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Establishment of relapse risk model and multivariate logistic regression analysis on risk factors of relapse in children with primary nephrotic syndrome

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Abstract

This study aimed to investigate relapse risk factors in children with primary nephrotic syndrome (PNS) for prevention and early intervention via logistic regression.

One hundred thirty-seven children with PNS were enrolled in this study. Clinical variables were analyzed by single-factor and multiple regression analysis to establish the regression equation. The predictive ability of the regression equation was investigated by the receiver operating characteristic curve (ROC).

Files of 17 patients were lost, and 120 patients were enrolled finally in the study, among whom 55 cases (45.8%) had frequently relapsed. Single-factor analysis and multiple regression analysis revealed that concurrent infection on first onset, irregular glucocorticoid therapy, severe hypoalbuminemia, and persistent severe hyperlipidemia were the significant risk factors for frequent relapse on PNS ($P < .05$), among which infection remained to be the main inductive factor. Among the 4 indicators, serum albumin had the best diagnostic efficacy based on the area under the ROC curve (0.933), sensitivity (89.09%), and specificity (81.54%). The area under curve, sensitivity, and specificity for the combined diagnostic model of the 4 indices were 97.8%, 98.18%, and 90.77%, respectively, which had good predictive power for the relapse of patients.

Concurrent infection, irregular glucocorticoid therapy, severe hypoalbuminemia, and persistent severe hyperlipemia were all the risk factors for PNS relapse. The established logistic regression model based on these factors above is reliable for predicting frequent PNS relapse. Much attention should be paid to these critical factors, and early intervention should be taken to reduce the incidence of relapse.

Abbreviations: CI = confidence interval, FSGS = focal and segmental glomerulosclerosis, MCNS = micro change nephrotic syndrome, PNS = primary nephrotic syndrome, ROC = receiver operating characteristic curve.

Keywords: children, logistic regression, primary nephrotic syndrome, relapse, risk factor

1. Introduction

Primary nephrotic syndrome (PNS) remains one of the children's most common glomerular diseases. Above 90% of the children suffering from this disease respond to steroid treatment and stay steroid-sensitive, among whom 60% of cases have frequent relapse,[1] which will lead to a delayed disease course and complex therapy. Even some patients develop end-stage renal disease.[2] The renal pathology of PNS is divided into micro change nephrotic syndrome (MCNS), mesangial proliferative glomerulonephritis, membranoproliferative glomerulonephritis, membranous nephropathy, and focal and segmental glomerulosclerosis (FSGS). Among the types, MCNS is the primary pathological type, accounting for about 80%, and is steroid-sensitive; steroid-resistant nephrotic syndrome is mainly familiar with FSGS.

Therefore, one of the aims to effectively treat PNS relapse in children is to identify the risk factors of relapse early and before treatment and adopt some preventive measures to prevent relapse. Researches[3–8] indicate that infection, lower adrenal cortical function, vaccination, atopic allergology, and mental/psychological pressure are the common inducers of PNS relapse. However, these researches only attach much importance to analyzing single relapse-related factors. No systematic study about relapse has yet been reported worldwide, and also, no

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The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

The ethics committee approved this study at Xuzhou Medical University (XFYF2014-xjs011-03). Written informed consent was taken from their parents before participating in the study. All methods were carried out following relevant guidelines and regulations.

The authors declare no competing interests.

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report provides a well-established model to predict relapse in PNS in children. The present study investigates relapse risk factors in children with PNS by single-factor analysis and multiple regression analysis, establishing a logistic regression model. The objective is to discriminate relapse factors in the early stages of PNS, thus providing sufficient evidence for preventing relapse and early intervention of PNS relapse.

2. Subjects and Methods

2.1. Subjects

One hundred thirty-seven children who were hospitalized in the Affiliated Hospital of Xuzhou Medical College between January 2015 and January 2020 were enrolled in the study. Only previously untreated and newly diagnosed patients were included to avoid selection bias. Patients with secondary nephritis (Henoch-Schonlein purpura nephritis, lupus nephritis, or hepatitis B–related nephritis), drug intoxication, or other systematic diseases were excluded. The ethics committee approved this study at Xuzhou Medical University. Written informed consent was obtained from child's parents or legal guardians.

2.2. Inclusion and exclusion

Children with PNS were included for the primary nephrotic syndrome, where the inclusion criteria included:

1. all met the diagnostic criteria for the primary nephrotic syndrome: 24-hour urine protein quantification ≥ 50 mg/kg or random urine protein/urine creatinine ratio > 2.0 and serum albumin < 25g/L;
2. initial onset.

Exclusion criteria:

1. purpura nephritis, lupus nephritis, and hepatitis B virus-associated nephritis, nephritis after atypical streptococcal infection;
2. drug-related kidney damage;
3. immunoglobulin (Ig) A nephropathy;
4. other immune system diseases with clinical manifestations of the nephrotic syndrome such as anti-neutrophil cytoplasmic antibody-associated nephritis, anti-glomerular basement membrane nephritis, heomlytic uremic syndrome, etc;
5. congenital kidney diseases;
6. hereditary kidney diseases;
7. preadmission already given to children with steroid and immunosuppressive therapy;
8. combined urinary tract abnormalities (e.g., polycystic kidney, vesicoureteral reflux, etc);
9. follow-up time < 1 month could not assess the treatment effect;
10. age ≤ 1 year or ≥ 18 years.[9]

2.3. Treatment and judgment of relapse

All patients received standard treatment with daily corticosteroid (prednisone) (Jiangsu Pengyao Pharmaceutical Co., Ltd) at a dose of 2 mg/kg/day (maximum 60 mg/day) for 4 weeks, and then were switched to alternate day therapy. The relapse of PNS referred to the urine protein turning positive for > 2 weeks, and the frequent relapse referred to the relapse > 2 times within half a year or 3 times within 1 year.[10,11]

2.4. Followed up

All subjects were followed up every 2 or 4 weeks after leaving the hospital, adopting the same criteria for initial glucocorticoid responsiveness. When the patients were in a stable condition, they came every month. The examined items included medication, blood pressure, intraocular pressure, biochemical indexes, clinical manifestation, urine routine, and growth situations. Each patient was followed up for 1 year.

2.5. Clinical and lab indexes

We obtained the following files from the cases included in the study and subsequent reexamination. The indexes included first onset age, gender (male/female), hypertension (yes/no; preschool, ≥120/80 mm Hg; school child, 130/90 mm Hg[12]), degree of edema (mild, moderate, or severe edema: whole-body edema, edema of the scrotum, body cavity effusion),[13] time of urine protein turning negative (from initial oral prednisone to urine protein turning negative for continuing 3 times), white blood count, blood C-reactive protein, blood IgE, blood urea nitrogen and creatinine, plasma albumin, total blood cholesterol, infections (respiratory tract infection, digestive infection, urinary infection, skin infections, etc), glucocorticoid administration (regular/irregular), family nursing (yes/no), specific body constitution (asthma, allergic rhinitis, etc), and area of residence (city/country). According to the follow-up results, the patients were divided into relapse-free and relapse groups, and the clinical differences between the 2 groups were analyzed.

2.6. Statistical analysis

SPSS 25.0 software was used for statistical analysis (SPSS Inc., USA). All data were presented as mean ± SD or as percentages. Continuous variables between 2 groups were evaluated via Student *t* test or Mann–Whitney *U* test. The applicable comparison of continuous variables among the 2 groups was achieved by Kruskal–Wallis variance analysis or 1-way analysis of variance test. Nonparametric variables were analyzed using the Kruskal–Wallis test or Mann–Whitney *U* test. Multiple regression analysis was performed to detect the variables. $P < .05$ was considered significantly different. Categorical variables were analyzed by chi-square test. Variables with statistical significance were termed as independent variables in the single-factor analysis. The relapse was the dependent variable, and multiple regression analysis was gradually made; thus, the regression equation was established.[14,15] Relapse relative risk value odds ratio and 95% confidence interval (CI) were determined. Stepwise multivariate logistic regression analysis on relapse risk factors ($\alpha = 0.05$, Backwards). The receiver operating characteristic (ROC) curve was used to analyze and evaluate the predictive ability of the regression model.

3. Results

3.1. General information on subjects

The included patients were collected from January 2015 to January 2020. During the follow-up, there were 13 patients lost 5 months after discharging (due to a change of telling phone number), with a dropout rate of 10.8%, and 4 patients migrated to another city. Finally, 120 cases (80 males and 40 females) were included. The first onset age of PNS was 2 to 13 years, with an average of 6.3 years. There were 55 cases (38 males and 17 females) that had a relapse (relapse group), and 65 cases (42 males and 23 females) had no relapse (relapse-free group). The relapse rate was 45.8%. No difference was found between 2 groups for gender constitute ($\chi^2 = 0.269$, $P = .604$). More details are shown in Table 1. There were significant differences between the relapse-free group and relapse group for the following items: first onset age, edema, time of urine protein turning negative, concurrent infections, glucocorticoid administration, white blood count, blood C-reactive protein, blood IgE, total

Table 1

Single-factor analysis of clinical indexes in PNS children.

Indexes	Relapse-free (65 cases)	Relapse (55 case)	$t/z/x^2$	*P* value
Gender (male/female)	42/23	38/17	0.269	.604
Age (years)	8 (5–9)	5 (3–7)	3.936	**<.001**
Edema (mild/severe)	32/33	16/39	5.035	**.025**
Hypertention (no/yes)	47/18	42/13	0.256	.613
Time of urine protein turn negative ≥ 10 days (no/yes)	48/17	23/32	12.649	**<.001**
Infection (no/yes)	53/12	8/47	53.498	**<.001**
Irregular GC reduction (no/yes)	52/13	23/32	18.531	**<.001**
No special family nursing (no/yes)	29/36	34/21	3.535	0.060
Special constitution (no/yes)	47/18	36/19	0.656	0.418
Patient source (city/countryside)	31/34	23/32	0.415	0.519
White blood cell ($\times 10^9$/L)	10.09 (8.98–13.80)	12.82 ± 2.73	2.700	**.007**
Serum albumin (g/L)	16.76 ± 2.28	12.44 ± 1.86	11.238	**<.001**
Serum cholesterol (mmol/L)	10.74 ± 1.79	14.42 (12.73, 15.62)	6.953	**<.001**
Blood IgG (mg/L)	4.57 ± 0.98	3.24 ± 0.84	7.931	**<.001**
Blood urea nitrogen (μmmol/L)	4.20 (3.29–5.75)	4.27 (3.25–6.45)	–0.221	.825
Serum creatinine(U/L)	34.0 (25.0–40.5)	35.0 (26.0–41.0)	–0.846	.397
Blood C-reactive protein (mg/L)	10.03 (8.66–12.02)	15.29 (11.03–18.93)	–5.520	**<.001**

Bold represents a statistical difference between the two groups ($P < 0.05$).

GC = Glucocorticoid, IgG = immunoglobulin G, PNS = primary nephrotic syndrome.

blood cholesterol (all $P < .05$, Table 1). However, there were no statistical differences between the 2 groups regarding hypertension, family nursing, and specific physical characteristics, etc (all $P > .05$).

3.2. Stepwise multivariate logistic regression analysis on risk factors of relapse

Ten variables with statistical significance, including onset age, time of urine protein turning negative, concurrent infections, glucocorticoid administration, white blood count, serum albumin, etc, were chosen as the independent variable ($P < .05$). Using relapse as the dependent variable, multivariate logistic regression analysis was made further (Backwards methods). After 7 iterations, 4 variables were reserved (Table 2). The regression equation was as follows: logit $(p) = 7.268 - 3.723 \times_1 + 2.886 \times_2 - 1.161 \times_3 + 0.409 \times_4$, statistical significance was found in the regression equation. The value of the Hosmer-Lemeshow fit index was 0.999, with $P > .05$, indicating good matching in this equation. Concurrent infections, irregular GC administration, severe lower serum albumin, and higher cholesterol concentration were independent risk factors of relapse in PNS children.

Table 2

Stepwise multivariate logistic regression analysis on risk factors of relapse.

Variable	β	SE	Ward	Sig.	OR	LL	UL
Infection (x1)	–3.723	1.248	8.900	0.003	0.024	0.002	0.279
Dosage reduction (x2)	2.886	1.235	5.461	0.019	17.919	1.593	201.602
Serum albumin (x3)	–1.161	0.438	7.006	0.008	0.313	0.133	0.740
Serum cholesterol (x4)	0.409	0.179	5.229	0.022	1.506	1.060	2.138
Constant	7.268	5.015	2.101	0.147	1434.246		

LL = lower limit, OR = odds ratio, SE = standard error, Sig. = significant, UL= upper limit.

3.3. Evaluation of the model

Among the 4 indicators, serum albumin had the best diagnostic efficacy based on the area under the ROC curve, sensitivity, and specificity of the diagnosis; the indicator with the worst diagnostic efficacy was Dosage reduction; it was calculated that the diagnostic efficacy of serum albumin and serum cholesterol were both better than dosage, and the difference was statistically significant ($P < .05$); however, there was no statistical difference between infection index and 3 other indicators ($P > .05$). The results of the multivariate regression analysis with statistically different areas under the ROC curve for the 4 metrics are summarized in Table 3.

The logistic regression equation was listed as follows: logit$(p) = 7.268 - 3.723 \times_1 + 2.886 \times_2 - 1.161 \times_3 + 0.409 \times_4$ (x_1 refer to combining with infection x_2 refer to improper using glucocorticoid x_3 refer to severe hypoproteinemia x_4 refer to severe hyperlipidemia). The diagnosis sensibility of the regression model derived from the ROC curve was 98.18%, with a specificity of 90.77%. The area under the ROC curve was 0.978 (standard error, 0.010; 95% CI, 0.933–0.996). This suggested that there was higher forecasting accuracy in the model. The Youden index of the model is 0.890 (Fig. 1).

We transformed the prediction model by natural logarithm to roughly predict the patient's relapse probability situation

Table 3

Multifactorial analysis of each factor ($P < .05$) and ROC curve results of the joint diagnostic model.

Variable	AUC	SE	95% CI	z	*P*	Youden	Associated Criterion	Sensitivity	Specificity
Infection	0.835	0.034	0.756–0.896	9.820	<.001	0.670	≤1	85.45	81.54
Dosage reduction	0.691	0.042	0.600–0.772	4.562	<.001	0.382	>1	58.18	80.00
Serum albumin	0.933	0.021	0.872–0.971	20.886	<.001	0.706	≤15.2	89.09	81.54
Serum cholesterol	0.869	0.035	0.795–0.924	10.412	<.001	0.685	>12.29	85.45	83.08
Model	0.978	0.010	0.933–0.996	45.809	<.001	0.890	>–5.73	98.18	90.77

AUC = area under curve, CI = confidence interval, ROC = receiver operating characteristic curve, SE = standard error.

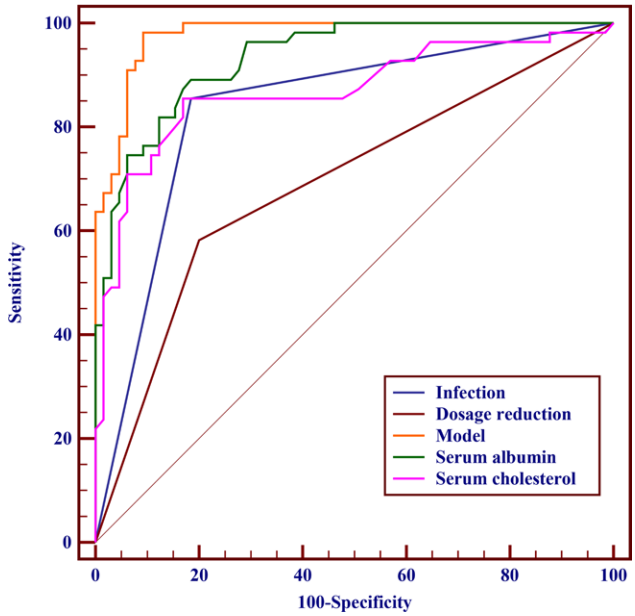

Figure 1. The results of ROC curves for multi-factor regression analysis of 4 risk factors and joint model.

by these 4 indicators. The detailed formula equation is as follows: $P = e^{logit(p)}/[1 + e^{logit(p)}]$. Then, the relationship between the obtained P value and 0.5 was used to determine whether a relapsed of PNS would occur in this patient ($P \geq .5$, relapsed; $P < .05$, relapse-free). Such as, we brought the values of the 4 indicators ($x_{1=1}$, $x_{2=2}$, $x_{3=12.48}$, $x_{4=15.27}$) of one patient included in this study into the above formula. The P value for relapse obtained for this patient was 0.745 (>0.5), which implies that it is highly likely that this PNS patient will experience a relapse in the future; in practice, the patient did experience a relapse. The predictive ability of the model was further validated from the above examples.

4. Discussion

It is well known that relapse remains one of the leading clinical problems in PNS children, and there has been a tendency to increase the relapse rate of children with PNS in recent years.[16] PNS children with frequent relapse in the treatment are usually administrated with cyclophosphamide, tacrolimus, and other immunosuppressants based on initial GC therapy. This increases the infection's opportunity, causes immune level decrease, liver/kidney damage, complications, and brings the family an economic burden.[17,18] Therefore, exploring the risk factors of PNS relapse as soon as possible is very important.

This article probes into the risk factors of children with PNS relapse and provides some theoretical foundation for clinical doctors to give an early evaluation of PNS children relapse and prognosis, and at the same time, to understand the patient's conditions severity, know well the timing of therapy. This present study uses a logistic regression model combined with clinical features of PNS patients with the related laboratory indexes, giving a comprehensive analysis of each factor to the children's PNS relapse of relative risk to control the interference of confounding factors. The single-factor analysis was applied to establish the multiple factors, unconditional regression model, and the correction of various factors that influence each other.

This study shows that at the first presentation of PNS, patients tend to have younger age, more severe edema, elevated peripheral blood leukocyte count, severe hypoproteinemia, severe hyperlipidemia, high blood C-reactive protein, recent urinary protein conversion, infection, and previous irregular administration of glucocorticoids during treatment.[3–8] This is similar to previous studies, such as Toyabe et al[4] and Lin et al[6] found that there is a positive correlation between PNS relapse and allergic constitution. A retrospective analysis of 176 PNS cases indicates that 70% of PNS relapse cases had higher serum IgE levels than controls, implying that PNS patients with elevated serum IgE levels are more susceptible to relapse.[19] However, the present study discovers no correlation between IgE levels and PNS relapse, inconsistent with the previously reported results. Clinical studies have shown that patients with PNS with low serum IgG levels are prone to infection and PNS recurrence.[20] Xia Yang et al[21] showed a characteristic abnormal distribution of peripheral B-cell subsets in PNS. A decrease in $CD19^+ IgG^+$ B cells is one of the important reasons for the low IgG levels in PNS. In this study, the concentration of Blood IgG was lower in the relapse group than in the nonrelapse group. The difference between the 2 groups was statistically significant ($P < .05$). Both groups' blood IgG expression showed the same trend as the above study. A multicentre large-sample randomized controlled trial is needed to give further evidence for our research.

In the present study, 17 factors are used for logistic regression analysis. Results show that the concurrent infection on the first attack, irregular glucocorticoid administration during treatment, severe hypoproteinemia, and severe hyperlipemia are the independent risk factors for PNS relapse. These results also coincide with the reports from Takahashi et al[5] and Macdonald et al.[22] Studies found that immune state imbalance, decreased plasma protein level, and loss of zinc-bound protein from urine are the initial reasons for impaired immunological and lymphocyte function, which is then inhibited after PNS glucocorticoid treatment relapse.[23] Second, the irregular administration of glucocorticoids, a common cause of PNS relapse, accounts for 58.2% of patients with relapse. Informal administration of glucocorticoids may suppress the regulatory function of the hypothalamus-pituitary-adrenal cortex axis, and then the hypoadrenocorticism leads to PNS relapse.[24] Results of the present study indicate that hypoproteinemia, another risk factor for PNS relapse, reduces immunological function, making the patients prone to infection and relapse. Meanwhile, the decline of glucocorticoid, which binds corticosteroid-binding globulin, can increase the free glucocorticoid level, which may also lead to relapse of the disease. Moreover, severe hypoproteinemia also gives rise to disturbance of lipid metabolism, and severe hyperlipidemia is a risk factor for relapse. Hyperlipidemia can increase the permeability of the glomerular membrane. Thus the deposition of macromolecular lipids proteins in the mesangial region may lead to glomerular sclerosis.[25,26] In addition, abnormal lipids metabolism may lead to PNS relapse by affecting the patient's response to glucocorticoid treatment.[27]

The present study shows that the area under the ROC curve in the regression model is 0.978, suggesting there is higher forecasting accuracy in the established model. $P > .05$ in the Hosmer-Lemeshow test of the model, with an accuracy rate of 89.0%, sensibility is 98.18%, and specificity is 90.77%, respectively, suggesting the regression model can meet requirements to forecast some clinical conditions like a relapse. The effect of each factor on the model can be found in the standardized regression coefficient. The larger the regression coefficient, the more influence the factor has on the model. P value calculated from the model means relapsing probability. The larger the P value is, the larger the relapse rate of PNS. The established model has provided timely and straightforward information for forecasting PNS relapse and various implementing steps to decrease relapse rates. According to the multiple regression model, the physician can evaluate prognosis in the early stage and prevent relapse as early as possible. Thus, reducing the relapse rate possesses important guiding significance clinically.

There has been increasing morbidity of PNS in recent years, among which the patients with relapse account for quite a large proportion.[2] There are many factors related to relapse and measures that can be taken to prevent the relapse rate. The Multicenter randomized, large-sample statistical files are needed to define the main risk factors affecting relapse and reasonably regulate the risk factors to achieve the best treatment effect. The probabilistic model's application range and practical value remain to be further verified in later clinical practice.

5. Conclusion

The present study investigates relapse risk factors in children with PNS by single-factor analysis and multiple regression analysis, establishing a logistic regression model. Our study showed that concurrent infection, irregular glucocorticoid therapy, severe hypoalbuminemia, and persistent severe hyperlipemia were all risk factors for PNS relapse. The established logistic regression model based on these factors above is reliable for predicting frequent PNS relapse. Much attention should be paid to these critical factors, and early intervention should be taken to reduce the incidence of relapse.

Author contributions

P.Q.Q. and G.F.J. conceived and designed the project, Z.P. analyzed the data, and P.Q.Q. drafted the initial manuscript. J.X.H. collected and analyzed the data and participated in patient management. All authors approved the final article as submitted.

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