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Original Article

Expression and prognostic value of MIP-1α in neonatal acute respiratory distress syndrome

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Abstract: Objective: To investigate the expression and prognostic value of macrophage inflammatory protein 1α (MIP-1α) in neonatal acute respiratory distress syndrome (NRDS). Methods: In this retrospective analysis, 96 newborns with NRDS in Affiliated Lianyungang Hospital of Xuzhou Medical University from January 2018 to June 2021 were included in the experimental group (EG), while the other 60 normal neonates were included as the control group (CG). The concentration of MIP-1α in umbilical cord blood was tested by Elisa method. The clinical value of MIP-1α in diagnosing NRDS was assessed via receiver operating characteristic (ROC) curve. According to the 28-day survival data, children were divided into a survival group and a death group. The prognostic factors were assessed by Cox regression analysis. The correlation between MIP-1α and IL-1β, IL-6, TNF-α, SNAPPE-II scores were evaluated by Pearson test. The relationship between the MIP-1α level and the severity of the disease was assessed. Results: The MIF-1α level in cord blood of children in the EG was dramatically higher than that in the CG ($P<0.05$). Besides, ROC curve further found that the area of MIF-1α under the curve of diagnosing NRSD was 0.949. MIF-1α was positively correlated with the levels of interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor α (TNF-α) and SNAPPE-II score ($P<0.001$). With the increase of NRDS, the serum MIF-1α level increased, showing a positive association ($P<0.05$). Cox regression analysis revealed that the severity and MIF-1α level were independent prognostic factors of survival ($P<0.001$). The survival rate of children with MIF-1α <281.58 pg/mL as well as children with I-II grade was higher than those with MIF-1α >281.58 pg/mL as well as children with III-IV grade ($P<0.05$). Conclusion: The increase of serum MIP-1α level is relevant to the condition and prognosis of NRDS children. The level of cord blood MIP-1α level is expected to become a potential outcome measure.

Keywords: MIP-1α, neonatal respiratory distress syndrome, prognosis, diagnosis

Introduction

Neonatal acute respiratory distress syndrome (NRDS) manifests as type II alveolar epithelial cell synthesis and secretion of pulmonary surfactant deficiency, which is caused by premature birth, gestational diabetes, elective cesarean section, perinatal asphyxia, abnormal protein genes etc. It results in extensive alveolar collapse, injury and exudation of neonatal acute respiratory failure [1, 2]. As a common respiratory disease in newborns, it is more life-threatening. The most important clinical manifestations are respiratory distress, hypoxemia that difficult to correct, diffuse hyperpermeability of both lungs and even white lungs [3]. According to statistics, NRDS accounts for 1%-2% of all causes for newborns requiring mechanical ventilation, and the case fatality rate is 50%-60%, which is one of the vital causes of neonatal death [4]. However, the diagnosis of neonatal ARDS still depends on the comprehensive diagnosis of clinical indicators. Thus, it is crucial to seek an effective and accurate biomarker to improve the diagnostic efficiency of neonatal ARDS.

The occurrence of NRDS is related to various internal and external factors, such as fetal lung dysplasia, severe infection and hypoxia. More and more studies have proposed that there is a close relationship between inflammation and NRDS [5]. In an animal experiment, Galinsky R [6] found that the NRDS reaction of intrauterine inflammation could increase the pulmonary vascular resistance of sheep fetus and damage

the development of fetal pulmonary vessels. Other studies have discovered that chorioamnionitis [7] has a certain effect on fetal lung development, and there is a marked correlation between chorioamnionitis and NRDS and perinatal death. Macrophage inflammatory proteins (MIPs) are an essential participants in the induction of other proinflammatory cytokines, such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor α (TNF-α) in activated macrophages and fibroblasts [8]. MIP-1α is a key chemokine related to immune surveillance and tolerance, and has become a prognostic biomarker of solid and hematological malignancies [9]. Recent studies have shown that MIP-1α can promote leukocyte aggregation to the inflammatory site, which plays a vital role in inflammation [10]. For example, Wu et al. [11] found that MIP-1α is an indicator of secondary acute lung injury in patients with mechanical ventilation. Other studies have shown that [12] alveolar MIP secretion mediates neutrophil lung injury in Nox2 deficient mice. This suggests that MIP-1α is involved in the development of many kinds of lung diseases, but it is vague about its value in NRDS children.

We analyzed the MIP-1α level in cord blood of NRDS children, so as to provide a potential reference for diagnosis and prognosis.

Methods and materials

Clinical data

In this retrospective analysis, 96 newborns with NRDS in Affiliated Lianyungang Hospital of Xuzhou Medical University from January 2018 to June 2021 were included in the experimental group (EG), while the other 60 normal neonates from the same period were included as the control group (CG). This study was approved by the Medical Ethics Committee of Affiliated Lianyungang Hospital of Xuzhou Medical University with ethical batch number of LSI2019-14.

Inclusion and exclusion criteria

Inclusion criteria: Neonates meeting the diagnostic criteria of Montelux criteria for Neonatal Acute Respiratory Distress Syndrome (2017 version) [13]; Neonates with acute onset, mechanical ventilation time ≥72 h, gestational age >34 weeks; Neonates whose imaging examination manifested diffuse shadow of both lungs with pulmonary edema, but without left atrial hypertension as indicated by echocardiography; Neonates with complete clinical data; and Neonates of singletons. The guardians of children were informed and signed an informed consent form.

Exclusion criteria: Neonates with severe extrapulmonary infection; Neonates with primary alveolar surfactant deficiency, congenital heart disease or congenital metabolic disorder; Neonates with deformities of the lung and chest wall and other severe congenital malformations; or Neonates with incomplete clinical data.

Elisa test

MIF-1α, IL-1β, IL-6, TNF-α kits were purchased from Shanghai Beyotime Biotechnology (Cat ID: PM715, PI305, PI330, PT518). Based on the instructions, 5 mL cord blood was collected and centrifuged (at 1509.3 g) for 10 min to obtain the serum, which was stored for follow-up experiment.

Outcome measures

Main outcome measures: The MIF-1α level in cord blood was compared between two groups. The clinical value of MIF-1α in diagnosing NRDS was assessed by ROC curve. In view of the 28-day survival, children were divided into survival group and death group. The prognostic factors were investigated by Cox regression analysis.

Secondary outcome measures: The clinical data of children in the EG were compared with those in the CG. The correlation between MIF-1α and IL-1β, IL-6, TNF-α, SNAPPE-II scores was assessed via Pearson test. The indicators used to assess the condition of newborns were scored, including mean arterial blood pressure, minimum body temperature, partial pressure of arterial blood oxygen/inhaled oxygen concentration ratio, minimum blood pH, whether there are repeated convulsive episodes, volume of urine per unit time of body mass, birth mass, relationship between birth mass and gestational age, and 5 min Apgar score, with a total score of 162, and the higher score indicated more severe condition. The relationship between the MIF-1α level and the severity of the disease was analyzed.

Table 1. Children baseline data sheet

Factor	Experience group (n=96)	Control group (n=60)	*P* value
Gestational week			
≥38 weeks	53	35	0.147
<38 weeks	43	25	
Gender			
Male	55	36	0.114
Female	41	24	
Birth weight			
≥3 kg	14	9	0.943
<3 kg	82	51	
Maternal age			
≥30 years old	44	29	0.761
<30 year old	52	31	
Cesarean section			
Yes	57	23	0.123
No	39	27	
Gestational diabetes			
Yes	25	8	0.058
No	71	52	
Pregnancy-induced hypertension syndrome			
Yes	20	5	0.038
No	76	55	
Preterm birth			
Premature	54	25	0.076
Term infant	42	35	
Etiology			
Asphyxia	35		
Meconium aspiration syndrome	24		
Pneumonia	23		
Septicemia	14		
Severity			
Grade I	30		
Grade II	28		
Grade III	23		
Grade IV	15		

Classification of neonatal respiratory distress syndrome

All patients underwent chest X-ray to determine the disease grade. Grade I: Both lungs have reduced translucency and uniform reticular shadows with fine particles are visible; Grade II: The lesion reaches the outer zone of the lung field and has bronchial inflation signs; Grade III: The translucency of both lungs is reduced and the lesions are deepened, with blurring of the diaphragmatic surface and cardiac margins; Grade IV: Both lungs are white-lung-like, and the bronchial inflation sign is severe like a bald leafy branch.

Statistical analysis

The collected data were statistically analyzed through SPSS20.0 software, and pictures were drawn via GraphPad Prism 8. The utilization rate of counting data (%) was indicated by chi-square test, expressed as χ^2. The measurement data were represented as mean ± standard deviation (SD), and all are in accordance with normal distribution. Independent sample t-test was used for inter-group comparison, paired t-test was used for intra-group comparison, ANOVA was used for multi-group comparison, and LSD-t test was used for post-test. The correlation between MIF-1α and IL-1β, IL-6, TNF-α, SNAPPE-II scores was assessed by Pearson test, and the ability of MIF-1α to diagnose and predict NRDS was evaluated by ROC. The survival curve based on disease severity and MIF-1α level within 28 days in NRDS patients was evaluated by K-M test, and the prognostic factors of NRDS were assessed via Cox regression analysis. Statistically significant difference was determined at $P<0.05$.

Results

Comparison of clinical data of children

No obvious differences were observed in gestational age, gender, birth weight, maternal age, cesarean section and etiology between both groups ($P>0.05$), but the proportion of patients with hyperemesis in the EG was significantly higher than that in the CG ($P<0.05$) (**Table 1**).

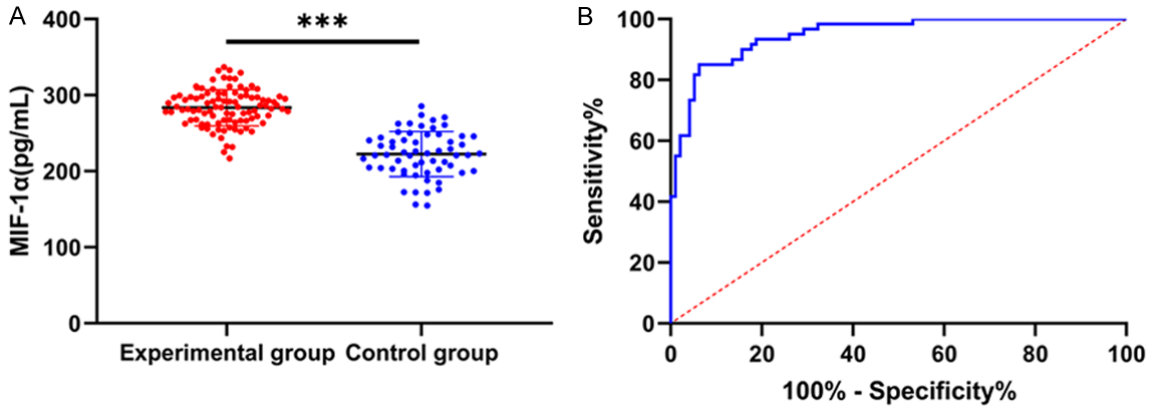

Figure 1. Expression and diagnostic curve of MIF-1α in NRDS children. A. The MIF-1α level in cord blood of children with NRDS was detected by Elisa. B. The value of MIF-1α in the diagnosis of NRDS was analyzed by ROC curve. Note: *** means P<0.001, macrophage inflammatory protein 1α (MIF-1α). Neonatal acute respiratory distress syndrome (NRDS).

Expression and diagnostic value of MIF-1α in NRDS children

Elisa method revealed that the MIF-1α level in the cord blood of the EG was obviously higher than that of the CG (P<0.05, **Figure 1A**). ROC curve further demonstrated that the area under the curve of MIF-1α in the diagnosis of NRSD was 0.949, with a sensitivity of 85.00% and a specificity of 93.75%, which was an ideal diagnostic indicator (**Figure 1B**).

Correlation between MIF-1α, inflammatory factors and SNAPPE-II scores

We analyzed the correlation between serum MIF-1α, inflammatory factors and SNAPPE-II scores in NRDS children by Pearson test. It was found that MIF-1α was positively correlated with IL-1β, IL-6, TNF-α and SNAPPE-II scores (all P<0.001, **Figure 2**).

Relationship between MIF-1α and condition of NRDS children

To further understand the relationship between MIF-1α and the severity of children with NRDS, we compared the serum MIF-1α level in children with different grades. It revealed that serum MIF-1α increased as the severity worsened, and there was remarkable difference between groups (P<0.05, **Figure 3A**). Spelman test found that the MIF-1α level was positively correlated with the severity of the disease (P<0.05, **Figure 3B**).

Prognostic factors of NRDS

The 28-day survival of the children with NRDS was analyzed. Statistics revealed that a total of 30 children (30/96) died within 28 days, with a survival rate of 68.75%. Then, the clinical data of patients were included and assigned (**Table 2**). Univariate analysis revealed that the severity, MIF-1α and SNAPPE-II score were the prognostic factors of patients. Afterwards, multivariate Cox regression analysis found that the severity and MIF-1α were independent factors for prognosis (P<0.01, **Table 3**). Based on the independent prognostic factors, we drew the survival curve and found that the survival rate of children with MIF-1α <281.58 pg/mL (median) as well as neonates with I-II grade was higher than those of MIF-1α >281.58 pg/mL (median) as well as neonates with I-II grade III-IV (P<0.05, **Figure 4**).

Discussion

The fatality rate of NRDS is high, which is one of the important causes of neonatal death. Due to the lack of specific markers, its treatment is easy to lag, thus affecting the final neonatal outcome [14]. We found that MIF-1α was highly expressed in NRDS children, and the area under the ROC curve was more than 0.9. In addition, Cox regression analysis revealed that MIF-1α was independently tied to the prognosis of NRDS. This suggests that NRDS can be used as a potential diagnostic and prognostic indicator of NRDS.

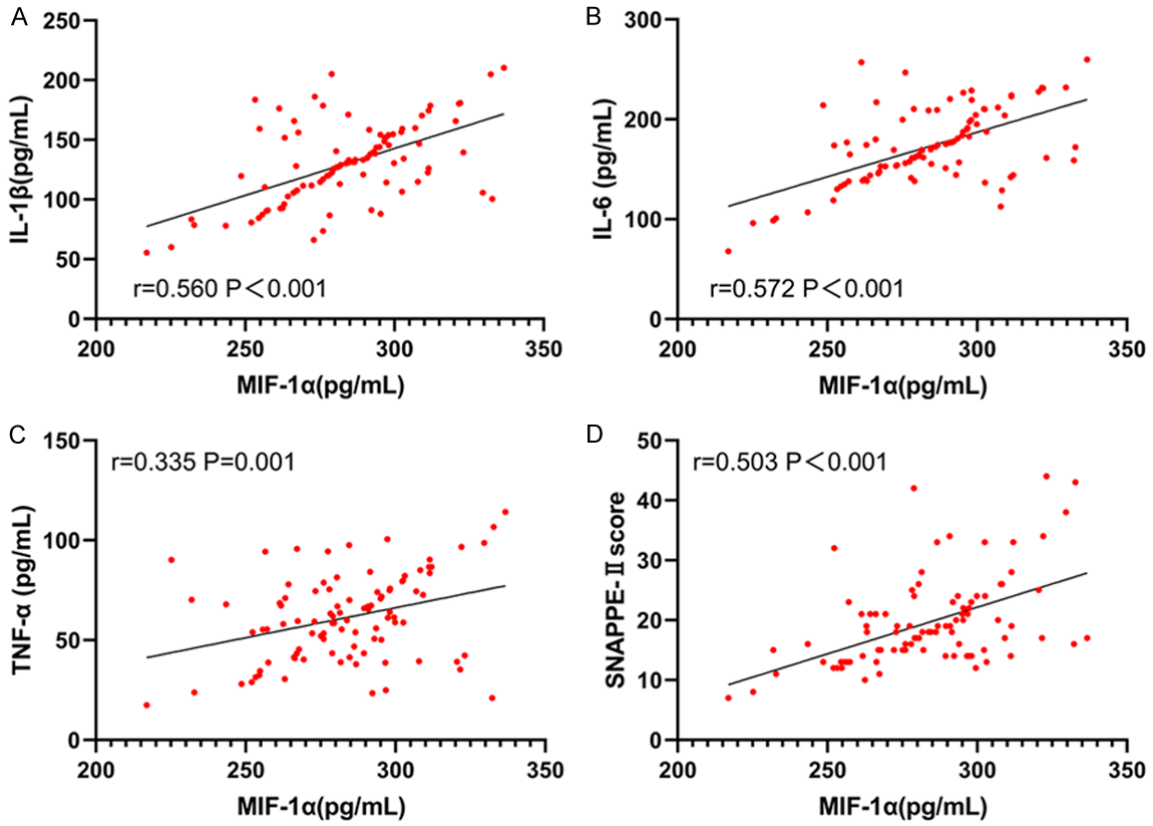

Figure 2. Correlation analysis between MIF-1α and IL-1β, IL-6, TNF-α, SNAPPE-II scores. A. Analysis of correlation between serum MIF-1α and IL-1β in children with NRDS. B. Analysis of correlation between serum MIF-1α and IL-6 in children with NRDS. C. Analysis of correlation between serum MIF-1α and TNF-α in children with NRDS. D. Analysis of correlation between serum MIF-1α and SNAPPE-II score in children with NRDS. Note: interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor α (TNF-α), macrophage inflammatory protein 1α (MIF-1α). Neonatal acute respiratory distress syndrome (NRDS).

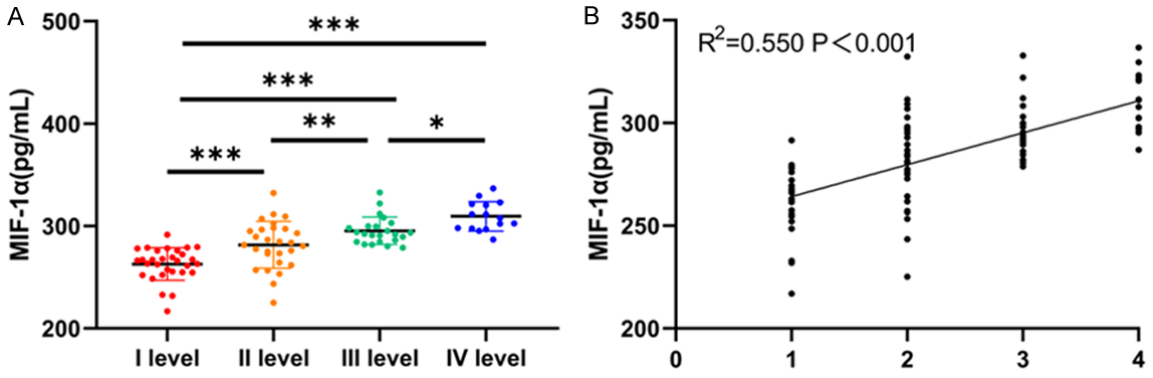

Figure 3. Correlation between MIF-1α and condition of children with NRDS. A. Comparison of serum MIF-1α levels in children with different grades of NRDS. B. Spearman test was conducted to assess the correlation between serum MIF-1α and children with different grades of NRDS. Note: * means P<0.05, ** means P<0.01, *** means P<0.001, macrophage inflammatory protein 1α (MIF-1α). Neonatal acute respiratory distress syndrome (NRDS).

Inflammation is considered to be a defense response of living tissues with vascular system to damaging factors, which has a huge impact on fetuses and neonates [15]. As a chemokine,

Table 2. Assignment table

Factor	Assignment
Gestational week	≥38 weeks =1, <38 weeks =0.
Gender	Male =1, female =0.
Birth weight	≥3 kg =1, <3 kg =0.
Maternal age	≥30 years =1, <30 year =0.
Cesarean section	Yes =1, no =0.
Etiology	Asphyxia =0, meconium aspiration syndrome =1, pneumonia =2, septicemia =3.
Severity	I-II =1, III-IV =0.
MIF-1α	Belonging to continuous variables using original data analysis.
IL-1β	Belonging to continuous variables using original data analysis.
IL-6	Belonging to continuous variables using original data analysis.
TNF-α	Belonging to continuous variables using original data analysis.
SNAPPE-II scores	Belonging to continuous variables using original data analysis.

Note: interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor α (TNF-α), macrophage inflammatory protein 1α (MIF-1α).

Table 3. Analysis of prognostic factors

Factor	Univariate analysis			Multivariate analysis		
	HR value	*P* value	95% CI	HR value	*P* value	95% CI
Gestational week	1.779	0.129	0.845-3.743			
Gender	1.898	0.099	0.887-4.062			
Birth weight	1.491	0.415	0.570-3.899			
Maternal age	1.476	0.287	0.720-3.023			
Cesarean section	0.557	0.113	0.270-1.149			
Etiology	0.920	0.618	0.662-1.278			
Severity	0.371	0.008	0.179-0.771	0.129	<0.001	0.049-0.343
MIF-1α	1.037	<0.001	1.020-1.054	1.054	<0.001	1.03-1.078
IL-1β	0.994	0.331	0.983-1.006			
IL-6	1.000	0.994	0.991-1.009			
TNF-α	0.983	0.058	0.967-1.001			
SNAPPE-II scores	1.088	<0.001	1.053-1.124	1.017	0.491	0.97-1.066

Note: interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor α (TNF-α), macrophage inflammatory protein 1α (MIF-1α).

MIF-1α can bind to the corresponding CC chemokine receptor and promote the aggregation of inflammatory cells [16]. Early studies have found that MIP-1α is enriched in epithelial cells in alveoli and bronchioles as well as in adjacent capillary endothelial cells in patients with lower respiratory diseases caused by respiratory syncytial virus [17]. Other research has found that when inflammation occurs in the lungs, the MIP-1α levels increase [18]. What's more, we compared the MIF-1α level in cord blood of normal infants with NRDS infants, and found that the MIF-1α level in serum of children with NRDS was increased, and it was positively correlated with the severity of the disease. This suggests that MIF-1α may be involved in the occurrence of NRDS. Nevertheless, Murch SH et al. [17] found that there was no obvious difference in MIF-1α level in bronchoalveolar lavage fluid between premature infants with and without NRDS, which was inconsistent with our results. We think this may be caused by differences in detection samples. In the study of intrauterine inflammatory factors, Otsubo Y et al. [19] found that the level of cord blood chemokine MIF-1α in premature infants was higher than that in full-term infants, indicating that the level in different samples may be inconsistent.

Inflammation plays an essential role in the occurrence and development of NRDS, in which IL-1β, IL-6 and TNF-α are cytokines that reflect

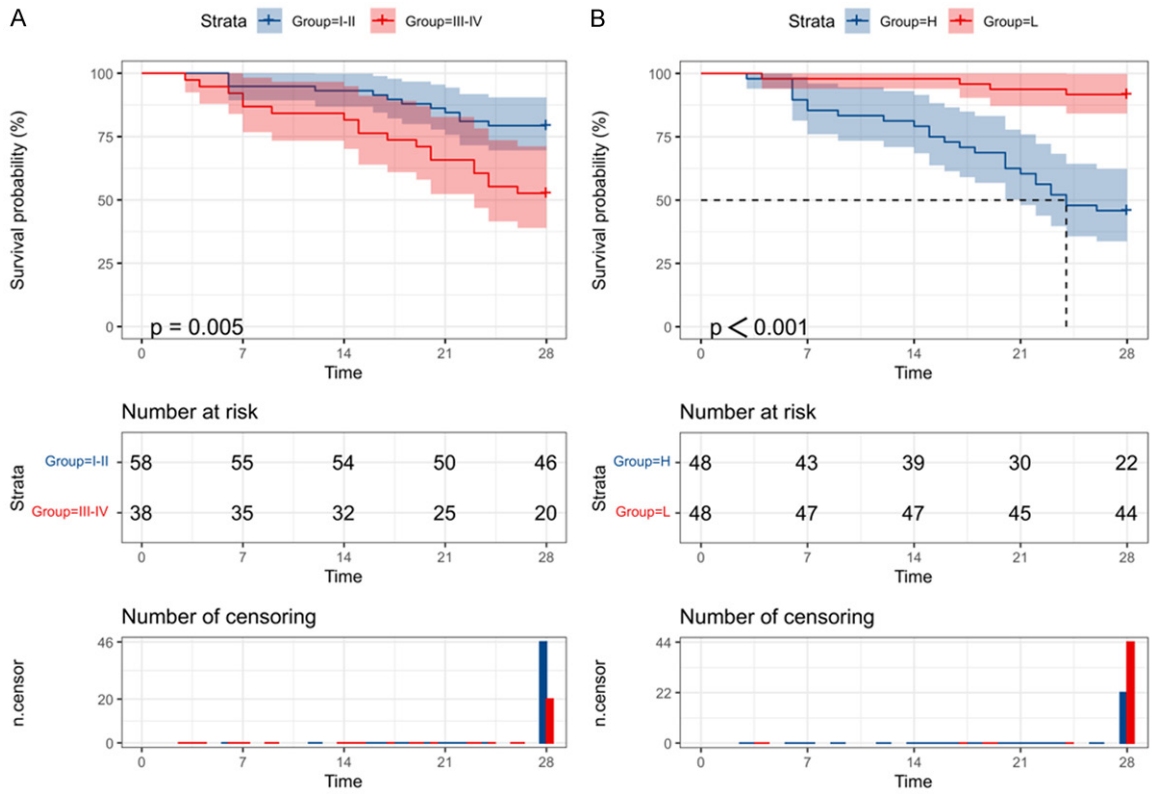

Figure 4. Survival curves drawn based on disease severity and MIF-1α level. A. K-M curve based on disease severity of children. B. K-M curve based on MIF-1α level of children. Not: macrophage inflammatory protein 1α (MIF-1α).

inflammation and injury [20]. Previous study [21] has shown that IL-1β, IL-6 and TNF-α are involved in the pathogenesis of NRDS. The SNAPPE-II scoring system was developed on the basis of the Neonatal Acute Physiology Score-II, which added birth weight, the relationship between birth weight and gestational age, and the 5-min Apgar score [22]. The SNAPPE-II scoring system has no requirement of gestational age and requires evaluation within 12 h of admission. It is convenient, rapid and widely used. It has been frequently-used in the prognosis evaluation of critical diseases [23]. We compared the correlation between MIF-1α and IL-1β, IL-6, TNF-α, SNAPPE-II scores by correlation analysis. And we found that MIF-1α was positively correlated with IL-1β, IL-6, TNF-α and SNAPPE-II scores. This further proves that MIF-1α is involved in the occurrence of NRDS.

In the end, we analyzed the factors affecting the prognosis of children with NRDS. Univariate Cox regression analysis demonstrated that the severity of the disease, MIF-1α and SNAPPE-II score were the prognostic factors. ÖZCAN et al. [24] conducted a study on 248 critically ill neonates in the neonatal intensive care unit and found that the average SNAPPE-II score of the deceased children was >37, which was much higher than that of the survived neonates, and could better predict the death of the children, which is consistent with our analysis results. Multivariate Cox regression analysis found that SNAPPE-II score was not an independent prognostic factor for NRDS children. A study reported the correlation between the severity of the disease and the survival of children [25]. We first found that MIF-1α was related to the survival of NRDS. We believe that the abnormal increase of MIP-1α level can induce chemotactic killer T cells and natural killer cells to bind to the corresponding receptors, promote the release of inflammatory regulatory factors such as leukotriene and calcium ions, cause and aggravate the inflammation of the body, and increase the risk of death in children [26, 27].

We found that MIF-1α has a high clinical value in diagnosing NRDS, so it is expected to become a prognostic indicator of NRDS. However,

there are still some limitations. First of all, as a retrospective study, we were unable to carry out long-term follow-up of children. Secondly, the MIF-1α level in bronchoalveolar lavage fluid was not detected. Thus, we hope to conduct randomized controlled trials in future studies to collect more sample types and sample sizes to refine our findings.

To sum up, the expression of serum MIP-1α is relevant to the severity and prognosis of NRDS children, which can be used as a potential outcome measure.

Disclosure of conflict of interest

None.

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