Original Article
The expression of serum macrophage MIF and PLTP in neonatal bronchopulmonary dysplasia (BPD) and its values and significances in clinical diagnosis

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Abstract: Objective: The aim of the current study was to investigate expression levels of serum macrophages MIF and PLTP in neonatal bronchopulmonary dysplasia (BPD), examining their value and significance in clinical diagnosis. Methods: A total of 31 BPD neonatorum cases, admitted from January 2017 to January 2018, were assigned to the experimental group. A total of 31 non-BPD neonatorum cases were assigned to the control group. This study analyzed various data, including gender, gestational age, birth body mass, and times of oxygen inhalation and mechanical ventilation. Samples of blood and bronchoalveolar lavage fluid (BALF) were collected. Expression levels of MIF and PLTP of all subjects in the 1st, 2nd, 3rd, and 4th weeks after birth were detected via ELISA. ROC curves were plotted in line with expression levels of MIF and PLTP of the two groups the first week after birth. Correlation levels between MIF and PLTP were also determined. Results: Gestational ages and birth body masses of the experiment group were substantially lower than the control group. Times of oxygen inhalation and mechanical ventilation were significantly longer than those of the control group. Differences were statistically significant (P<0.05). At all time-points after birth, levels of MIF in the serum and BALF of the experimental group were higher, while levels of PLTP were lower than those of the control group (P<0.05). According to ROC curves, areas under the MIF curve, and critical values of diagnosis, sensitivity and specificity levels were 0.860 (0.771-0.948), 10.49 ng/mL, 64.52%, and 87.10%, respectively. Levels of PLTP curves were 0.761 (0.641-0.881), 12.89 ng/mL, 64.52%, and 83.87%, respectively. A positive correlation was exhibited between MIF expression in serum and in BALF (r=0.682, P<0.001), as well as PLTP expression in serum and in BALF (r=0.714, P<0.001). A negative correlation was determined between expression levels of serum MIF and serum PLPT in BPD neonatorum cases (r=-0.741, P<0.001), as well as expression levels of MIF and PLTP in BALF (r=-0.576, P<0.001). Conclusion: MIF was overexpressed and PLTP was under-expressed in the serum and BALF of BPD neonatorum cases. A negative correlation was exhibited between expression levels of MIF and PLTP. Early detection of serum MIF and serum PLTP expression in BPD neonatorum cases is of diagnostic significance.

Keywords: Bronchopulmonary dysplasia (BPD), MIF, PLTP, neonatorum, diagnosis

Introduction

Bronchopulmonary dysplasia (BPD), one of the most common chronic pulmonary diseases in premature infants [1], mainly refers to pulmonary vascular dysplasia, pulmonary fibrosis, and inflammation of various degrees resulting from suppressed lung development. The pathogenic factors of BPD require further investigation [2]. Clinical data shows that LOS (length of stay) and pyemia might be risk factors for BPD [3]. Infant patients may have difficulty with res-

piration, even in the early stages of the disease. Severe hypoxia and secondary changes often occur without prompt treatment. This will affect respiratory function and lead to respiratory failure. It may also threaten the survival of infant patients, influencing clinical prognosis [4]. Without early clinical diagnosis, a huge impact may be exerted on the long-term prognosis of infant patients. Damage of pulmonary function can continue into adulthood [5]. As a result, early diagnosis of BPD neonatorum and gauging the severity of the disease is imperative in

clinical BPD prognosis. However, BPD treatment has experienced no major breakthroughs. Thus, early diagnosis and prompt treatment serve as key points in BPD treatment.

Macrophage migration inhibitory factor (MIF) is an inflammatory medium. It plays an important role in innate immunity, stemming from the stimulation of microbial products and proinflammatory cytokines. It participates in systemic inflammatory reactions [6]. Moreover, many studies have determined the association between MIF and pulmonary pathology, as well as cellular infiltration. This may be regarded as an effective target for pneumonia treatment, neutralizing and regulating pulmonary inflammation [7].

Phospholipid transfer protein (PLTP), a phosphatide that is secreted in plasma and participates in phosphatidylcholine biosynthesis, is able to regulate the transfer of pulmonary phosphatide through its interaction with transferase [8]. This may strengthen the transfer of the alveolar surfactant, phosphatide, maintaining the stability of alveolus and facilitating gas exchange [9]. Inflammation is a major aetiological agent for BPD, such normal operation as mechanical ventilation, however, would aggravate pulmonary inflammation in most cases [10]. The occurrence mechanism of pulmonary inflammation has always been the emphasis in current BPD study, yet few researches have been conducted on correlation between MIF, PLTD and BPD. As a result, we laid great emphasis on MIF and PLTD expression in serum and BALF of BPD neonatorums in this study, aiming to investigate the diagnostic significance of new biomarker for BPD, now the report are as follows.

Materials and methods

General information

A total of 31 BPD neonatorum cases, admitted from January 2017 to January 2018, were assigned to the experimental group. A total of 31 non-BPD neonatorum cases, in the same admission period, were assigned to the control group. Various information was collected, including gender, gestational age, birth body mass, cases of premature rupture of membrane (PROM) and chorioamnionitis, history of asphyx-

ia, times of oxygen inhalation and mechanical ventilation, cases of cesarean delivery, administration of alveolar surfactant and dexamethasone, and days of admission.

Inclusion criteria: (1) BPD neonatorum cases in the experiment group should met the criterion of BPD diagnosis published by the U.S National Institutes of Health (NIH) [11]; (2) LOS (length of stay) of all neonatorum cases was ≥28 days with implementation of mechanical ventilation; and (3) Respiratory distress occurred after 3 days of birth and the time of mechanical ventilation was ≥1 week. During hospitalization, bronchoalveolar lavage (BAL) is a necessity in investigating pulmonary disease. Thus, bronchoalveolar lavage fluid was kept as a sample.

Exclusion criteria: (1) Mortality during hospitalization; (2) Congenital malformation, complicating congenital heart disease, inherited metabolic diseases, or communicable disease; and (3) Abandonment of therapy.

The current study was approved by the Medical Ethics Association. All patients and family members were informed of the details and procedures of the experiment, providing informed consent.

Experimental methods

Reagents and instruments

Human MIF ELISA Kit (Shanghai Hengfei Biotechnology Co. Ltd, CSB-E08330h-1); Human PLTP Kit (Shanghai Hengfei Biotechnology Co. Ltd, CSB-E08330h-1); Multimode Reader (Beijing Keyuehuacheng Science and Technology Co. Ltd, Clariostar); Midazolam (Jiangsu Enhua Pharmaceutical Co. Ltd, Lot number: 201206-04); Lidocaine (Chengdu No. 1 Pharmaceutical Co. Ltd, SFDA approval number: H51021661).

Approaches

Collection of serum and BALF

One mL of blood was obtained from the radial artery of all subjects using an evacuated blood taking needle. It was separately placed in disposable blood collection tubes for 10 minutes. At 4°C, the samples were centrifuged at 1,000 g for 10 minutes. The serum was carefully extracted from the upper liquid and stored at -20°C, separately.

Bronchoalveolar lavage of both groups was collected under the guidance of the Bronchoscopy Manual [12]. First, 5 ml of midazolam was diluted by normal saline and injected into both groups for preoperative sedation. Next, 2 mL of 1% lidocaine was applied to narcotize the pharyngeal mucosal surface. The bronchus inlet was washed with 0.5-1.0 mL/kg normal saline at 37°C. BALF were collected using a negative pressure aspirator 2 to 3 times. It was then centrifuged at 1,000 g for 10 minutes. The upper liquid was extracted with caution and stored in a freezer at -20°C.

Expression levels of MIF and PLTP in the serum and BALF via ELSA

Expression levels of MIF and PLTP in the samples were detected using ELISA. Procedures were as follows. The standard was diluted on the plate in strict accordance with kit instructions, with wells of samples and standard prepared. Moreover, 40 µl and 50 µl diluents were added into the wells of samples and standard, respectively, and shaken gently. Separate blank wells were then set out. These wells were covered with microplate sealers and incubated at 37°C for 30 minutes. They were diluted with wash buffer 20 times using distilled water. The wells were uncovered and the residual liquid in the wells was completely removed. Each well was then filled with diluted buffer and allowed to stand for 30 seconds. The liquid in the well was completely abandoned as above ("the wash" for short). This procedure was repeated 5 times. Afterward, 50 µl conjugate reagent was added into the wells of samples and standard and covered with microplate sealers. It was incubated for 30 minutes at 37°C once again. The washing procedure was performed 5 additional times. With 50 µl color developing agents A and B added into each well, respectively, the samples were placed in a dark place for 15 minutes at 37°C for the color reaction. Finally, 50 µl stop solution was filled into each well. An appearance of yellow denoted the end of the reaction. With blank wells as a zero-setting reference, optical density values of each well in 450 nm were determined after 15 minutes.

Observation indicators

Comparison of clinical general information, including gender, gestational age, birth body mass, and times of oxygen inhalation and mechanical ventilation, were conducted. This study also compared expression levels of MIF and PLTP in the serum and BALF the 1st, 2nd, 3rd, and 4th weeks after birth, respectively.

Statistical analysis

Data was analyzed using SPSS 19.0 (SPSS Shanghai, China) statistical software and plotted by GraphPadPrism7 (Huanzhongruichi Science and Technology Co. Ltd, Beijing, China). Enumeration data are expressed as percentages and x^2 tests were applied for group comparisons. Measurement data are expressed as ($\overline{x}$ ± sd) and were analyzed by Kolmogorov-Smirnov tests, aiming to confirm if the data conformed to normal distribution. Independent-sample t-tests were applied for group comparisons. ROC curves were plotted in accordance with expression levels of MIF and PLTP in the serum of both groups. The diagnostic value of expression levels of MIF and PLTP in BDP was evaluated. Moreover, correlation levels between expression of MIF and PLTP were measured using Pearson's analysis. *P*-values less than 0.05 indicate statistical significance.

Results

Comparison of clinical data

Differences in clinical general information, including gender, days of admission, cases of PROM and chorioamnionitis, cases of cesarean delivery, times of oxygen inhalation and mechanical ventilation, administration of alveolar surfactant and dexamethasone, and history of asphyxia, between the two groups showed no statistical significance (*P*>0.05). Gestational ages and birth body masses of the experimental group were substantially lower than those of the control group. Times of oxygen inhalation and mechanical ventilation were longer than those of the control group. Differences were statistically significant (P<0.05) (**Table 1**).

Comparison of MIF levels in serum

In the 1st, 2nd, 3rd, and 4th weeks after birth, levels of serum MIF in the experiment group were substantially higher than those of the control group, showing statistical significance (P<0.05) (**Table 2**; **Figure 1**).

Table 1. Comparison of clinical data ($\overline{x} \pm sd$) [n (%)]

Indicator	Experiment group (n=31)	Control group (n=31)	t/x^2	P
Gender			0.791	0.374
Male	25 (80.65)	22 (70.97)		
Female	6 (19.35)	9 (29.03)		
Gestational age (week)	28.83±3.02	31.44±3.65	3.067	0.003
Birth body mass (g)	1322.12±305.41	1678.52±326.87	4.436	<0.001
PROM	9 (29.03)	12 (38.71)	0.648	0.421
Chorioamnionitis	10 (32.26)	16 (51.61)	2.385	0.123
History of asphyxia	18 (58.06)	14 (45.16)	1.033	0.309
Time of mechanical ventilation (d)	16.27±5.38	2.39±0.75	14.227	<0.001
Time of oxygen inhalation (d)	33.86±7.37	5.98±1.39	20.697	<0.001
Cesarean delivery	13 (41.94)	15 (48.39)	0.261	0.610
Use of alveolar surfactant	19 (61.29)	22 (70.97)	0.648	0.421
Use of dexamethasone	7 (22.58)	10 (32.26)	0.729	0.393
Days of admission	5.97±4.69	4.92±4.11	0.937	0.352

Table 2. Comparison of MIF levels in serum ($\overline{x} \pm sd$, ng/mL)

Group	n	1st (week)	2nd	3rd	4th
Experiment group	31	12.45±1.72*	15.79±2.28*	18.53±2.17*	20.43±2.55*
Control group	31	9.95±2.38	10.88±3.46	11.05±2.72	10.96±2.63
t		4.740	6.579	11.970	14.390
P		<0.001	<0.001	<0.001	<0.001

Note: At each time point, the expression level of serum MIF in experiment group were higher than that of control group (P<0.05). *means there was a significant statistical difference between the experiment group and the control group.

Comparison of MIF levels in BALF

In the 1st, 2nd, 3rd, and 4th weeks after birth, levels of MIF in BALF of the experiment group were substantially higher than those of the control group. Differences were statistically significant (P<0.05), in accord with serum testing (**Table 4**; **Figure 3**).

Comparison of PLTP levels in BALF

At all time-points after birth, PLTP levels in BALF of the experiment group were lower than those of the control group. Differences were statistically significant (P<0.05) (**Table 5**; **Figure 4**).

Comparison of the diagnostic value between MIF and PLTP in serum

ROC curves were plotted in accordance with expression levels of MIF and PLTP in the serum of both groups after 1 week of life. Areas under MIF curves, critical value of diagnosis, sensitivity, and specificity levels were 0.860 (0.771-0.948), 10.49 ng/mL, 64.52%, and 87.10%, respectively. Levels of the PLTP curves were 0.761 (0.641-0.881), 12.89 ng/mL, 64.52%, and 83.87%, respectively. Early detection of expression levels of serum MIF and serum PLTP in BPD neonatorum cases is of diagnostic
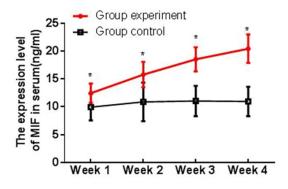

Figure 1. Comparison of MIF levels in serum. Note: At each time point, expression levels of serum MIF in the experiment group were higher than those of the control group (P<0.05).

Comparison of PLTP levels in serum

In the 1st, 2nd, 3rd, and 4th weeks after birth, levels of serum PLTP in the experiment group were substantially lower than those of the control group, showing statistical significance (P<0.05) (**Table 3**; **Figure 2**).

Table 3. Comparison of PLTP levels in serum ($\bar{x} \pm sd$, ng/mL)

Group	n	1st (week)	2nd	3rd	4th
Experiment group	31	10.72±2.23	11.85±3.42*	12.14±4.68*	10.25±2.99*
Control group	31	12.26±1.94	13.24±1.67	14.03±1.72	12.07±1.86
t		2.901	2.033	2.110	2.878
P		0.005	0.046	0.039	0.005

Note: At each time point, the expression level of serum PLTP in experiment group were lower than that of control group (P<0.05). *means there was a significant statistical difference between the experiment group and the control group.
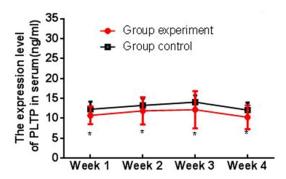

Figure 2. Comparison of PLTP levels in serum. Note: At each time point, expression levels of serum PLTP in the experiment group were lower than those of the control group (P<0.05).

significance, along with high sensitivity and specificity. See **Figure 5** for details.

Correlation between MIF expression in the serum and BALF, along with PLTP expression, of BPD neonatorum cases

Analyzing MIF expression levels in the serum and BALF, as well as PLTP expression, of BPD neonatorum cases after 1 week of life, a positive correlation was found between expression levels of MIF in serum and in BALF (r=0.682, P<0.001). This correlation was also found in expression levels of PLTP in serum and PLPT in BALF (r=0.714, P<0.001). In addition, a notable negative correlation was determined between expression levels of serum MIF and serum PLTP in BPD neonatorum cases (r=-0.741, P<0.001), as well as expression levels of MIF in BALF and PLTP in BALF (r=-0.576, P<0.001). See **Figure 6**.

Discussion

BPD is currently a major contributor to morbidity and mortality of premature infants. BPD infant patients are more likely to suffer from pul-

monary hypertension. However, the mechanisms of BPD have not yet been fully recognized. There has been a popular conception in clinic practice that antenatal factors can exert a long-term impact on the lung development of infants. Some scholars also believe that there is correlation between the function of the placenta and an infant lung development [13]. Though death rates have decreased in recent years due to the constant advancement of modern medical technology, researchers have documented that BPD remains the most common disease of premature infants with gestational ages under 30 weeks. Furthermore, chronic pulmonary disease during the neonatal period tends to increase the risk of lung disease in infants at a later stage [14]. Of infants with low birthweights, BPD appears more frequently. It is often associated with severe complications, such as respiratory distress syndrome (RDS), hypoxemia, and lower respiratory tract infections (LRTI). These may influence quality of life and long-term prognosis [15].

Although early diagnosis is of great significance to BPD patient quality of life and long-term prognosis, a biomarker identifying BPD during the early stages has yet to be discovered. It usually mixes with other symptoms of neonatal lung disease. Therefore, the discovery of a simple and convenient serum marker would make a big difference to the diagnosis and prognosis of BPD disease.

According to current results, gestational ages and birth body masses of the experiment group were substantially lower than those of the control group. Times of oxygen inhalation and mechanical ventilation were longer than those of the control group, indicating that gestational age, birth body mass, and times of oxygen inhalation and mechanical ventilation are all risk factors for BPD disease among neonatorum cases. Present results are in accord with viewpoints of other scholars, such as Yu [16], who believes that neonatorum cases with low gestational ages and birthweights show more risks in lung underdevelopment and pulmonary dis-

Table 4. Comparison of MIF levels in BALF ($\overline{x} \pm$ sd, ng/mL)

Group	n	1st (week)	2nd	3rd	4th
Experiment group	31	8.74±1.56*	9.02±2.02*	9.81±1.95*	10.32±1.88*
Control group	31	5.28±1.78	5.74±1.85	6.03±1.87	7.10±1.97
t		8.139	6.667	7.790	6.584
P		0.001	<0.001	<0.001	<0.001

Note: At each time point, the expression level of MIF in BALF of experiment group were higher than that of control group (P<0.05). *means there was a significant statistical difference between the experiment group and the control group.
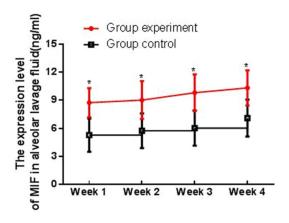

Figure 3. Comparison of MIF levels in BALF. Note: At each time point, expression levels of MIF in BALF of the experiment group were higher than those of the control group (P<0.05).

ease. Moreover, lungs of premature infant with BPD are still at the balloon or canalicular stage. The structure and function have not reached full maturity. Oxygen inhalation and mechanical ventilation becomes a necessity to sustain life under these circumstances [17]. As a result, BPD patients need more oxygen inhalation and mechanical ventilation.

At all time-points after birth, levels of MIF in the serum and in BALF of the experiment group were higher than those of the control group. Levels of PLTP in the serum and in BALF were lower than those of the control group. According to ROC curves, areas under the MIF curves, critical value of diagnosis, sensitivity, and specificity were 0.860 (0.771-0.948), 10.49 ng/mL, 64.52%, and 87.10%, respectively. Levels of PLTP curves were 0.761 (0.641-0.881), 12.89 ng/mL, 64.52%, and 83.87%, respectively, suggesting abnormal expression of MIF and PLTP in BPD neonatorum cases. Overexpression of MIF and under-expression of PLTP are able to facilitate early diagnosis of BPD disease. MIF, a key upstream regulatory factor in the body's immune response, can induce expression of inflammation mediators, such as TNF-α and interleukin, stimulate immune cells to migrate to the tissues, and contribute to inflammation and tissue injuries [18]. A rising trend of MIF has also been found in the serum of septic infants and adult patients. There is a positive correlation between expression levels and degrees of the disease [19]. Some other studies have shown that MIF might inhibit DNA damage of endothelial cells and control the death of mediator p53, exerting an impact on pulmonary stability [20]. Abnormal expression can alter the pattern of alveolar development of neonatal rats. This supports current research results, indirectly, suggesting that MIF might participate in the development of BPD and be overexpressed.

Phospholipid transfer protein (PLTP), which is related to apolipoprotein, is a protein involved in the transport of phosphatidylcholine between phospholipid proteins. It can neutralize the inflammatory reaction of polysaccharides by binding to serum lipase [21]. In addition, PLTP provides protective effects on the lungs. Reportedly, PLTP activity has been positively correlated with lung function. Moreover, cigarette smoke and serum lipase may increase the release of serine protease, triggering PLTP protein lysis. This causes inflammation and aggravation of disease damage [22]. The above studies have indicated that high expression of MIF or low expression of PLTP may cause or aggravate occurrence of BPD. Thus, early detection of serum MIF and PLTP levels can provide help for the early diagnosis of BPD neonatorum.

There was a positive correlation exhibited between MIF expression in serum and in BALF, as well as PLTP expression. A notable negative correlation was determined between expression levels of serum MIF and serum PLTP in BPD neonatorum cases. With illness development and prolonged times of oxygen inhalation, an abnormal oxygen environment can lead to the damage of alveolar type II cells [23] and restrict neonatal lung development. It was assumed that MIF is involved in BDP formation.

Table 5. Comparison of PLTP levels in BALF ($\bar{x} \pm sd$, ng/mL)

Group	n	1st (week)	2nd	3rd	4th
Experiment group	31	13.84±1.62*	16.91±2.07*	20.22±2.97*	25.89±1.70*
Control group	31	23.98±2.54*	32.58±2.78*	44.71±2.61*	53.28±1.52*
t		18.740	25.172	34.486	66.874
P		<0.001	<0.001	<0.001	<0.001

Note: At each time point, the expression level of PLTP in BALF of experiment group were lower than that of control group (P<0.05). *means there was a significant statistical difference between the experiment group and the control group.
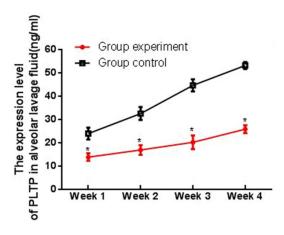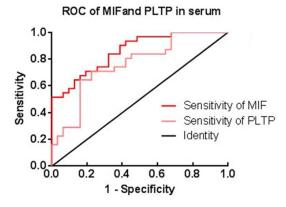

Figure 4. Comparison of PLTP levels in BALF. Note: At each time point, expression levels of PLTP in BALF of the experiment group were lower than those of the control group (P<0.05).

Figure 5. ROC of MIF and PLTP in serum.

However, this study could not fully explain why expression levels of MIF in serum would be higher than those in BALF. This requires further investigation. Alveoli damage is also able to inhibit PLTP-mediated phospholipid synthesis pathways. This, in turn, may reduce the content of pulmonary surfaces active substances and increase the permeability of pulmonary capillary membranes. Subsequently, PLTP in lung tissues enters the blood barriers and participates in the blood circulation, elevating expression levels of PLTP in serum [9, 23]. As a result, there is a consistency between changes in MIF and PLTP expression in serum, as well as in BALF, of BPD neonatorum cases. Moreover, there is a remarkable negative correlation between MIF and PLTP expression in serum, as well as in BALF, of both groups. Results suggest that BPD formation might be attributed to MIF overexpression and PLTP inactivation. This may release inflammatory factors and aggravate inflammatory response.

However, there were several limitations tot the current study. First, due to an insufficient sample size, accidental factors, such as experiment errors, may have influenced results to some degree. Second, some uncertainties in this study are yet to be determined. Further comparative analysis between different time points, as well as in-depth analysis of MIF and PLTP expression in BDP, is a necessity for follow-up research. This subject requires in-depth discussion of other scholars from different perspectives.

In summary, MIF was overexpressed and PLTP was under-expressed in the serum and BALF of BPD neonatorum cases. A negative correlation was shown between expression levels of MIF and PLTP. Early detection of expression levels of serum MIF and serum PLTP in BPD neonatorum cases is of diagnostic significance, offering a new perspective for early diagnosis of BDP. Thus, this method is worthy of promotion in clinical practice.

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Disclosure of conflict of interest

None.

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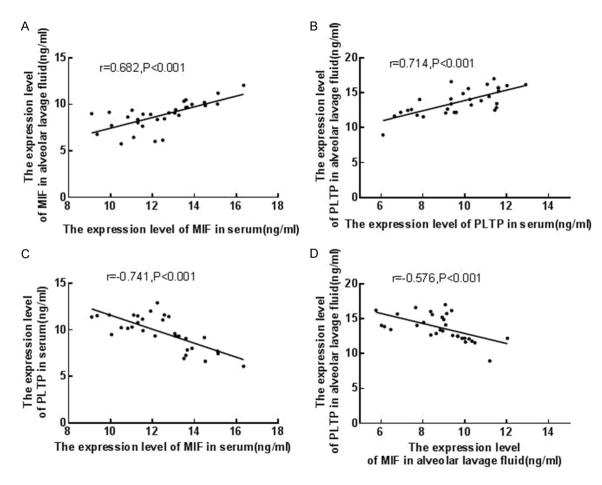
Figure 6. Correlation analysis of MIF expression in serum and BALF, as well as PLTP expression, in serum and BALF of BPD neonatorum cases.

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