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Correlation between serum transforming growth factor β1, interleukin-6 and neonatal respiratory distress syndrome

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Abstract. Trend and correlation of transforming growth factor β1 (TGF-β1) and interleukin-6 (IL-6) in serum of children with neonatal respiratory distress syndrome (NRDS) were investigated. A total of 75 NRDS children born in the Xiangyang Central Hospital from July 2015 to August 2017 were analyzed retrospectively. A total of 45 NRDS premature infants who received pulmonary surfactant (PS) within 12 h after birth were treated as PS group, 30 who did not receive PS treatment as non-PS group, and 32 premature infants without NRDS in the same period were selected as control group. Serum levels of TGF-β1 and IL-6 were detected by enzyme linked immunosorbent assay (ELISA) at various time points after birth and their correlation was analyzed. The expression level of TGF-β1 in serum of children in PS group was significantly higher than that in control group on days 1 and 3 after birth (P<0.05). The expression level of TGF-β1 in non-PS group increased continuously with the increase of number of days and was significantly higher than that in control group on days 1, 3 and 7 after birth (P<0.05), and significantly higher than that in PS group on days 3 and 7 after birth (P<0.05). The analysis of the correlation between the severity of the disease and the expression levels of TGF-β1 and IL-6 showed that the expression levels were elevated with the increase of the disease severity. The expression levels of TGF-β1 and IL-6 were positively correlated with severity of the disease (r=0.7509, P<0.05; r=0.8056, P<0.05). The expression levels of TGF-β1 and IL-6 in PS and non-PS groups were positively correlated (r=0.9042, P<0.05; r=0.8905, P<0.05). The results showed that serum TGF-β1 and IL-6 were elevated in NRDS children, and there was a positive correlation between them.

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Key words: transforming growth factor β1, interleukin-6, neonatal respiratory distress syndrome, correlation study

Introduction

Neonatal respiratory distress syndrome (NRDS) is a very serious disease during the neonatal period, which can even lead to neonatal death in severe cases (1). According to epidemiological studies, the incidence of respiratory distress syndrome (RDS) is between 0.7 and 1.6% (2), and the incidence can increase to 3-4 times when complicated with respiratory diseases (3). In recent years, the rapid development of overall medical technology and wide application of pulmonary surfactant (PS) and mechanical ventilation in clinical practice have greatly improved the survival rate of children with extremely low birth weight in China (4,5). However, continuous oxygen supply and mechanical ventilation are risk factors for NRDS to further develop into bronchopulmonary dysplasia (BDP) (6). At present, PS, as an alternative therapy, has achieved certain curative effect in clinical practice. Still, there are some children whose condition has not been well controlled and develops into BDP. Severe impairment of pulmonary function reduces the life quality and survival rate of children (7). In recent years, related studies have found that changes in serum glycoproteins and related cytokines are of great significance to early prediction and evaluation of NRDS prognosis of premature infants (8).

Transforming growth factor β1 (TGF-β1), a group of multifunctional cytokines that regulate cell growth and differentiation, is mainly from macrophages, epithelial cells, endothelial cells and fibroblasts (9). Related research has found that TGF-β1 plays an important role in the occurrence and development of various diseases, which can lead to acute and chronic lung injury through a series of signal transduction *in vivo* (10). Interleukin-6 (IL-6), as a glycoprotein, is mainly produced by T cells, mononuclear macrophages and endothelial cells. It can activate neutrophils, thus promoting the liver to secret acute proteins and causing acute inflammatory reactions. Moreover, it is a key inflammatory factor in acute respiratory distress syndrome (ARDS) (11). The physiological characteristics of IL-6 are to induce T cells

to activate, proliferate and differentiate, to induce B cells to differentiate and produce antibodies, thus participating in the body's immune response as a trigger of inflammatory reaction (12). Therefore, the expression of TGF-β1 and IL-6 plays an important role in ARDS. However, there are few studies on the expression of these two factors in NRDS and their correlation.

In this study, the correlation between TGF-β1 and IL-6 in NRDS was examined by means of retrospective study in order to provide reference for clinical diagnosis and treatment.

Patients and methods

General data. A total of 75 NRDS children born in the Xiangyang Central Hospital (Xiangyang, China) from July 2015 to August 2017 were included in the study. The NRDS diagnostic criteria refer to the relevant criteria in Practical Neonatology (13). Of these, 45 NRDS children who were given PS within 12 h after birth were treated as PS group, including 25 males and 20 females, with a gestational age of 30.4±1.1 weeks and a birth weight of 1.4±0.4 g. A total of 30 NRDS children who were not treated with PS due to family difficulties or other factors were taken as non-PS group, including 19 males and 11 females, with a gestational age of 30.8±0.9 weeks and a birth weight of 1.4±0.5 g. In addition, 32 premature infants without NRDS were selected as the control group, including 18 males and 14 females, with a gestational age of 30.9±1.3 weeks and a birth weight of 1.6±0.7 g. There were no significant differences in sex, average birth time, gestational age, birth weight and birth mode between the three groups (P>0.05), which were comparable.

Inclusion criteria: i) combining with clinical symptoms (shortness of breath, dyspnea, cyanosis and other symptoms), children were diagnosed with NRDS by chest X-ray and blood biochemical examination; ii) patients with hypoxemia confirmed by blood gas analysis (14); iii) patients with normal body mass index (BMI); and iv) patients with or without carbon dioxide retention.

Exclusion criteria: i) patients with aspiration pneumonia; ii) serious congenital heart disease; iii) respiratory malformation; iv) severe asphyxia and respiratory failure; v) pneumonia caused by meconium and other factors; vi) intracranial hemorrhage; and vii) family members who refused to sign informed consent.

This study was approved by the Ethics Committee of the hospital and the experimental contents of the subjects were described in detail. The parents of the child subjects agreed and signed an informed consent.

Treatment methods. During the hospital stay, the patient's condition was observed at all times, and effective breathing maintenance, infection prevention measures, vitamin supplementation for resistance enhancement were conducted. The children were kept warm and breastfeeding was recommended. Proper acidosis correction and blood volume expansion were carried out to maintain the balance of water and electrolytes in the body, and dopamine and dobutamine were used in time to stabilize blood pressure. i) Non-PS group: conventional symptomatic and supportive treatment was given to the children, and infant incubator, far-infrared radiation bed and rescue equipment were allocated. Ventilator-assisted breathing, warmth preservation, sputum suction, oxygen inhalation and nutritional support was provided, and water, electrolyte and acidolysis disorder was corrected to maintain internal environment stability. Clinical indicators such as heart rate, respiratory condition and oxygen saturation in children were continuously monitored, regular biochemical, blood routine and chest X-ray examinations were performed, and effective antibiotic treatment was given to infected children. ii) Healthy control group: children were fed with breast milk or 20% glucose water, and other measures were the same as the observation group. iii) PS group: on the basis of the observation group, children were treated with PS (Curosurf) (imported drug registration no. H20080428; Chiesi Farmaceutici S.p.A.) at a dose of 100 mg/kg. Before treatment, the children were placed on a rescue table and respiratory secretions were cleaned quickly with a sputum aspirator. The drug was placed in an incubator for heating before administration, and after the temperature reached 37˚C, medicine was instilled intratracheally by a sterile syringe in each position of the child. In order to reduce the loss of drugs, children can not be treated with sputum excretion care for 6 h after medication. According to the clinical manifestations, chest X-ray and blood gas analysis results, the auxiliary ventilation model and parameters were selected. Blood gas and sternum were reviewed regularly and disease changes were observed to adjust auxiliary ventilation model and parameters. When the condition improved, the ventilator parameters were gradually reduced, and the ventilator removed in time.

Detection of TGF-β1 and IL-6 in serum. After the children were diagnosed with NRDS, 2 ml of fasting venous blood was collected at 0, 1, 3 and 7 days after birth, and then placed in anticoagulation tubes and sent to the clinical laboratory. In the control group, 2 ml of fasting venous blood was taken from the children in the morning on the day of physical examination. After coagulation for 60 min (20-25˚C), centrifugation was carried out at 3,000 x g at 4˚C for 10 min. Supernatant was collected and placed at -80˚C for testing. Repeated freezing and thawing were avoided. Serum TGF-β1 and IL-6 levels were determined by enzyme linked immunosorbent assay (ELISA). TGF-β1 and IL-6 kits were provided by Jiangsu Baolai Biotechnology Co., Ltd. (Jiangsu, China), with the cargo numbers of MM-0090H1 and MM-0049H2, respectively. The instrument was BS-1101 ELISA analyzer from Beijing Limao Technology Co., Ltd. (Beijing, China). All operations were strictly carried out in accordance with the instructions of the kits.

Assessment of severity of NRDS children (15). The severity of NRDS children was assessed according to the chest X-ray examination results. The higher the grade, the more serious the disease was. Grade I: all the children show fine miliary and ground-glass shadows with clear cardiac shadows and decreased pulmonary brightness. Grade II: in addition to miliary shadows, the air bronchogram sign was visible and extended to the outer zone of the lung field. Grade III: in addition to the above images, the diaphragmatic and cardiac boundaries were blurred, the lungs were ground glassy, and the air bronchogram sign was obvious. Grade IV: the whole

Table I. Comparison of clinical indexes between PS, non-PS and control groups [n (%)]/(mean ± standard deviation).

Variables	PS group (n=45)	Non-PS group (n=30)	Control group (n=32)	χ^2/F	P-value
Sex				0.501	0.779
Male	25 (55.6)	19 (63.3)	18 (56.3)		
Female	20 (44.4)	11 (36.7)	14 (43.7)		
Gestational age	30.4±1.1	30.8±0.9	30.9±1.3	2.204	0.1155
Birth weight	1.4±0.4	1.4±0.5	1.6±0.7	1.583	0.2104
Average birth time	3.7±0.9	3.9±1.1	4.1±1.6	1.045	0.3553
Birth mode				3.337	0.185
Natural delivery	11 (24.4)	14 (46.7)	10 (31.2)		
Cesarean section	34 (75.6)	16 (53.3)	22 (68.8)		
Multiple pregnancy	16 (35.6)	6 (20)	2 (6.3)	9.372	<0.05
Premature rupture of membranes	21 (46.7)	10 (33.3)	1 (3.1)	17.15	<0.05
Intrauterine distress or asphyxia	39 (86.7)	17 (56.7)	0 (0)	56.52	<0.05
Gestational diabetes	18 (40)	7 (23.3)	0 (0)	16.71	<0.05
Amniotic fluid aspiration	21 (46.7)	9 (30)	0 (0)	20.27	<0.05
Umbilical cord abnormality	12 (26.7)	5 (16.7)	0 (0)	9.97	0.007
Placental abnormality	9 (20)	3 (10)	0 (0)	7.57	0.023
Intrauterine infection	17 (37.8)	6 (20)	0 (0)	15.87	<0.05
Prenatal glucocorticoid use	23 (51.1)	16 (53.3)	1 (3.1)	26.22	<0.05

PS, pulmonary surfactant.

lung field was seen as an extensive white shadow called 'white lung', air bronchogram sign was more and more obvious, thorax was well expanded and diaphragmatic position was normal. Grade I and II indicated mild illness, while Grade III and IV indicated severe one.

Outcome measures. The expression levels of TGF-β1 and IL-6 in children's serum at various time points were observed, the expression of these two factors in PS, non-PS and control groups were compared, and the correlation between the severity of illness and their expression and the correlation between TGF-β1 and IL-6 were analyzed.

Statistical analysis. SPSS 17.0 statistical software (Tianjin KSoft Science and Technology Co., Ltd., Tianjin, China) was used to statistically analyze the experimental data. The enumeration data were expressed as n (%), the inter-group comparison was performed by Chi-square test. The measurement data were expressed in mean ± standard deviation, and the single-factor variance analysis was used for the multi-group average comparison, Pearson's correlation coefficient was used for the bivariate normal distribution data, and Spearman correlation coefficient was used for the ranked data. P<0.05 was considered to indicate a statistically significant difference.

Results

Comparison of clinical indexes. The clinical indexes of newborns in each group were collected. It was concluded that there were no significant differences between the three groups in clinical baseline data such as sex, gestational age, birth weight, average birth time and birth mode (P>0.05), but there were significant differences between the three groups in multiple pregnancy, premature rupture of membranes, intrauterine distress or asphyxia, gestational diabetes, amniotic fluid aspiration, umbilical cord abnormality, placental abnormality, intrauterine infection or prenatal glucocorticoid use (P<0.05; Table I).

Comparison of TGF-β1 expression in the three groups. As shown in Table II, TGF-β1 expression was low in the healthy control group at all time points *in vivo*, and there was no significant difference in its expression at any time point in the group (P>0.05). The expression level of TGF-β1 in the serum of children in PS group was significantly higher than that in the control group on days 1 and 3 after birth (P<0.05), and decreased on day 7, but there was no significant difference compared with that in the control group (P>0.05). The expression of TGF-β1 in children in non-PS group increased with the increasing number of days, the expression was significantly higher than that in the control group on days 1, 3 and 7 after birth, and the difference was statistically significant (P<0.05). The expression was significantly higher than that in PS group on days 3 and 7 after birth (P<0.05; Fig. 1).

Comparison of IL-6 expression in the three groups. Table III shows that IL-6 was slightly expressed in the healthy control group at various time points *in vivo*, and there was no significant difference in its expression at various time points in the group (P>0.05). The expression level of serum IL-6

Table II. Comparison of TGF-β1 expression in the three groups at different time points (mean ± standard deviation).

Group	Day 0	Day 1	Day 3	Day 7
PS group (n=45)	38.67±6.82	41.43±5.31[a,c]	42.12±6.47[a,c]	38.01±6.28
Non-PS group (n=30)	38.75±6.36	42.87±6.13[a,c]	47.01±5.59[a-c]	48.98±3.03[a-c]
Control group (n=32)	35.78±5.35	35.81±5.21	35.71±5.18	35.67±5.29
F	2.41	14.90	29.95	61.06
P-value	0.0953	<0.05	<0.05	<0.05

Compared with the control group at the same time, [a]P<0.05; compared with the PS group at the same time, [b]P<0.05; compared with the same group at day 0, [c]P<0.05. TGF-β1, transforming growth factor β1; PS, pulmonary surfactant.

Table III. Comparison of IL-6 expression in the three groups at different time points (mean ± standard deviation).

Group	Day 1	Day 2	Day 3	Day 7
PS group (n=45)	13.67±4.78	14.79±4.98[a]	16.69±5.01[a,c]	15.03±4.68
Non-PS group (n=30)	13.87±4.63	14.93±3.46[a]	18.75±3.11[a-c]	20.94±5.01[a-c]
Control group (n=32)	12.58±3.65	12.57±3.70	12.55±3.73	12.59±3.63
F	0.80	3.25	18.01	28.38
P-value	0.4516	<0.05	<0.05	<0.05

Compared with the control group at the same time, [a]P<0.05; compared with the PS group at the same time, [b]P<0.05; compared with the same group at day 0, [c]P<0.05. IL-6, interleukin-6; PS, pulmonary surfactant.

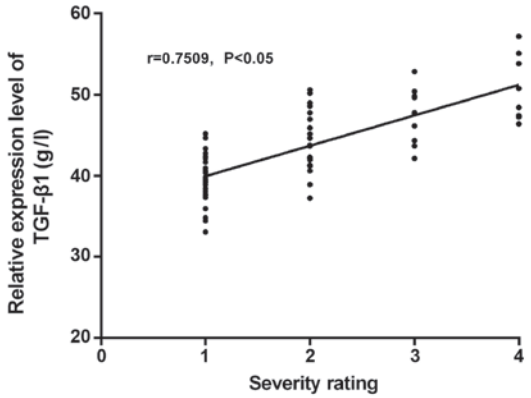

Figure 1. Correlation analysis between severity of disease and TGF-β1 expression level in NRDS children. Correlation analysis between the severity of the disease and the expression level of TGF-β1 showed that, the expression level of TGF-β1 increased with the increase of disease severity, so there was a positive correlation between them (r=0.7509, P<0.05). TGF-β1, transforming growth factor β1; NRDS, neonatal respiratory distress syndrome.

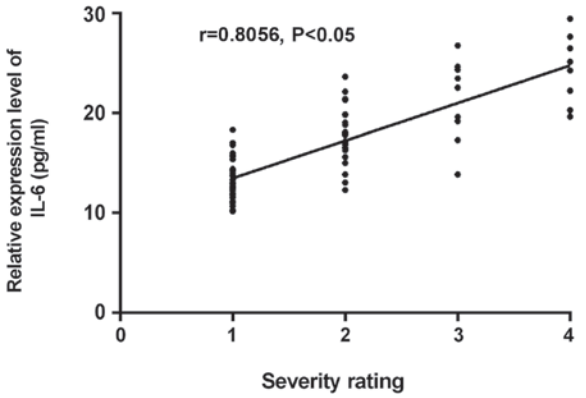

Figure 2. Correlation analysis between severity of disease and IL-6 expression level in NRDS children. Correlation analysis between the severity of the disease and the expression level of IL-6 showed that, the expression level of IL-6 increased with the increase of disease severity, so there was a positive correlation between them (r=0.8056, P<0.05). Therefore, the higher the grade, the higher the IL-6 expression and the higher the risk of the disease. IL-6, interleukin-6; NRDS, neonatal respiratory distress syndrome.

in PS group peaked on day 3 after birth, decreased on day 7, and was significantly higher than that in the control group on days 1 and 3 (P<0.05). The expression level of IL-6 in the non-PS group increased continuously after birth, and was significantly higher than that in the control group on days 1, 3 and 7 (P<0.05), and higher than that in the PS group on days 3 and 7 (P<0.05, Fig. 2).

Comparison and correlation analysis of TGF-β1 and IL-6 expression levels in NRDS children with different severity. A total of 75 NRDS children were graded according to the disease severity examined by chest X-ray, and the results showed that there were 32 children in Grade I, 24 in Grade II, 11 in Grade III and 8 in Grade IV. Table IV, shows that there were significant differences in the expression levels of TGF-β1 and IL-6 in the groups (P<0.05). Correlation analysis between the severity of the disease and the expression levels of TGF-β1 and IL-6 showed that, the expression level of TGF-β1 increased with the increase of disease severity, so there was a positive correlation between them (r=0.7509, P<0.05). As the expression level of IL-6 increased with the increase of disease severity, there was also a

Table IV. Comparison of TGF-β1 and IL-6 expressions in NRDS children with different severity (mean ± standard deviation).

Grade	n	TGF-β1 (g/l)	IL-6 (pg/ml)
I	32	39.11±3.12	14.01±2.83
II	24	43.95±3.34	17.23±3.05
III	11	46.83±3.62	19.97±3.62
IV	8	50.11±4.23	23.32±4.47
F		31.13	22.70
P-value		<0.05	<0.05

TGF-β1, transforming growth factor β1; IL-6, interleukin-6; NRDS, neonatal respiratory distress syndrome.

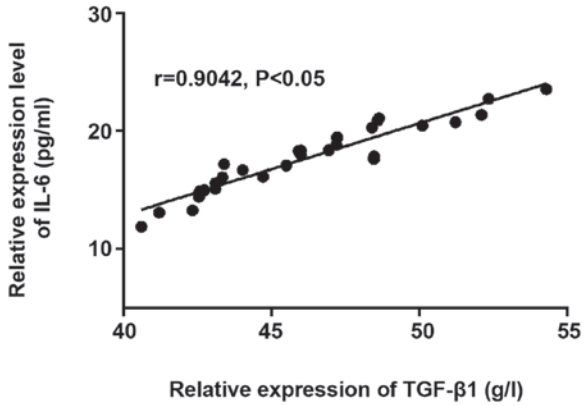

Figure 3. Correlation analysis between expression level of TGF-β1 and IL-6 in PS group. TGF-β1 and IL-6 were positively correlated in PS group (r=0.9042, P<0.05). The expression level of IL-6 increased gradually with the increase of the expression level of TGF-β1 *in vivo*. PS, pulmonary surfactant; TGF-β1, transforming growth factor β1; IL-6, interleukin-6.

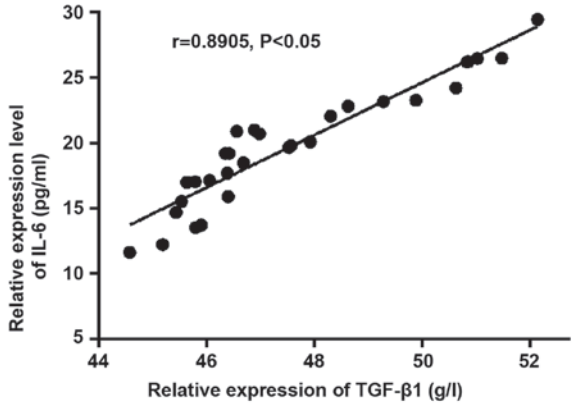

Figure 4. Correlation analysis between expression level of TGF-β1 and IL-6 in non-PS group. TGF-β1 and IL-6 were positively correlated in non-PS group (r=0.8905, P<0.05). The expression level of IL-6 increased gradually with the increase of the expression level of TGF-β1 *in vivo*. TGF-β1, transforming growth factor β1; IL-6, interleukin-6.

positive correlation between them (r=0.8056, P<0.05) (Fig. 2). Therefore, the higher the grade, the higher the expression levels of TGF-β1 and IL-6, and the higher the risk of illness.

Correlation between TGF-β1 and IL-6. The correlation analysis chart was made according to the expression levels of TGF-β1 and IL-6 in PS and non-PS groups (Figs. 3 and 4). TGF-β1 and IL-6 were positively correlated in PS group (r=0.9042, P<0.05), and they were also positively correlated in non-PS group (r=0.8905, P<0.05). The expression level of IL-6 increased gradually with the increase of the expression level of TGF-β1 *in vivo*.

Discussion

NRDS is mainly characterized by respiratory failure and progressive dyspnea shortly after birth (16). The occurrence of RDS is mainly related to the long-term injury of respiratory epithelial cells and insufficient secretion of surfactant in alveolar epithelium. Genetics is also an important factor leading to RDS. Especially in high risk groups such as premature infants, its incidence is higher than that in the general population (55-75%) (17,18). Therefore, early prediction and evaluation of NRDS in clinical treatment is of great significance in minimizing the occurrence of BPD. Infection, mechanical ventilation and high oxygen concentration may interfere with the normal programmed development of immature lung (19), and then produce a series of inflammatory reactions, resulting in acute and chronic lung injury in newborn children.

As a cytokine, TGF-β1 plays a vital role in the multifunctional regulation of cell growth and differentiation (20). Moreover, it is also very important in the occurrence and development of acute and chronic lung injury (21). It has been found that TGF-β1, interleukin 8 (IL-8) and staphylococcal protein A (SPA) are highly expressed in pulmonary lavage fluid of BDP children (22). TGF-β1 can not only promote the process of pulmonary fibrosis, but also induce the high expression of connective tissue growth factor (CTGF) in lung, thereby promoting the development of pulmonary fibrosis (23). Studies have shown that TGF-β1 is activated at the early stage of ARDS, the occurrence of pulmonary fibrosis suggests strong expression of TGF-β1 (24,25), and the degree of pulmonary fibrosis is closely related to the mortality of ARDS (26). As an inflammatory cytokine with multiple effects, IL-6 is a member of the immunomodulatory cytokine family and has anti-inflammatory and pro-inflammatory effects (27). The binding of IL-6 to its receptor (IL-6R) activates the target cell and further recruits the dimer formed by human glycoprotein 130 (gp130), thereby initiating the downstream signaling pathway (28).

Comparison of clinical baseline data in this study showed that there were no significant differences between the three groups in general data such as sex, gestational age, birth weight, average birth time or birth mode. While there were significant differences in multiple pregnancy, premature rupture of membranes, intrauterine distress or asphyxia, gestational diabetes, amniotic fluid aspiration, umbilical cord abnormality, placental abnormality, intrauterine infection and prenatal glucocorticoid use (P<0.05), indicating that these factors may be the cause of NRDS (29,30). In this study, the expression levels of TGF-β1 and IL-6 in the three groups were compared and analyzed, and it was found that expression of TGF-β1 and IL-6 was low in the healthy control group at all

time points, indicating that they were secreted in normal lung tissue. The expression level of serum TGF-β1 in PS group was significantly higher than that in control group on days 1 and 3 after birth, and decreased on day 7, which indicated that PS treatment could alleviate the inflammatory reaction *in vivo* (31). However, the expression level of serum TGF-β1 in non-PS group increased continuously with the increase of the number of days, indicating that the inflammatory reaction in the children's body was always present and showed a high expression, which would easily lead to the occurrence of BDP. In this study, the expression level of IL-6 in the three groups were compared and analyzed, the results showed that the expression level of serum IL-6 in the PS group peaked on day 3 after birth, decreased at day 7, and there was no significant difference when compared with the control group, suggesting that the child was recovering gradually. The expression level of IL-6 in the PS group was significantly higher than that in the control group on days 1 and 3 ($P<0.05$). The expression level of IL-6 in the non-PS group increased continuously after birth and was significantly higher than that in the control group on days 1, 3 and 7 ($P<0.05$), and higher than that in the PS group on days 3 and 7 ($P<0.05$). Because many families can not afford the high cost of PS treatment, it is crucial to find a more suitable alternative for the general population to control the inflammatory reaction of the body. Yu *et al* (32) found that serum tumor necrosis factor α (TNF-α) and IL-6 play an important role in the pathogenesis of ARDS in children and are closely related to the occurrence, development and severity of ARDS. In this study, by comparing the expression of TGF-β1 and IL-6 in NRDS children with different severity, it was found that both TGF-β1 and IL-6 were positively correlated with the severity of the disease. In other words, the more severe the disease, the higher their expression. There are few references on the correlation between TGF-β1 and IL-6 with the severity of NRDS, so they are of great research value. Correlation analysis of the expression of TGF-β1 and IL-6 in PS and non-PS groups showed that, TGF-β1 and IL-6 were correlated in the two groups. IL-6 expression level increased with the increase of TGF-β1 *in vivo*, with a positive correlation between them. Findings have shown that TGF-β1 and signal transduction protein (smad3) are closely related to fibrosis (33), and IL-6 can activate the signal transduction pathway of TGF-β1/smad3 (34). However, there is no reference concerning the correlation between these two factors in NRDS children. Therefore, this study was conducted to provide reference value for clinical research.

Understanding the trends and correlations of TGF-β1 and IL-6 in NRDS can help early clinical prevention and treatment and improve the prognosis of children. There were some limitations in this study such as few samples and short observation time. Therefore, in order to understand the condition of the children in detail, it is necessary to perform regularly follow-up and pulmonary function test after the discharge.

In conclusion, TGF-β1 and IL-6 are associated with NRDS, which can provide some references for clinical practice. TGF-β1 and IL-6 have important value in identifying NRDS. It is suggested that decreasing TGF-β1 or IL-6 level by treatment has certain significance for the development of the children's condition.

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Availability of data and materials

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

Authors' contributions

FC interpreted the data and drafted the manuscript. FH conceived and designed the study. FC and FH collected and analyzed the data. FZ was responsible for the detection of TGF-β1 and IL-6 in serum. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Xiangyang Central Hosptial (Xiangyang, China). Patients who participated in this study had complete clinical data. Signed informed consents were obtained from the parents of the child patients.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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