high as 2.7%⁵. Proteins leak from blood to urine through glomeruli in patients with nephrotic syndrome, resulting in hypoproteinemia and generalized edema. Although most patients enter the clinical remission stage after initial treatment by glucocorticoids, a considerable number of patients (about 20%) still have or subsequently develop clinical steroid resistance in the development of disease^{6,7}. They failed to enter the clinical remission stage, which greatly increases the risk of suffering from various complications.

Glucocorticoid has become the cornerstone of treating nephrotic syndrome in children during the past 60 years, because more than 80-90% nephrotic syndrome patients can get complete remission after treatment with prednisone and prednisolone⁸. Unfortunately, 80% of those patients would suffer from one or more relapses, and additional glucocorticoid treatment is needed. In addition, about 10% children with nephrotic

ic syndrome are resistant to steroids and do not respond to standard steroid therapy. Infection is also considered to be one of the most common major complications of nephrotic syndrome⁹. Infection is one of the most common main complications of nephrotic syndrome. Voriconazole is a triazole broad-spectrum antifungal drug, which is mainly used to treat patients with progressive or potentially life-threatening fungal infection¹⁰. It is a broad-spectrum antifungal drug and has therapeutic effects on fungal infections in humans and animals. However, it is still not clear whether glucocorticoid combined with voriconazole can take effective therapeutic effect. At present, clinical detection of serum creatinine is one of the main methods commonly used to understand renal function. Elevated serum creatinine indicates deterioration of renal function, implying adverse consequences and the highest risk of death¹¹. Therefore, the expression of serum creatinine and urine protein was detected in children with nephrotic syndrome treated with glucocorticoid combined with voriconazole. The predictive value of its efficacy on children was also explored, aiming at providing reference for future clinical practice.

Patients and Methods

Clinical Data of Children

A total of 62 children with nephrotic syndrome treated in our hospital from February 2016 to August 2019 were enrolled as research participants. Among which, 35 children were treated with glucocorticoid as a control group, including 21 males and 14 females, with an average age of (6.9±3.9) years. The other children were treated through glucocorticoid combined with voriconazole as a research group, including 17 males and 10 females, with an average age of (6.2±3.8) years. This experiment was approved by the Ethics Committee of Yantaishan Hospital.

Inclusion and Exclusion Criteria

Inclusion criteria: Patients met the diagnostic criteria of the Italian Society for Pediatric Nephrology (SINePe)¹²; patients diagnosed and treated in our hospital; patients between 3 and 15 years old with complete clinical data; and those whose immediate family members signed informed consent forms.

Exclusion criteria: patients with other comorbid tumors; patients with physical disability; pa-

tients transferred to our hospital; patients resistant or allergic to drugs used in this study; and those with mental disease, language disorder, or diseases affecting the results of this study.

Therapeutic Regimen

Children in the control group were treated with glucocorticoid, the steps were as follows: Each child was given prednisolone (Xianju Pharmaceutical Co., Ltd., Zhejiang, China, State Food and Drug Administration (SFDA) approval number: H33021225) according to his/her body mass at an oral dose of 160 mg/m²/d. When the condition became stable, the dose should be gradually reduced. The maintenance dose is 5 to 10 mg, depending on the condition of patients. After 3 months, the disease condition of the child was evaluated, and the oral dose of prednisolone was adjusted. The oral dose was reduced by 10% of the original dose within 2 weeks, and then a small dosage was maintained for treatment. Children in the research group were treated with glucocorticoid combined with voriconazole (Laimei Longyu Pharmaceutical Co., Ltd., Chongqing, China, SFDA: H20051152). The steps were as follows: Each child was treated with 100 ml 0.9% sodium chloride solution mixed with 200 mg voriconazole (BaiteMedical Products Co., Ltd., Shanghai, China, SFDA: H20013250) according to the child's clinical symptoms and medical history for more than 1 h, twice a day, a total of 7 continuous days (1 course). After 7-10 days of intravenous dripping, the child took the medicine orally instead. During treatment, the physical condition of the child was closely monitored, and timely symptomatic treatment should be carried out in case of abnormal conditions.

Evaluation of Clinical Efficacy on Children

Efficacy evaluation standard: treatment with the following outcomes was defined as markedly effective. Symptoms and signs of the child completely disappeared, and urine protein and serum creatinine returned to normal. Treatment with the following outcomes was defined as effective: Symptoms and signs of the child were alleviated, and urine protein and serum creatinine remained stable. Treatment with the following outcomes was defined as ineffective. Symptoms and signs of the child were not significantly alleviated, and urine protein and serum creatinine were unstable.

Determination Methods

Fasting venous blood was sampled from each child one day before treatment and 2 months after treatment. The sample was stored at 4°C for 20 min, and then centrifuged at 1500 g and 25°C for 10 min. Subsequently, the blood was detected using the double antibody sandwich enzyme-linked immunosorbent assay (ELISA). In addition, mid-stream urine was sampled from each child one day before treatment and 2 months after treatment. The urine sample was also detected using the double antibody sandwich ELISA. The Serum Creatinine Kit was purchased from Shanghai Heng Yuan Biotechnology Co., Ltd., with item number HD39799, and the Urine Protein Kit was purchased from Shanghai Blue Gene Biotechnology Co., Ltd., with item number E01U0011. All operations were carried out in strict accordance with the kit instructions.

Outcome Measures

Primary outcome measures:

The efficacy on the two groups was evaluated, and risk factors affecting the efficacy on the children with nephrotic syndrome were also analyzed.

Secondary outcome measures:

The expression of urine protein and serum creatinine in the children was determined, and its predictive value for efficacy was explored.

Statistical Analysis

In this study, the obtained data were analyzed statistically using SPSS 20.0 (IBM, Armonk, NY, USA) and visualized into required figures using GraphPad 7. The distribution of quantitative data was analyzed using the Kolmogorov-Smirnov (K-S) test, in which data in normal distribution were expressed as the mean \pm standard deviation (Mean \pm SD). The independent-samples *t*-test was used to make comparison between groups, and the paired *t*-test was used to make comparison among multiple groups. Enumeration data were expressed as rate (%), analyzed using the chi-square test, and expressed as χ^2 . In addition, receiver operating characteristic (ROC) curves were drawn to analyze the predictive value on the efficacy of urine protein and serum creatinine in children with nephrotic syndrome. Univariate and multivariate analyses were carried out to find out independent risk factors for efficacy on the children. $p < 0.05$ indicates a significant difference.

Results

Clinical Data of Children

There was no significant difference between the research group and the control group in clinical data including age, sex, weight, nationality, place of residence, course of disease, genetic disease history of parents, urinary protein, and serum creatinine, so the two groups were comparable (all $p > 0.05$; Table I).

Efficacy on the Children

The marked efficacy and the total effective rate in the research group were significantly higher than those in the control group, while the non-efficacy rate in the research group was significantly lower than those in the control group (all $p < 0.05$). In addition, there was no significant difference between the two groups in efficacy ($p > 0.05$; Table II).

The Expression of Urine Protein and Serum Creatinine in the Children and its Predictive Value for Efficacy

Before treatment, the expressions of urine protein and serum creatinine in children from the research group were 52.37 \pm 19.31 (g/L) and 127.13 \pm 59.72 (μ mol/L), respectively. After treatment, the expressions of the two indicators in the children were 102.15 \pm 8.75 (g/L) and 101.33 \pm 23.52 (μ mol/L), respectively. In contrast, before treatment, the expressions of urine protein and serum creatinine in children from the control group were 151.52 \pm 18.01 (g/L) and 125.65 \pm 63.68 (μ mol/L), respectively. After treatment, the expressions of the two indicators in the children were 113.58 \pm 11.35 (g/L) and 109.89 \pm 29.57 (μ mol/L), respectively. Therefore, before treatment, there was no significant difference in the expressions of the two indicators between the research group and the control group, and after treatment, the expressions of the two indicators in the research group were significantly lower than that in the control group ($p < 0.05$). Furthermore, ROC curves of urine protein and serum creatinine for predictive value in efficacy showed that the AUC of urine protein was 0.798, and its sensitivity and specificity were 96.77% and 58.06%, respectively. The AUC of serum creatinine was 0.724, and its sensitivity and specificity were 41.94% and 96.77%, respectively (Table III and Figure 1).

Univariate Logistic Regression Analysis

The patients were divided into a markedly effective group ($n=28$) and an effective + ineffective

Table I. Basic clinical data of the children [n(%)].

	The control group (n = 35)	The research group (n = 27)	χ^2 or t	p-value
Age	6.9±3.9	6.2±3.8	0.709	0.481
Sex				
Male	21 (60.00)	17 (62.96)	0.056	0.812
Female	14 (40.00)	10 (37.04)		
Weight (kg)	22.1±2.3	22.5±2.1		
Nationality				
Han nationality	25 (71.43)	19 (70.37)	0.008	0.928
Minority nationality	10 (28.57)	8 (29.63)		
Place of residence			0.010	0.921
Urban area	19 (54.29)	15 (55.56)		
Rural area	16 (45.71)	12 (44.44)		
Course of disease (days)	19.63±8.12	18.27±8.57	0.638	0.526
Genetic history of parents			0.598	0.439
Yes	3 (8.57)	1 (3.70)		
No	32 (91.43)	26 (96.30)		
Urine protein (g/L)	151.52±18.01	152.37±19.31	0.179	0.859
Serum creatinine (μ mol/L)	125.65±63.68	127.13±59.72	0.093	0.926

group (n=34) according to the efficacy. Univariate analysis was carried out on the clinical data of the two groups and found that there was no significant difference between the two groups in age and sex (both $p > 0.05$), but there were differences between them in serum albumin, high edema, infection, serum creatinine, and urine protein (All $p < 0.05$; Table IV).

Multivariate Logistic Regression Analysis

The indexes (serum albumin, high edema, infection, serum creatinine, and urine protein) with differences in the univariate analysis were included in the assignment (Table V). The results of regression analysis showed that serum albumin (OR: 1.082, 95%CI: 1.061-1.069), high edema (OR: 1.274, 95%CI: 1.085-1.496), infection (OR: 1.016, 95%CI: 1.015-1.028), serum creatinine (OR: 4.634, 95%CI: 1.358-5.726), and urine protein (OR: 4.729, 95%CI: 1.474-5.833) were independent risk factors for efficacy on children with nephrotic syndrome (Table VI).

Discussion

Nephrotic syndrome is the most common glomerular disease in children, the second most common kidney disease in pediatric nephrosis, and the most common congenital malformation of kidney and urinary tract¹³. It is characterized

by massive proteinuria, hypoproteinemia, peripheral edema, and hyperlipidemia¹⁴. According to statistical estimations, the incidence of nephrotic syndrome in children may be 15, 000/16, 900, and its prevalence rate in children may be 16/100,000. Its incidence and prevalence rate vary along with different geographical regions and races in the world. The reported incidences for children of European, South Asian, East/South-East Asian, and African descent were 2.40, 15.83, 1.81, and 3.01 respectively^{15,16}. Therefore, it is an urgent problem for clinicians to alleviate nephrotic syndrome.

Glucocorticoid is an effective anti-inflammatory and immunosuppressive drug, whose effect is mediated by genomic and non-genomic mechanisms. Genomic mechanisms involve activation or inhibition of specific genes encoding anti-inflammatory and pro-inflammatory proteins. Glucocorticoids have been the cornerstone of nephrotic syndrome treatment in children for decades because the symptoms on most children can be completely relieved through treatment with prednisone or prednisolone^{17,18}. One of the most common major complications of nephrotic syndrome is infection. Voriconazole is a broad-spectrum antifungal drug for the treatment of fungal infection, with therapeutic effect on fungal infection in both humans and animals¹⁹. However, it is still unclear whether glucocorticoid combined with voriconazole can play a role in nephrotic syndrome in children. Therefore, in this study, we

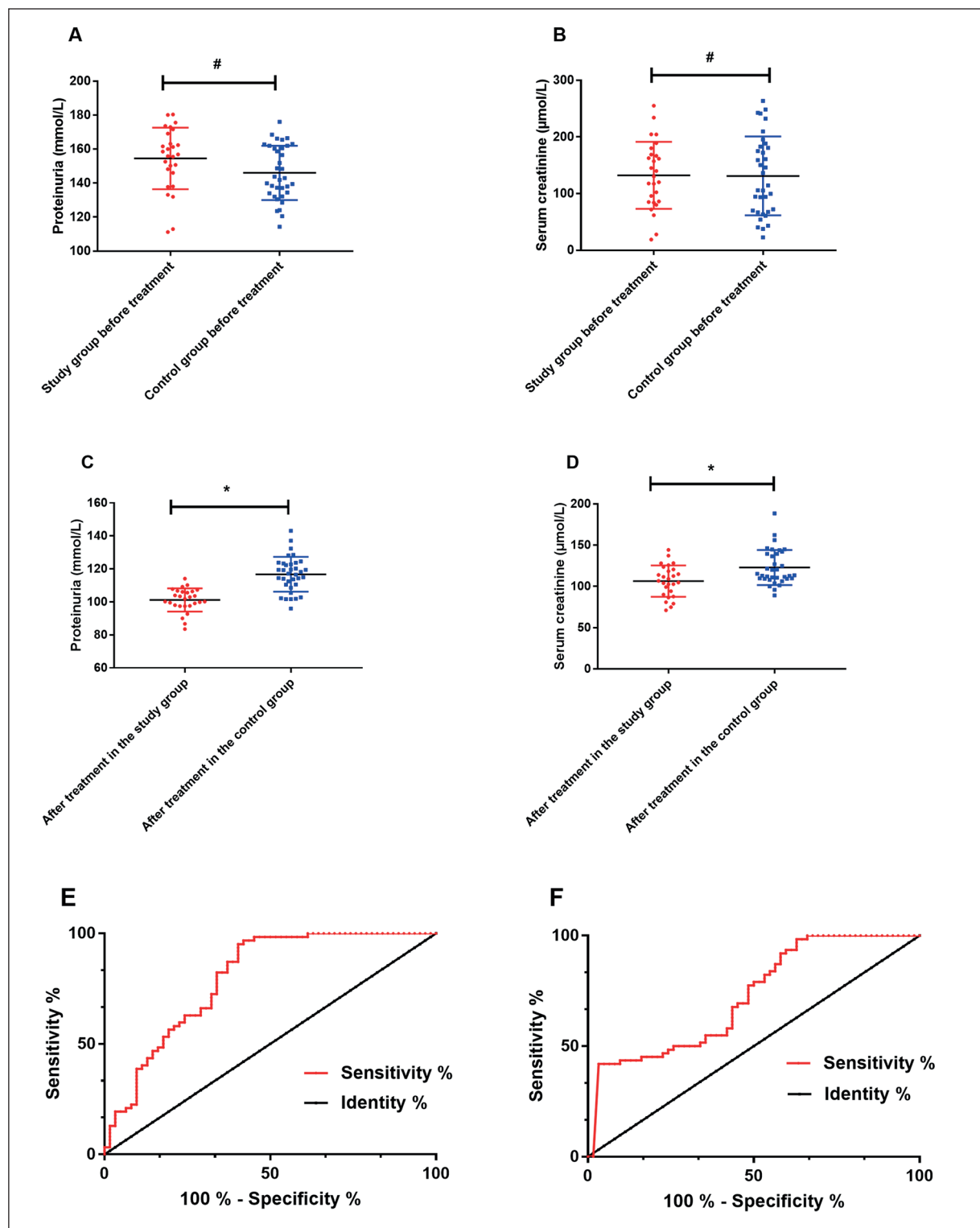


Figure 1. The expression of urine protein and serum creatinine in children and its predictive value for efficacy. **A**, There was no significant difference in the expression of urine protein between the research group and the control group before treatment ($p > 0.05$). # indicates that there was no difference between the two groups. **B**, There was no significant difference in expression of serum creatinine between the research group and the control group before treatment ($p > 0.05$). # indicates that there was no difference between the two groups. **C**, The expression of urine protein in the research group was significantly lower than that in the control group after treatment ($p < 0.05$). * indicates a difference between the two groups. **D**, The expression of serum creatinine in the research group was significantly lower than that in the control group after treatment ($p < 0.05$). * indicates a difference between the two groups. **E**, The AUC of proteinuria was 0.798, and its sensitivity and specificity were 96.77% and 58.06%, respectively. **F**, The AUC of serum creatinine was 0.724, and its sensitivity and specificity were 41.94% and 96.77%, respectively.

Table II. Efficacy on the children.

	The number of cases (n)	Efficacy [n(%)]			
		Patients with markedly effective treatment	Patients with effective treatment	Patients without effective treatment	Effective treatment rate (%)
The control group	35	11 (31.43)	15 (42.86)	9 (25.71)	74.29%
The research group	27	17 (62.96)	9 (33.33)	1 (3.71)	96.29%
χ^2		6.120	0.583	5.459	5.459
p-value		0.013	0.445	0.020	0.020

Table III. Analysis on the ROC curves of urine protein and serum creatinine for predictive value in efficacy.

	Urine protein (g /L)	Serum creatinine (μ mol/L)
AUC	0.798	0.724
Std.Error	0.040	0.045
95%5CI	0.719-0.877	0.636-0.813
p-value	0.001	0.001
Cut-off	151.100	223.400
Sensitivity (%)	96.77%	41.94%
Specificity (%)	58.06%	96.77%

Table IV. Univariate analysis [n(%)].

Clinicopathological feature	Markedly effective group (n=28)	Effective + ineffective group (n=34)	χ^2 or t	p-value
Age of onset			1.966	0.161
<5 years old	6 (21.43)	3 (8.82)		
\geq 5 years old	22 (78.57)	31 (91.18)		
Sex			0.668	0.414
Male	17 (60.71)	24 (70.59)		
Female	11 (39.29)	10 (29.41)		
Serum albumin			8.381	0.004
\geq 35 g/L	21 (75.00)	13 (38.24)		
<35 g/L	7 (25.00)	21 (61.76)		
High edema			28.490	0.001
Yes	4 (14.29)	28 (82.35)		
No	24 (85.71)	6 (17.65)		
Infection			10.690	0.001
Yes	5 (17.86)	25 (56.82)		
No	23 (82.14)	19 (43.18)		
Serum creatinine (μ mol/L)	99.87 \pm 22.97	110.92 \pm 20.16	2.017	0.048
Urine protein (g /L)	102.26 \pm 8.86	112.79 \pm 11.43	3.986	0.001

treated children with nephrotic syndrome through glucocorticoid combined with voriconazole, and analyzed the efficacy on the children, with the goal of providing references for clinical treatment.

Firstly, we compared the clinical efficacy of the two groups after treatment. It was found that the non-efficacy rate in the research group was lower

than that in the control group. The total effective rate in the research group was significantly higher than that in the control group, indicating that glucocorticoid combined with voriconazole can improve the effective treatment rate on patients. One study by Warejko et al²⁰ has revealed that nephrotic syndrome in children is characterized by

Table V. Assignment.

Factor	Assignment
Serum albumin	≥35 g/L=1, <35 g/L=0
High edema	Yes=1, No=0
Infection	Yes=1, No=0
Serum creatinine	Raw data of those belonging to continuous variable were used for analysis.
Urine protein	Raw data of those belonging to continuous variable were used for analysis.

Table VI. Multivariate logistic regression analysis.

Factor	B	S.E	Wals	Sig.	Exp (B)	95% CI of EXP (B)	
						Lower limit	Upper limit
Serum albumin	0.523	0.362	1.271	0.001	1.082	1.061	1.069
High edema	0.581	0.763	2.842	0.001	1.274	1.085	1.496
Infection	0.626	0.639	1.269	0.001	1.016	1.015	1.028
Serum creatinine	0.767	0.548	5.519	0.021	4.634	1.359	5.726
Urine protein	0.774	0.556	5.623	0.001	4.729	1.474	5.833

proteinuria, hypoproteinemia, edema, and hyperlipidemia. It may give rise to hypertension, severe infection, and thrombosis. Williamson et al²¹ had pointed out that serum creatinine is a widely used marker for evaluating renal function, and it is almost completely excreted through the kidney as a waste of skeletal muscle metabolism. Therefore, serum creatinine can be used to estimate glomerular filtration rate. An increase in the expression of serum creatinine indicates renal insufficiency or renal failure. In this study, the expression of serum creatinine and urine protein was detected. It was found that before treatment, there was no significant difference between the research group and the control group, and after treatment, the expression of serum creatinine and urine protein in the research group was significantly lower than that in the control group. It implied that glucocorticoid combined with voriconazole can better inhibit the expression of serum creatinine and urine protein. We further drew ROC curves and found that the AUCs of urinary protein and serum creatinine were 0.724 and 0.798, respectively, so both indexes had high clinical predictive value. According to the ROC curves in one study by Stone et al²², the AUC of proteinuria was 0.870, which is approximately the same as the results of our study. It can support the results of our study. In the end, the patients were divided into a markedly effective group, an effective + ineffective group for multivariate logistic regression analysis. The result indicated that serum albumin, high edema,

infection, serum albumin, and urine protein were independent risk factors of nephrotic syndrome in children. It suggested that serum albumin, high edema, infection, serum creatinine, and urine protein can be used as predictive indexes for efficacy in children with nephrotic syndrome.

We have preliminarily verified the clinical value of urine protein and serum creatinine and the efficacy of glucocorticoid combined with voriconazole on children with nephrotic syndrome. However, there are still some limitations in this study. First, the drug dosage used in this study is single, and we have not conducted any in-depth study on whether the effective treatment rate on patients can be improved by increasing drug dosage. Secondly, we did not follow up the patients for prognosis analysis. Therefore, we will increase the therapeutic schemes of different drug dosages to analyze the efficacy on children and follow up the children to improve our research results.

Conclusions

To sum up, glucocorticoid combined with voriconazole can improve the clinical efficacy on patients and increase the overall treatment rate of patients, and serum creatinine and urine protein in children with nephrotic syndrome after treatment can be used as predictive factors for clinical efficacy on the children.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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