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# Predictive value of C-reactive protein and the Pediatric Risk of Mortality III Score for occurrence of postoperative ventilator-associated pneumonia in pediatric patients with congenital heart disease

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**ABSTRACT**

**Importance:** Ventilator-associated pneumonia (VAP) is one of the most common complications after cardiac surgery in children with congenital heart disease (CHD). Early prediction of the incidence of VAP is important for clinical prevention and treatment.

**Objective:** To determine the value of serum C-reactive protein (CRP) levels and the Pediatric Risk of Mortality III (PRISM III) score in predicting the risk of postoperative VAP in pediatric patients with CHD.

**Methods:** We performed a retrospective review of clinical data of 481 pediatric patients with CHD who were admitted to our pediatric intensive care unit. These patients received mechanical ventilation for 48 hours or longer after corrective surgery. On the basis of their clinical manifestations and laboratory results, patients were separated into two groups of those with VAP and those without VAP. CRP levels were measured and PRISM III scores were collected within 12 hours of admission to the pediatric intensive care unit. The Pearson correlation coefficient was used to evaluate the association of CRP levels and the PRISM score with the occurrence of postoperative VAP. A linear regression model was constructed to obtain a joint function and receiver operating curves were used to assess the predictive value.

**Results:** CRP levels and the PRISM III score in the VAP group were significantly higher than those in the non-VAP group ($P < 0.05$). Receiver operating curves suggested that using CRP + the PRISM III score to predict the incidence of VAP after congenial heart surgery was more accurate than using either of them alone (CRP + the PRISM III score: sensitivity: 53.2%, specificity: 85.7%). When CRP + the PRISM III score was greater than 45.460, patients were more likely to have VAP.

**Interpretation:** Although using CRP levels plus the PRISM III score to predict the incidence of VAP after congenial heart surgery is more accurate than using either of them alone, its predictive value is still limited.

**KEYWORDS**

Congenital heart disease (CHD), Ventilator-associated pneumonia (VAP), C-reactive protein (CRP), Pediatric Risk of Mortality III (PRISM III)

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## INTRODUCTION

Congenital heart disease (CHD) is one of the most common birth defects in children, and it seriously endangers the physical and mental health of children. However, with technical progress in cardiopulmonary bypass (CPB) and mechanical ventilation (MV), the postoperative survival rate of children with CHD has been greatly improved. MV is an important auxiliary breathing support technique, and it uses a ventilator to maintain the pressure difference between the respiratory tract and the alveoli. MV can effectively maintain gas exchange and improve the internal environment by reducing the work of the respiratory muscles and ensuring appropriate ventilation. This is effectively used to treat multiple organ dysfunction syndrome.[1]

In recent years, operations on pediatric patients with CHD have become increasingly more difficult. Furthermore, use of a ventilator after surgery for patients with CHD is significantly prolonged, resulting in a significant increase in complications, which seriously affects the recovery of patients.[2] Among them, ventilator-associated pneumonia (VAP) is one of the most common complications after cardiac surgery. Most children with CHD need to use ventilator-assisted ventilation after surgery until spontaneous breathing is restored. However, CHD can be severe and be associated with possible malnutrition, lung infection, low immunity, and other factors, as well as intraoperative intubation, establishment of cardiopulmonary bypass, and improper use of antibiotics. Therefore, children with CHD are more likely to develop VAP during MV, resulting in prolonged use of MV and endangering children's lives.[3] Therefore, early prediction of the incidence of VAP is important for clinical prevention and treatment.

This study retrospectively analyzed children with CHD who underwent cardiac surgery in our hospital and received mechanical ventilation for more than 48 hours. This study assessed the predictive value of a method of combining serum CRP levels and the Pediatric Risk of Mortality III (PRISM III) score for predicting the incidence of postoperative VAP in pediatric patients.

## METHODS

### Study subjects

From January 1, 2012 to December 31, 2015, 496 pediatric patients with CHD received cardiac surgery in our hospital. All of the children were transferred to the pediatric intensive care unit (PICU) where they received mechanical ventilation for different durations. Patients who received mechanical ventilation for 48 hours or longer were included in our study. We collected clinical data, such as age, gender, weight, surgical records, and physiological variables.

### Standard for diagnosis of VAP

The diagnosis of VAP strictly followed the "Guidelines for the Diagnosis, Treatment and Prevention of Nosocomial Pneumonia"[4] issued by the Chinese Medical Association in 2013. VAP was diagnosed if the patient met the following (1) (2) and (3) or (1) (2) and (4): (1) mechanical ventilation for ≥ 48 hours or within 48 hours after weaning from mechanical ventilation; (2) new or progressive radiographic pulmonary infiltrate; (3) a pathogenic test with cultures of respiratory secretion suggesting new pathogens; and (4) other signs of infection. Signs of infection (at least one) were as follows: high body temperature (> 38°C); increased respiratory secretion that was purulent; new-onset rales; and a routine blood test that indicated an abnormal inflammation index, with a white blood cell count > $10.0 \times 10^9$/L or < $4.0 \times 10^9$/L and an increased proportion of neutrophils.

### Detection of CRP levels

Each patient had serum CRP levels measured within 12 hours of admission to the PICU (enzyme-linked immunosorbent assay; Roche). The test procedure was in strict accordance with the manufacturer's instructions. If the CRP level was < 8 mg/L, this was below the level of detection and no value was assigned.

### Calculation of the PRISM III score

Pollack et al presented the PRISM III scoring system on the basis of the Physiologic Stability Index. The PRISM III has 17 physiological variables, including systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, oxygenation index ($PaO_2/FiO_2$), partial pressure of carbon dioxide, pupillary reactions, prothrombin time/partial thromboplastin time, and serum potassium, sodium, and glucose levels.[5] In this study, two researchers independently analyzed and recorded the worst values of relevant physiological variables that were obtained within 12 hours of admission to the PICU. These values were used to calculate the PRISM III score. If the PRISM III scores of one patient were different as computed by two researchers, a third researcher was introduced to determine the appropriate score.

### Statistical analysis

Statistical analysis of collected data was performed using the statistical software SPSS 18.0 (Chicago, American). Measurement data are expressed as mean ± standard deviation ($\bar{x} \pm s$) and the $t$ test was used for comparison of inter-group data. Count data are expressed as a percentage or composition ratio (%), and the $\chi^2$ test was used for inter-

group comparison. Correlations were assessed using the Pearson correlation coefficient and a joint function was obtained from the linear regression model. SPSS software was used to draw the receiver operating characteristic (ROC) curve and the area under the curve was compared. $P < 0.05$ was considered to be statistically significant.

## RESULTS

### General data

Among the 496 pediatric patients, 481 who received mechanical ventilation for 48 hours or longer were included in our study. The patients were separated into two groups of those with VAP (VAP group) and those without VAP (non-VAP group). The VAP group comprised 47 patients, of whom 38 (80.85%) recovered and 9 (19.15%) died. The non-VAP group comprised 434 patients, of whom 380 (87.56%) recovered and 54 (12.44%) died.

The clinical data of the two groups were collected within 12 hours of admission to the PICU and the PRISM III score was calculated. There were no significant differences in gender, age, weight, CPB time, aortic cross-clamping time, operation duration, duration of urethral catheter placement, and blood loss in surgery between the two groups (Table 1).

### Inter-group differences in CRP levels and PRISM III scores

Patients were divided into two groups by CRP levels as follows: CRP levels < 8 mg/L and CRP levels ≥ 8 mg/L Patients were also divided into two groups by the PRISM III score as follows: moderately ill with a score < 10 and critically ill with a score ≥ 10.[7] We found significant differences in the serum CRP level and the PRISM III score between the VAP and non-VAP groups ($P < 0.05$) (Table 2).

**TABLE 2** Inter-group differences in CRP levels and PRISM III scores

| Variables | VAP group ($n$ = 47), $n$ | Non-VAP group ($n$ = 434), $n$ | $\chi^2$ | $P$ |
|---|---|---|---|---|
| CRP (mg/L) | | | | |
| < 8 | 22 | 385 | 42.520 | < 0.001 |
| ≥ 8 | 25 | 49 | | |
| PRISM III | | | | |
| Moderately ill | 22 | 344 | 16.137 | < 0.001 |
| Critically ill | 25 | 90 | | |

CRP, C-reactive protein; PRISM III, Pediatric Risk of Mortality III

### Comparison the correlation of CRP levels, the PRISM III score, and CRP + PRISM III score

The consistency of CRP levels and the PRISM III score was poor (both $P > 0.05$). Using an SPSS linear regression model, we obtained the function conversion mode of CRP + (−0.172/−0.050) × PRISM III (termed CRP + PRISM III), and we used it to convert and consolidate the PRISM III score and serum CRP levels. Notably, CRP + PRISM III showed better consistency than did CRP levels or the PRISM III alone (both $P < 0.05$) (Table 3).

### Predictive value of CRP levels, the PRISM III score, and CRP+PRISM III for use of VAP

On the basis of the gold standard for diagnosis of VAP, the ROC curves showed that the area under the curve of CRP serum levels was 0.684 and that of the PRISM III score was 0.677. The optimal point for CRP levels and the PRISM III score was 9.500 mg/L and 9.500, respectively. Diagnostic accuracy was higher when serum CRP levels were > 9.500 mg/L or the PRISM III score was > 9.500. Additionally, when the value of CRP + PRISM III was greater than 45.460, it had better specificity and sensitivity (Table 4 and Figure 1).

**TABLE 1** Clinical data of pediatric patients with congenital heart disease with or without ventilator-associated pneumonia (VAP)

| Clinical data | VAP group ($n$ = 47) | Non-VAP group ($n$ = 434) | $t$ | $P$ |
|---|---|---|---|---|
| Gender (Male/Female) | 28/19 | 253/181 | 0.029* | 0.866 |
| Age (d) | 253.89 ± 450.90 | 305.11 ± 495.88 | 0.678 | 0.666 |
| Body weight at admission (kg) | 5.77 ± 2.40 | 6.90 ± 3.69 | 2.058 | 0.092 |
| Birth weight (kg) | 2.95 ± 0.55 | 3.53 ± 9.56 | 0.418 | 0.673 |
| CPB time (min) | 117.62 ± 54.14 | 112.44 ± 54.85 | 0.615 | 0.965 |
| Aortic cross-clamping time (min) | 58.68 ± 35.99 | 57.29 ± 31.84 | 0.281 | 0.099 |
| Operation duration (min) | 213.14 ± 75.11 | 199.03 ± 71.70 | 1.276 | 0.675 |
| Urethral catheter (days) | 5.04 ± 3.88 | 3.97 ± 2.51 | 2.620 | 0.056 |
| Blood loss in surgery (mL) | 27.26 ± 34.35 | 25.87 ± 32.94 | 0.272 | 0.489 |

Data are presented as $n$ or mean ± standard deviation. *$\chi^2$ value. CPB, cardiopulmonary bypass.

**TABLE 3** Comparison the correlation of CRP levels, the PRISM III score, and CRP + PRISM III ($n = 481$)

| Variables | Statistics | CRP | PRISM III | CRP + PRISM III |
|---|---|---|---|---|
| CRP | Pearson correlation | 1 | 0.063 | 0.620 |
| | *P* | NA | 0.170 | < 0.001 |
| PRISM III | Pearson correlation | 0.063 | 1 | 0.822 |
| | *P* | 0.170 | NA | < 0.001 |
| CRP + PRISM III | Pearson correlation | 0.620 | 0.822 | 1 |
| | *P* | < 0.001 | < 0.001 | NA |

CRP, C-reactive protein; PRISM III, Pediatric Risk of Mortality III; NA, not applicable.

**TABLE 4** Optimal operating point (OOP) for serum CRP levels, the PRISM III score, and CRP + PRISM III

| Variables | OOP | Specificity | Sensitivity | +LR | −LR | Youden index |
|---|---|---|---|---|---|---|
| CRP | 9.500 | 0.010 | 0.468 | 5.200 | 53.200 | 0.378 |
| PRISM III | 9.500 | 0.705 | 0.574 | 1.946 | 0.604 | 0.279 |
| CRP+PRISM III | 45.460 | 0.857 | 0.532 | 3.720 | 0.546 | 0.389 |

CRP, C-reactive protein; PRISM III, Pediatric Risk of Mortality III; −LR, negative likelihood ratio; +LR, positive likelihood ratio.

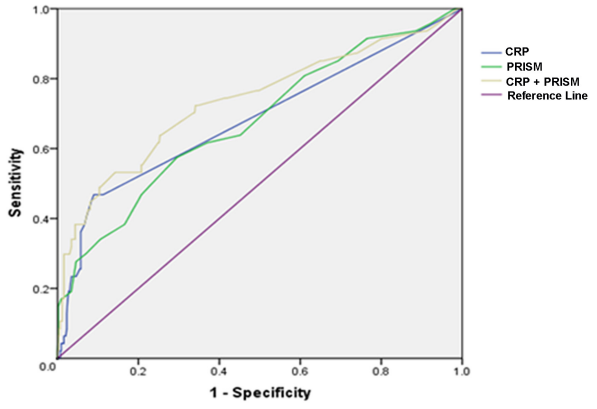


**FIGURE 1** Receiver operating characteristic (ROC) curves of C-reactive protein (CRP) levels, the Pediatric Risk of Mortality III (PRISM III) score, and CRP + PRISM III.

## DISCUSSION

CHD is one of the most important causes of infant and child death. In recent years, there has been continuous improvement in diagnosis and treatment of CHD and widespread application of mechanical ventilation. Therefore, early surgical treatment of CHD has become an inevitable trend in clinical practice, and has greatly improved the survival rate of children with CHD. However, abnormal hemodynamics in children with CHD can easily affect their respiratory function, leading to pulmonary infection. With some other unfavorable conditions, such as malnutrition and low immunity, as well as tracheal intubation, establishment of CPB, and use of broad-spectrum antibiotics, the incidence of postoperative VAP has significantly increased in children with CHD.[6]

VAP is one of the most common nosocomial infections in patients in the PICU who have received mechanical ventilation for 48 hours or longer. Previous studies have shown that the incidence of VAP in the PICU ranges from 3%–13.3%.[7-10] According to reports by Melsen et al, the mortality rate of children caused by VAP is 13%.[11] The mortality rate of patients with VAP and high risk factors, such as those after CHD surgery, can be up to 49.2%.[12,13]

In clinical work, CRP is often used as a marker of inflammation to indicate the severity of infection. Serum CRP levels of healthy people are low, but CRP levels are significantly elevated in patients with autoimmune disease, tissue necrosis, and infectious disease.[14,15] When the immune response subsides, serum CRP levels rapidly drop. In congenial heart surgery, long periods of CPB and aortic cross-clamping may affect the immune response, leading to elevated levels of inflammatory markers.[16] Therefore, whether CRP can be used to predict the incidence of VAP in the early stage is controversial, and the conclusions from relevant clinical studies are also inconsistent. Póvoa et al[17] believe that CRP can be an indicator for early diagnosis of VAP and for predicting a poor prognosis. Studies have shown that a significant increase in CRP levels is mainly associated with postoperative complications, including low cardiac output syndrome, myocardial infarction during surgery, pulmonary dysfunction, renal failure, and infection. Daily monitoring of CRP levels can help predict the risk of VAP. However, Hillas et al[18] found almost the opposite result, with the finding that CRP levels did not help predict the incidence of VAP and development of disease. Similarly, Tanriverdi et al observed no significant difference in CRP levels between survivors and non-survivors with VAP.[19]

In the present study, we measured serum CRP levels and performed PRISM III scoring in children with or without VAP after cardiac surgery. We found that the CRP value at the optimal point for predicting the incidence of

VAP was > 9.500 mg/L, but its sensitivity (46.8%) and specificity (10%) were low. The PRISM III score at the optimal point for predicting the incidence of VAP was > 9.500, and its sensitivity was average (57.4%), but the specificity was relatively high (70.5%). However, the combined CRP + PRISM III was highly specific (85.7%) and sensitive (53.2%) for predicting the incidence of VAP. Additionally, the mean CRP level and PRISM III score were significantly higher in the VAP group than in the non-VAP group. However, correlation analysis showed that the PRISM III score did not increase correspondingly with an increasing CRP level, while CRP + PRISM III and CRP or PRISM III had better consistency. ROC analysis showed that when CRP + PRISM III > 45.460 was used as the predicted value of VAP, the area under the ROC curve was 0.736, the sensitivity was 53.20%, and the specificity was 85.70%, which was more accurate than each one alone.

Our results of the current retrospective study suggest that the sensitivity and specificity of serum CRP levels are poor and not suitable as a predictor of VAP. The PRISM III score alone is also not suitable for predicting the incidence of VAP because of its low sensitivity. Although using CRP + PRISM III to predict the incidence of VAP after congenial heart surgery is more accurate than using either of these indicators alone, its predictive value is still limited. Therefore, whether CRP + PRISM III can be used for predicting VAP requires further study. In this study, a relatively small sample size may have affected the accuracy of the diagnosis. The next step is to expand the sample size and use daily monitoring of serum CRP levels and the PRISM III score to further assess the clinical utility in predicting VAP. Additionally, multi-center clinical research on this issue should be performed in the future. The level of sensitivity and specificity found in our study was not satisfactory. Further prospective, large-sample studies need to be performed to obtain more effective prediction results.

## CONFLICT OF INTEREST

The authors have no conflicts of interest relevant to this article.

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