Original Article
Value of blood gas analysis and immunological indicators in early diagnosis and treatment monitoring of children with severe pneumonia and sepsis

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Abstract: Objective: This study was designed to investigate the clinical value of blood gas analysis and related immunological indicators in the early diagnosis and treatment monitoring of children with severe pneumonia and sepsis. Methods: A retrospective study was conducted on children with pneumonia and sepsis and healthy children undergoing physical examination in the First People's Hospital of Fuyang Hangzhou from January 2020 to December 2020. A total of 31 children with pneumonia and sepsis (observation group) and 31 healthy children (control group) were included. The levels of partial pressure of carbon dioxide ($PaCO_2$), partial pressure of oxygen (PaO_2), pH, immunoglobulin A (IgA), immunoglobulin M (IgM), immunoglobulin G (IgG), complement 3 (C3) and complement 4 (C4) were compared between the two groups. The changes of blood gas analysis indices and immune indices in the observation group before treatment (T0), as well as after 1 month (T1), 2 months (T2) and 3 months (T3) of treatment were dynamically analyzed. Results: Compared with the control group, the level of $PaCO_2$ was significantly increased, and the levels of PaO_2, pH, IgA, IgM, IgG, C3 and C4 were significantly decreased in the observation group, showing statistically significant differences ($P < 0.05$). With the progress of treatment, the levels of PaO_2, PH, IgA, IgM, IgG, C3 and C4 showed a slowly increasing trend, while $PaCO_2$ gradually decreased, and the differences between T3 and T0 were statistically significant ($P < 0.05$). ROC curve analysis showed that $PaCO_2$, PaO_2, PH, IgA, IgM, IgG, C3 and C4 had good diagnostic value for severe pneumonia combined with sepsis ($P < 0.05$). Conclusion: Blood gas analysis and immune indices exhibited high precision in early diagnosis and treatment monitoring of children with severe pneumonia and sepsis.

Keywords: Blood gas analysis, immune indices, severe pneumonia, diagnosis, treatment

Introduction

Pediatric pneumonia, as a common respiratory disease in clinic, may lead to serious complications without timely and appropriate treatment, and its morbidity and mortality account for a relative high proportion of childhood diseases [1-3]. The exacerbation of pneumonia in children can lead to impaired immune regulation, inducing malignant complications such as shock, sepsis, septicemia and multiple organ failure [4, 5], which causes great harm to the children and their families. Studies have shown that children with pneumonia and sepsis may have specific pathological changes. For instance, their immune system is in an unbalanced state, and the immune cells rapidly release large amounts of inflammatory factors, leading to inflammatory cytokine storm, as well as disturbance of the coagulation and fibrinogen system, thereby resulting in disseminated intravascular coagulation, shock, multiple organ failure, and acidosis caused by water-salt metabolic imbalance [6, 7], consequently increasing the risk of death in children.

Severe pneumonia is the critical stage of pneumonia, accounting for about 5-15% of all pneumonia in children. There is no unified standard for the diagnosis of severe pneumonia in children worldwide, but severe pneumonia in children is often complicated with multiple organ failure and shock, especially sepsis, which is an important risk factor [8-10]. Sepsis is an inflam-

matory syndrome involving lungs and bile ducts, and patients with sepsis are often accompanied by serious complications such as shock.

Blood gas analysis is one of the methods for the diagnosis of pneumonia, and can be used to evaluate pulmonary ventilation function and acid-base balance state by determining the pressure value of carbon dioxide and oxygen as well as the pH value in blood [11, 12]. Blood gas analysis plays a decisive guiding role in correcting acid-base imbalance in children with pneumonia. Clinically, the conditions of children with pneumonia can be comprehensively analyzed and evaluated based on blood gas indices. Therefore, blood gas analysis is an important means to improve the recovery and reduce the mortality.

The imbalance of immune response mechanisms and impaired immune function are mainly manifested as apoptosis of spleen cells and significant hypofunction of T lymphocytes (including T lymphocytes, helper T lymphocytes and immune response products) [13]. Helper T lymphocytes are an important subgroup of T lymphocytes that play a key role in the resistance to disease progression in patients with bacterial sepsis. Due to the invasion of infectious factors and inflammatory response, immunocompromise is the main cause of sepsis [14, 15]. The levels of immunoglobulin A (IgA), immunoglobulin M (IgM), immunoglobulin G (IgG), complement 3 (C3) and complement 4 (C4) can reflect the strength of the body's cellular immunity and assess the condition of sepsis.

This study was designed to investigate the value of blood gas analysis and immune indices in early diagnosis and treatment monitoring of children with pneumonia and sepsis, with the hope to provide scientific data and basis for improving the prognosis of children with pneumonia.

Materials and methods

General information

A retrospective study was conducted on children with pneumonia and sepsis and healthy children undergoing physical examination in the First People's Hospital of Fuyang Hangzhou

from January 2020 to December 2020. The clinical data of 31 children with pneumonia and sepsis (observation group) and 31 healthy children (control group) were collected.

Inclusion criteria: children in the observation group met the diagnostic criteria for pneumonia combined with sepsis; children aged 1 month to 12 years. Exclusion criteria: children with primary major organ failure; children who had received anti-infective or symptomatic treatment drugs; children with incomplete case data.

All data analysis ensured the privacy of patient information. The basic clinical data such as age, sex and weight of all children were collected, analyzed and compared. There was no statistically significant difference in the basic data between the two groups (P>0.05), indicating comparability between the two groups. This study was approved by Ethics Committee of the First People's Hospital of Fuyang Hangzhou (approval number: NCT03268468).

Investigation methods

The name, sex, age, telephone number and other personal information of patients were recorded. Besides, body temperature, concomitant symptoms and signs, epidemiological history, blood gas analysis, including arterial partial pressure of carbon dioxide ($PaCO_2$), partial pressure of oxygen (PaO_2), pH and other clinical data were recorded. Results of blood tests, throat swabs, imaging or other laboratory tests were recorded. Immune indicators including levels of IgA, IgM, IgG, C3 and C4 were recorded. The blood gas analysis and immune indices were recorded before treatment (T0), as well as 1 month (T1), 2 months (T2) and 3 months (T3) after treatment.

Statistical analysis

SPSS22.0 statistical software was adopted to analyze the collected data. Measurement data were represented by mean ± standard deviation (mean ± SD). Normal distribution and homogeneity of variance tests were carried out. T-test was carried out for comparison between groups of data satisfying normal distribution or homogeneity of variance, and the approximate t-test was applied for data with heterogeneity of variance. Bonferroni post hoc test was adopted
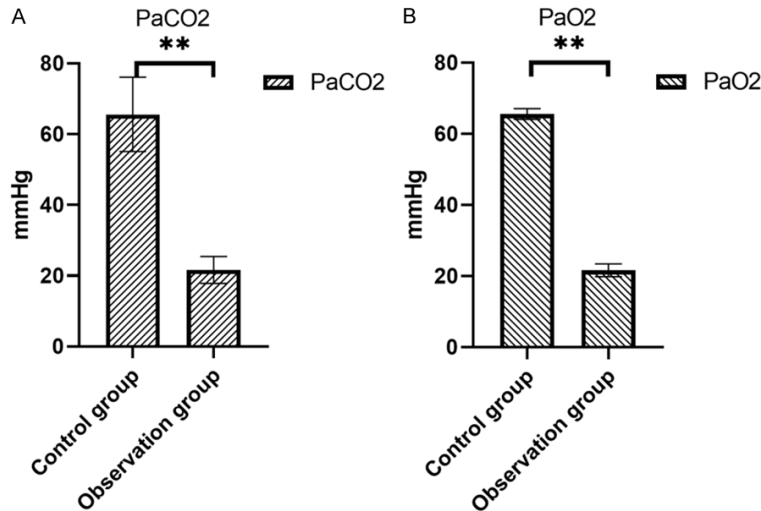
Figure 1. Comparison of blood gas analysis indices. A. $PaCO_2$; B. PaO_2. Note: Compared with the control group, $^{**}P < 0.01$; t-test. $PaCO_2$: partial pressure of carbon dioxide; PaO_2: partial pressure of oxygen.
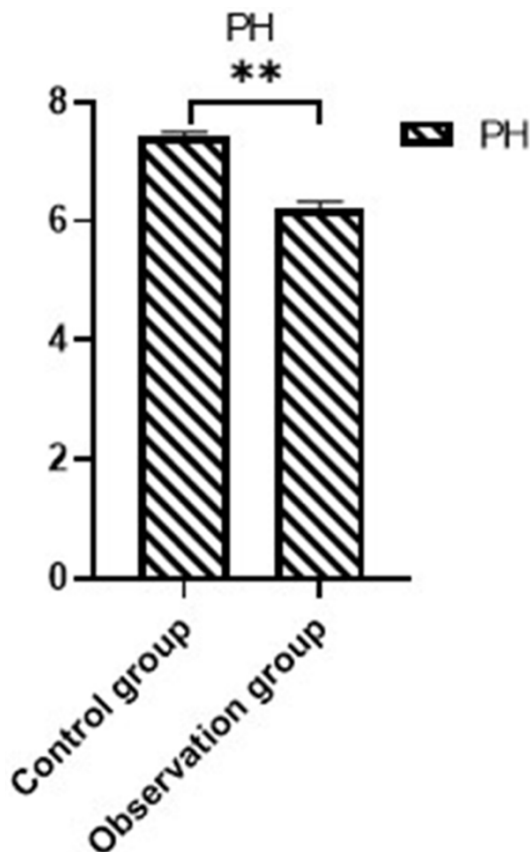

Figure 2. Comparison of pH values. Note: Compared with the control group, $^{**}P < 0.01$; t-test.

for the comparison between two groups after ANOVA. Chi-square test was performed for the

difference of counting data between groups. $P < 0.05$ was taken as a statistically significant difference. Graphpad Prism 8.3 was used for plotting the graphs in this study [13].

Results

Comparison of blood gas analysis indices between the two groups

The observation group exhibited significantly lower PaO_2 and pH levels and significantly higher $PaCO_2$ level than the control group, with statistically significant differences ($P < 0.05$) (**Figures 1**, **2**).

Comparison of immune indices between the two groups

The observation group showed significantly lower levels of IgA, IgM, IgG, C3 and C4 compared with the control group ($P < 0.05$). This suggested that severe pneumonia combined with sepsis could lead to a remarkable decline in immune function and a reduction in immune system parameters in children (**Figures 3**, **4**).

Dynamic observation of blood gas analysis indices of children in the observation group

Blood gas analysis indices showed that PaO_2 and pH levels in the observation group were significantly increased from T0 to T3, while $PaCO_2$ level in the observation group was significantly decreased from T0 to T3, and the intra-group comparison differences were statistically significant ($P < 0.05$), indicating that blood gas indices could reflect the treatment efficacy in children with severe pneumonia and sepsis, which could effectively guide the treatment and the evaluation of prognosis (**Figures 5, 6**).

Dynamic observation of immune indices of children in the observation group

Monitoring of immune indices revealed that the levels of IgA, IgM, IgG, C3 and C4 in the observation group were significantly increased from T0 to T3, and the differences were statistically
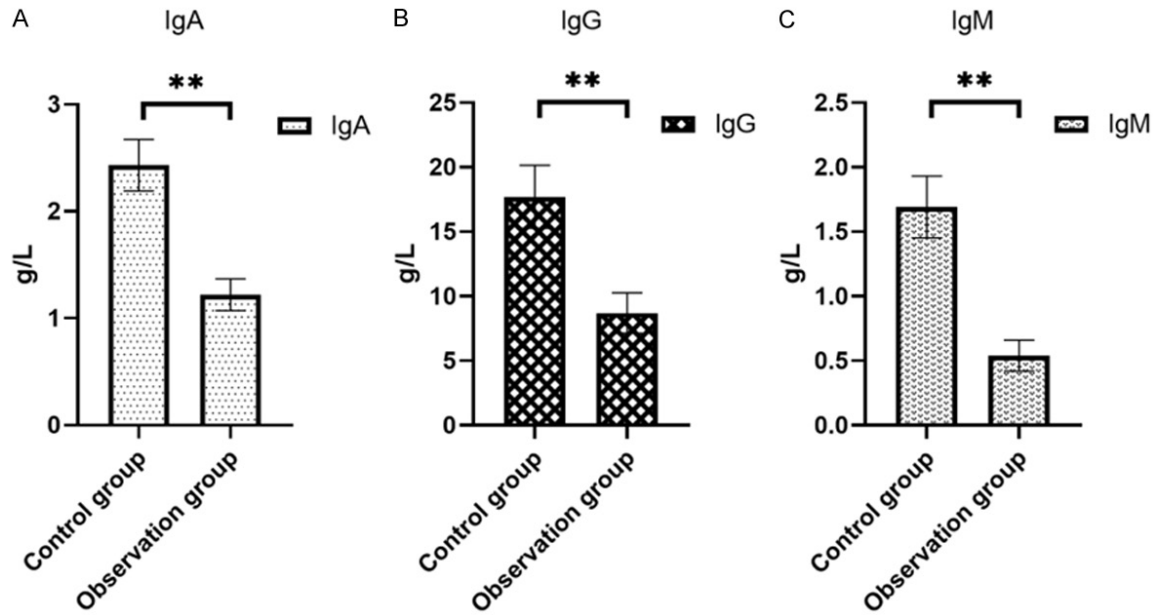
Figure 3. Comparison of immunoglobulin levels. A. IgA; B. IgG; C. IgM. Note: Compared with the control group, **P < 0.01; t-test. IgA: immunoglobulin A; IgG: immunoglobulin G; IgM: immunoglobulin M.
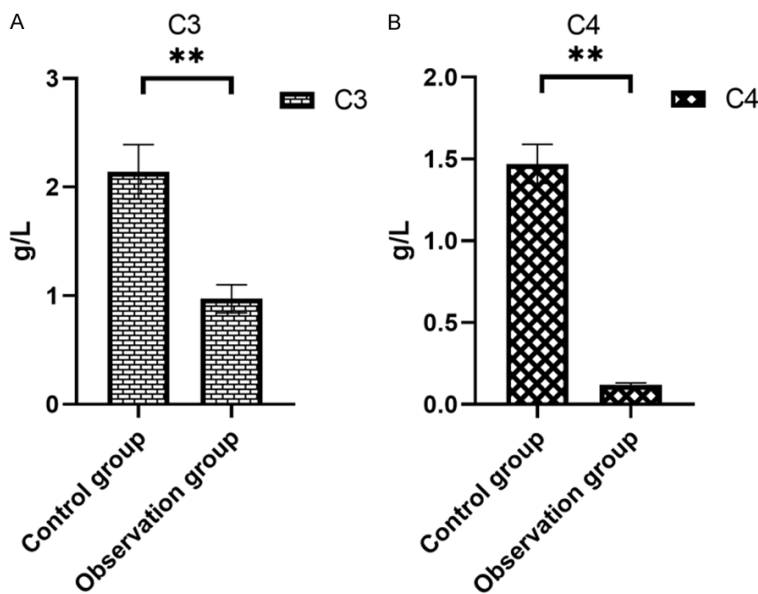

Figure 4. Comparison of C3 and C4 levels between the two groups. A. C3; B. C4. Note: Compared with the control group, **P < 0.01; t-test. C3: complement 3; C4: complement 4.

Analysis of the diagnostic value of blood gas analysis indices and immune indices in children with severe pneumonia combined with sepsis

The ROC curves of $PaCO_2$, PaO_2, pH, IgA, IgM, IgG, C3 and C4 were plotted for the diagnosis of severe pneumonia combined with sepsis, and the calculation showed that the above indices had good diagnostic value for severe pneumonia combined with sepsis ($P < 0.05$) (**Table 1**; **Figure 9**).

Discussion

significant ($P < 0.05$), indicating that immune indices were a powerful tool for accessing the treatment progress of severe pneumonia with sepsis. So, monitoring immune indices could help physicians to effectively control the disease and avoid its deterioration and development (**Figures 7**, **8**).

Pneumonia, as a common respiratory disease in China, is susceptible to all age groups and is the main cause of infectious disease-associated deaths. According to statistics, about 21 million children in China are infected with pneumonia each year, and pneumonia is listed as one of the four major diseases among children by the National Health and Family Planning Commission. Severe pneumonia is a severe form of pneumonia that
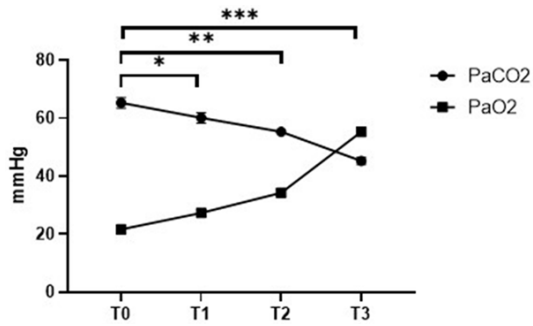
Figure 5. Comparison of $PaCO_2$ and PaO_2 levels at different time points in the observation group. Note: Compared with T1, *$P < 0.05$; compared with T2, **$P < 0.01$; compared with T3, ***$P < 0.001$; ANOVA with post hoc Bonferroni test. $PaCO_2$: partial pressure of carbon dioxide; PaO_2: partial pressure of oxygen.
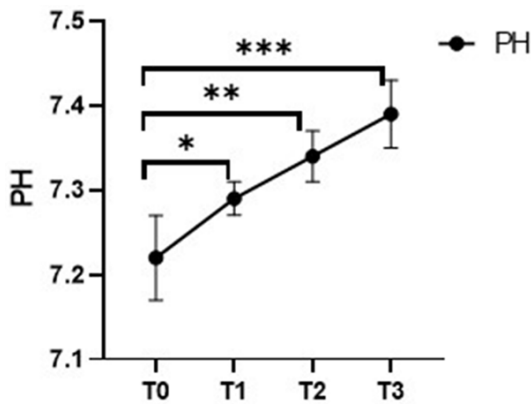

Figure 6. Comparison of pH values at different time points in the observation group. Note: Compared with T1, *$P < 0.05$; compared with T2, **$P < 0.01$; compared with T3, ***$P < 0.001$; ANOVA with post hoc Bonferroni test.

Figure 7. Comparison of immunoglobulin levels at different time points in the observation group. A. IgA, IgM; B. IgG. Note: Compared with T1, *$P < 0.05$; compared with T2, **$P < 0.01$; compared with T3, ***$P < 0.001$; ANOVA with post hoc Bonferroni test. IgA: immunoglobulin A; IgG: immunoglobulin G; IgM: immunoglobulin M.

Figure 8. Comparison of C3 and C4 levels at different time points in the observation groups. Note: Compared with T1, *$P < 0.05$; compared with T2, **$P < 0.01$; compared with T3, ***$P < 0.001$; ANOVA with post hoc Bonferroni test. C3: complement 3; C4: complement 4.

depends on the degree of local inflammation of the pneumonia and systemic inflammatory response.

Severe pneumonia may be considered when patients develop severe hypoxemia, acute respiratory failure, shock, or other organ failure. Severe pneumonia combined with sepsis is an acute and critical clinical disease, which has the characteristics of rapid onset, rapid development, multiple complications, systemic involvement, poor prognosis and high mortality. Accurate diagnosis and early intervention are important prerequisites for improving the prognosis of these patients. This study analyzed the application value of blood gas analysis and immune indices in early diagnosis and treat-
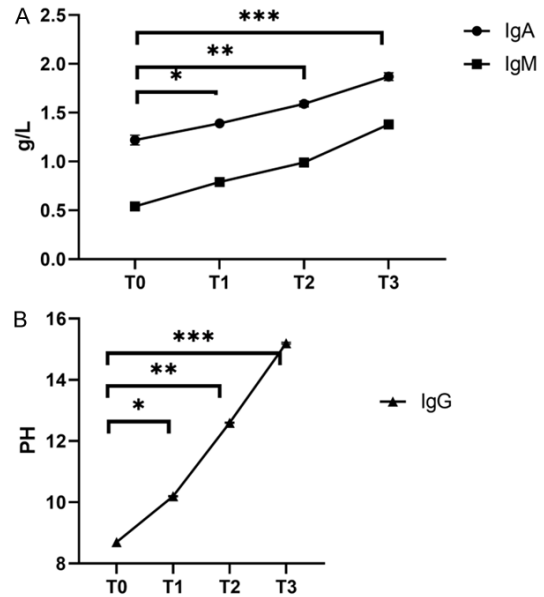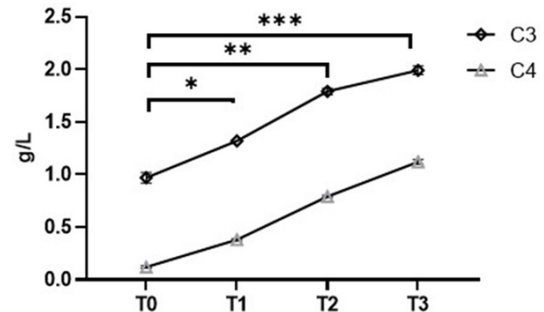
ment monitoring of children with severe pneumonia and sepsis by setting up two groups. The results showed that in terms of early diagnosis, the level of $PaCO_2$ in the observation group was significantly higher than that in the control group, while the levels of PaO_2, pH, IgA, IgM, IgG, C3 and C4 in the observation group were significantly lower than those in the control group. Although $PaCO_2$, PaO_2 and pH are crucial

Table 1. Diagnostic value of blood gas analysis and immune indices in children with severe pneumonia and sepsis

Parameter	Critical value	AUC	95% CI	P
$PaCO_2$	20.21 mmHg	0.7075	0.5615-0.8535	0.0067
PaO_2	28.19 mmHg	0.6944	0.5393-0.8495	0.0184
pH	7.01	0.8409	0.7111-0.9708	0.0001
IgA	1.87 g/L	0.8475	0.7232-0.9718	0.0002
IgG	7.19 g/L	0.7004	0.5409-0.8599	0.0199
IgM	0.78 g/L	0.8488	0.7275-0.9701	< 0.0001
C3	1.12 g/L	0.6730	0.5075-0.8384	0.0444
C4	0.89 g/L	0.8068	0.6734-0.9403	0.0005

$PaCO_2$: partial pressure of carbon dioxide; PaO_2: partial pressure of oxygen; IgA: Immunoglobulin A; IgG: immunoglobulin G; IgM: immunoglobulin M; C3: complement 3; C4: complement 4.

Figure 9. Diagnostic value of blood gas analysis and immune indices in children with severe pneumonia and sepsis. Note: Analysis showed that $PaCO_2$, PaO_2, pH, IgA, IgM, IgG, C3 and C4 had good diagnostic value for severe pneumonia combined with sepsis (P < 0.05). $PaCO_2$: partial pressure of carbon dioxide; PaO_2: partial pressure of oxygen; IgA: immunoglobulin A; IgG: immunoglobulin G; IgM: immunoglobulin M; C3: complement 3; C4: complement 4.
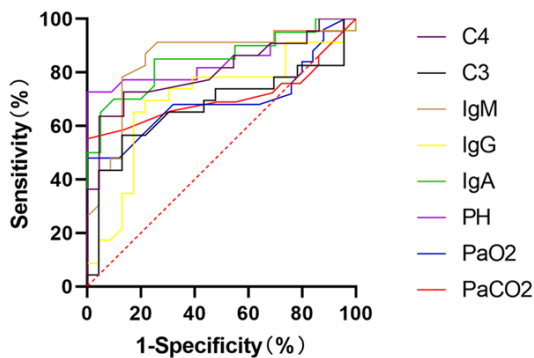
indicators for the diagnosis and treatment of children with severe pneumonia and sepsis, the differences of $PaCO_2$, PaO_2 and pH levels measured at different sites may be an issue. Therefore, it is particularly critical to optimize the selection of appropriate sites for the monitoring of these indicators, so as to effectively guarantee the safety during the treatment cycle and improve the prognosis of children [16, 17]. Therefore, future efforts may be placed on the combination of PaO_2, pH, IgA, IgM, IgG, C3 and C4, to develop appropriate diagnosis methods.

In terms of immune function, children in the observation group had significantly lower levels of IgA, IgM, IgG, C3 and C4 as compared with the control group. The results indicated that severe pneumonia combined with sepsis resulted in a dramatic decrease in immune function. The levels of IgA, IgM, IgG, C3 and C4 were significantly increased in the observation group from T0 to T3 (P < 0.05), suggesting that immune indices could be used to determine the efficacy of treatment, which can help physicians to effectively control the disease and avoid the deterioration. IgA, IgM and IgG are often used to assist the diagnosis of the severity of impaired immune function, since these substances can effectively indicate the activity of antibodies in the immune system. C3 and C4 are important immuno-modulatory receptors with the ability to deliver antigens, enhance antigen-antibody responses and directly kill infected cells [18]. The expression levels of C3 and C4 can reflect the strength of cellular immunity. Our study indicated that levels of IgA, IgM, IgG, as well as C3 and C4 are lowly expressed in children with pneumonia and sepsis. Therefore, these indicators provided potential targets for future treatments.

At present, autoimmune diseases are usually characterized by Th1 drift, i.e., elevated Th1/Th2 ratio (elevated level of Th1 and decreased level of Th2), while Th2 drift, i.e., decreased Th1/Th2 ratio (decreased level of Th1 and elevated level of Th2), occurs in diseases such as tumors and bronchial asthma. In bacterial sepsis, Th2 drift can impair immune function of the organism.

However, the limitation of this study is that there is no clear definition of combination of serum factors. Besides, the inflammation levels were not detected, which means the targets in this study are not comprehensive. So, more combinations of serum factors should be explored in the future.

In conclusion, blood gas analysis and immune indices can be used for early diagnosis and treatment monitoring in children with pneumonia and sepsis.

Disclosure of conflict of interest

None.

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References

[1] Frenzen FS, Kutschan U, Meiswinkel N, Schulte-Hubbert B, Ewig S and Kolditz M. Admission lactate predicts poor prognosis independently of the CRB/CURB-65 scores in community-acquired pneumonia. Clin Microbiol Infect 2018; 24: 306.e301-306.e306.

[2] Faria DA, da Silva EM, Atallah ÁN and Vital FM. Noninvasive positive pressure ventilation for acute respiratory failure following upper abdominal surgery. Cochrane Database Syst Rev 2015; 2015: CD009134.

[3] Li H, Guo J, Wang K, Zhang NR, Zheng ZN and Jin SQ. Effect of open-lung ventilation strategy on oxygenation-impairment during laparoscopic colorectal cancer resection. Zhonghua Wei Chang Wai Ke Za Zhi 2020; 23: 1081-1087.

[4] Yaghouby F, Daluwatte C, Fukuda S, Nelson C, Salsbury J, Kinsky M, Kramer GC, Strauss DG, Enkhbaatar P and Scully CG. Progression and variability of physiologic deterioration in an ovine model of lung infection sepsis. J Appl Physiol (1985) 2017; 123: 172-181.

[5] Norrby-Teglund A, Pauksens K, Norgren M and Holm SE. Correlation between serum TNF alpha and IL6 levels and severity of group A streptococcal infections. Scand J Infect Dis 1995; 27: 125-130.

[6] Enkhbaatar P, Joncam C, Traber L, Nakano Y, Wang J, Lange M, Connelly R, Kulp G, Saunders F, Huda R, Cox R, Schmalstieg F, Herndon D and Traber D. Novel ovine model of methicillin-resistant Staphylococcus aureus-induced pneumonia and sepsis. Shock 2008; 29: 642-649.

[7] Ben Jaballah N, Khaldi A, Mnif K, Bouziri A, Belhadj S, Hamdi A and Kchaou W. High-frequency oscillatory ventilation in pediatric patients with acute respiratory failure. Pediatr Crit Care Med 2006; 7: 362-367.

[8] Yadav B, Bansal A and Jayashree M. Clinical profile and predictors of outcome of pediatric acute respiratory distress syndrome in a PICU: a prospective observational study. Pediatr Crit Care Med 2019; 20: e263-e273.

[9] Solé A, Jordan I, Bobillo S, Moreno J, Balaguer M, Hernández-Platero L, Segura S, Cambra FJ, Esteban E and Rodríguez-Fanjul J. Venoarterial extracorporeal membrane oxygenation support for neonatal and pediatric refractory septic shock: more than 15 years of learning. Eur J Pediatr 2018; 177: 1191-1200.

[10] Grocott MP, Dushianthan A, Hamilton MA, Mythen MG, Harrison D and Rowan K. Perioperative increase in global blood flow to explicit defined goals and outcomes after surgery: a cochrane systematic review. Br J Anaesth 2013; 111: 535-548.

[11] Butler DF and Myers AL. Changing epidemiology of haemophilus influenzae in children. Infect Dis Clin North Am 2018; 32: 119-128.

[12] Thimmulappa RK, Lee H, Rangasamy T, Reddy SP, Yamamoto M, Kensler TW and Biswal S. Nrf2 is a critical regulator of the innate immune response and survival during experimental sepsis. J Clin Invest 2006; 116: 984-995.

[13] Schuijt TJ, Lankelma JM, Scicluna BP, de Sousa e Melo F, Roelofs JJ, de Boer JD, Hoogendijk AJ, de Beer R, de Vos A, Belzer C, de Vos WM, van der Poll T and Wiersinga WJ. The gut microbiota plays a protective role in the host defence against pneumococcal pneumonia. Gut 2016; 65: 575-583.

[14] Schultz MJ and van der Poll T. Modulation of innate immune responses in the treatment of sepsis and pneumonia. Curr Drug Targets Inflamm Allergy 2004; 3: 11-17.

[15] Chow EJ, Doyle JD and Uyeki TM. Influenza virus-related critical illness: prevention, diagnosis, treatment. Crit Care 2019; 23: 214.

[16] Poropat G, Radovan A, Peric M, Mikolasevic I, Giljaca V, Hauser G, Milic S and Stimac D. Prevention of infectious complications in acute pancreatitis: results of a single-center, randomized, controlled trial. Pancreas 2019; 48: 1056-1060.

[17] Ticinesi A, Lauretani F, Nouvenne A, Porro E, Fanelli G, Maggio M and Meschi T. C-reactive protein (CRP) measurement in geriatric patients hospitalized for acute infection. Eur J Intern Med 2017; 37: 7-12.

[18] Bouras M, Asehnoune K and Roquilly A. Contribution of dendritic cell responses to sepsis-induced immunosuppression and to susceptibility to secondary pneumonia. Front Immunol 2018; 9: 2590.