An Analysis of the Risk Factors for the Failure of Respiratory Support With High-flow Nasal Cannula Oxygen Therapy in Children with Acute Respiratory Dysfunction: a case-control study

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Abstract

Objective:High-flow nasal cannula oxygen therapy (HFNC) is a new type of non-invasive respiratory support technique that widely used in pediatric intensive care units (PICUs);however,improper use of HFNC is likely to bring adverse outcomes to critically ill children.Our objective of this study was to identify the risk factors for the failure of HFNC.Study design: Divided the patients into different categories: HFNC success group, a 48h failure group, a 24h failure group, and a 2h failure group.The clinical indexes and the change trend in HFNC before and after treatment were dynamically observed in 67 pediatric patients. Risk factors for HFNC failure were determined using multivariate logistic regression analysis.Results:PRISM III score>4 points and PaCO2>43 mmHg were risk factors for 48h failure (OR were 4.064, 4.516, P<0.05); PaCO2>43 mmHg was risk factors for 24 h failure (OR was 3.152, P<0.05); PRISM III score>6.5 points and PaCO2/PaO2 ratio>0.67 were risk factors for 2 h failure (OR were 27.977, 64.366, P<0.05) and the risk of HFNC failure increased more than 5 times when the PaO2/FiO2 ratio decreased by>28% after 2 h of HFNC treatment, and the invasive mechanical ventilation time was statistically longer in the patients that upgraded from HFNC to invasive respiratory support than that of patients who received invasive respiratory support directly(P<0.05).Conclusions:The PRISM III score, PaCO2 and PaCO2/PaO2 ratio were risk factors for HFNC failure.Totally the shorter the failure time, the higher the values of the risk factors were, and the higher the failure risk of HFNC was. The change in the PaO2/FiO2 ratio before and after HFNC is a warning indicator for early HFNC failure. And early HFNC failure might lead to prolonged invasive mechanical ventilation.

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Respiratory Dysfunction: a case-control study

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Abstract

Objective:

Different causes of acute respiratory insufficiency threaten the lives of pediatric patients, while High-flow nasal cannula oxygen therapy (HFNC) is a new type of non-invasive respiratory support technique that widely used in pediatric intensive care units (PICUs);however,improper use of HFNC is likely to bring adverse outcomes to critically ill children. Our objective of this study was to identify the risk factors for the failure of HFNC, which can guide clinicians to use HFNC correctly.

Study design:

Divided the patients into different categories: HFNC success group (237 patients), a 48 h failure group (112 patients), a 24 h failure group (84 patients), and a 2 h failure group (24 patients). The clinical indexes and

the change trend in HFNC before and after treatment were dynamically observed in 67 pediatric patients. Risk factors for HFNC failure were determined using multivariate logistic regression analysis.

Results:

PRISM III score >4 points and $PaCO_2$>43 mmHg were risk factors for 48 h failure (OR were 4.064, 4.516, P <0.05); $PaCO_2$ >43 mmHg was risk factors for 24 h failure (OR was 3.152,P <0.05); PRISM III score >6.5 points and $PaCO_2/PaO_2$ ratio >0.67 were risk factors for 2 h failure (OR were 27.977, 64.366,P <0.05) and the risk of HFNC failure increased more than 5 times when the PaO_2/FiO_2 ratio decreased by >28% after 2 h of HFNC treatment, and the invasive mechanical ventilation time was statistically longer in the patients that upgraded from HFNC to invasive respiratory support than that of patients who received invasive respiratory support directly(P <0.05).

Conclusions:

The PRISM III score, $PaCO_2$ and $PaCO_2/PaO_2$ ratio were risk factors for HFNC failure. Totally the shorter the failure time, the higher the values of the risk factors were, and the higher the failure risk of HFNC was. The change in the PaO_2/FiO_2 ratio before and after HFNC is a warning indicator for early HFNC failure. And early HFNC failure might lead to prolonged invasive mechanical ventilation.

Keywords : Acute respiratory insufficiency, high-flow nasal cannula oxygen therapy (HFNC), risk factors, pediatric patients, failure, non-invasive respiratory support.

Introduction

Different causes of acute respiratory insufficiency threaten the lives of pediatric patients; therefore, respiratory support via oxygen therapy has been widely used in pediatric intensive care units (PICUs).Many studies have shown that the complications of invasive respiratory support,such as ventilator-induced lung injury (VILI), might increase the fatality rate of pediatric patients[1].In the past few years, non-invasive respiratory support has become an important means of ventilation support in the early stages of emergencies involving respiratory insufficiency diseases.High-flow nasal cannula oxygen therapy (HFNC) is a new type of non-invasive respiratory support technique that is not only easy to manipulate, well tolerated, and has a low risk of nasal mucosa and septum injury but also avoids invasive ventilation complications such as VILI.HFNC has been widely used in PICUs.Some surveys showed that 77% of hospitals in the United States, and 63% of medical units in Australia and New Zealand use HFNC[2].Studies have found that HFNC can reduce the use of endotracheal intubation for invasive mechanical ventilation[3].Despite the advantages of HFNC in patients with respiratory dysfunction, its inappropriate use will bring adverse consequences to patients. One study in adult patients with respiratory failure stated that the extended use of HFNC before intubation may be deleterious[4].Similarly, a retrospective study by Taha DK et al in 2016 found that if infants with very low birth weight received HFNC, respiratory support failure could increase death or the risk of bronchial pulmonary dysplasia (BPD), increase the incidence of respiratory system disorders, and extend the length of hospital stay[5]. However, the data regarding on the risk factors for HFNC failure in children is still scarce and at present, there is no unified guidance or standard for the selection of respiratory support modes for critically ill children, we therefore hypothesized that improper use of HFNC is likely to cause adverse outcome to critically ill children. In this study, we analyzed clinical data from pediatric patients who underwent HFNC treatment by comparing various clinical indexes from the HFNC success group to those from the 48 h failure group, 24 h failure group and 2 h failure group and the change trend of clinical indexes before and after treatment to identify risk factors for HFNC failure and sum up our experience for improving use of HFNC.

Materials and Method

Study Object

We prospectively analyzed the clinical data of 377 pediatric patients with acute respiratory insufficiency who received respiratory support synchronously directly after admission in the PICU of the West China Second Universally Hospital of Sichuan University from March 2017 to February 2019. The study protocol

was reviewed by the medical ethics committee of the participating hospitals(No. 026)and written informed consent was obtained from all parents/guardians.

A total of 237 patients who did not need upgrade respiratory support and successfully weaned from HFNC were classified as the HFNC success group. The remaining 140 patients need upgrade respiratory support during hospitalization. According to the time to upgrade respiratory support of these 140 patients (see Figure 1), 80% of these patients had upgraded respiratory support within 48 h, 60% had it within 24 h, and 17% had it within 2 h. Because of the complicated circumstances influencing the failure of HFNC after 48 h, it is hard to confirm whether failure was caused by inappropriate choice to initial respiratory support, and this study is aimed to explore the risk factors for HFNC as the initial treatment; hence, the failure cases after 48 h were not included in this study. The earlier HFNC failed, the less possibility there was of failure caused by disease progression; therefore, we divided the 112 patients that used HFNC and required to upgrade respiratory support within 48 h into a 48 h failure group (112 patients), a 24 h failure group (84 patients), and a 2 h failure group (24 patients) according to the failure time and performed further analyses. We also dynamically observed clinical indicators before and after 2 h of HFNC in 67 patients included in the study from January to February 2019 to distinguish the risk factors for failure to HFNC. Because new residents always change their shifts into PICU in the 1^{st} half of a month, 349 patients were still divided into the 1^{st} half of a month group (174 patients) and the 2^{nd} half of a month group (175 patients) according to their date of hospitalization, which HFNC failure rate were compared in order to identify whether the failure was caused by the inexperience of residents. 20 patients among the 112 patients in 48 h failure group were upgraded to non-invasive bilevel positive airway pressure (BIPAP); after that, their condition was alleviated, and they successfully weaned from non-invasive respiratory support. The remaining 92 patients were upgraded to invasive respiratory support and classified into the group that changed from HFNC to invasive respiratory support. Then we compared them with 129 patients synchronously admitted to the PICU and directly received invasive respiratory support in terms of invasive mechanical ventilation time, PICU stay time, hospitalization expenses and hospital mortality to explore the consequences of HFNC failure (see Figure 2).

The clinical information and laboratory data of the patients enrolled in this study were reviewed by using a standardized table to collect in medical charts. Blood samples were collected from 349 patients upon admission to the PICU before HFNC treatment for laboratory tests, including arterial blood gases, complete blood count, C-reactive protein (CRP), procalcitonin (PCT), serum electrolytes, random blood glucose, liver function tests, kidney function tests, Coagulation function test. Of those, 67 were implemented blood sample for arterial blood gases after 2 h initial treatment of HFNC.

Inclusion Criteria[6-8]

The definition of acute respiratory insufficiency was as follows: lack of consciousness or restlessness, cough, fatigue, increased heart rate, polypnea (infants¡2 months, respiratory rate[?]60 times/min; 2-12 months, respiratory rate[?]50 times/min; 1-5 years, respiratory rate[?]40 times/min;[?]5 years, respiratory rate[?]30 times/min), mouth cyanosis, positive for the three concave signs during inspiration or auxiliary respiratory muscles participating in respiratory movement, accompanied by blood gas analysis without oxygen inhalation PaO_2¡8.0 kPa (60 mmHg) and/or $PaCO_2$¿6.67 kPa (50 mmHg), or the PaO_2/FiO_2 ratio[?]300 in oxygen inhalation. Those patients with percutaneous oxygen saturation (SpO_2) maintained between 88% and 92% by nasal catheter or mask are also included. All the patients requested all-out rescue efforts,and no one has given up for economic reasons.

1.3 Exclusion Criteria[9,10]Cardiac and respiratory arrest, requiring emergency endotracheal intubation and invasive mechanical ventilation;Weak spontaneous respiration or the PaO_2/FiO_2 ratio¡100mmHg;Upper airway obstruction, facial trauma,deformity or poor upper airway protection, difficulty in removing large amounts of sputum or risk of aspiration;Fidgety or HFNC intolerance;post-surgery pediatric patients;Respiratory support had been used outside the hospital;Voluntary discharge within 24 h after admission or upgraded respiratory support after 48 h of HFNC treatment;incomplete HFNC support parameter record.

1.4 Definition of HFNC Failure

The criteria for HFNC failure were as follows[11]: HFNC failure was defined as in the presence of disturbance of consciousness, dysphoria, dyspnea, blood oxygen saturation that would not remain above 90% or carbon dioxide retention that could not be improved within 2 h, 24 h or 48 h of undergoing HFNC (with an oxygen concentration[?]60%, oxygen flow[?]2 L/kg.min, and a maximum no more than 60 L/min) which required to upgrade the respiratory support mode to BIPAP or invasive respiratory support therapy.

1.5 Statistical Analysis

SPSS 22.0 statistical software was used for the statistical analysis. Measurement data that had a normal distribution were expressed as the mean±standard deviation (X±s), and two independent sample t tests were used for comparisons between groups. Measurement data that did not have a normal distribution were expressed as the median (four-digit interval) [P_{50} (P_{25}, P_{75})], and comparisons between groups were conducted with Mann-Whitney U tests. Enumeration data were expressed as percentages (%). Chi-square tests, Pearson chi-square tests or Fisher's exact probabilistic tests were used for intergroup comparisons.Significant indexes were analysed by multivariate logistic regression analysis to determine the risk factors, and P <0.05 was considered statistically significant.

Results

2.1 General Condition

The initial parameters for the HFNC success group included the following: fraction of inspired oxygen (FiO_2) 30-100%; and flow 2-3 L/kg.min. The initial parameters for the HFNC failure groups were as follows: fraction of inspired oxygen (FiO_2) 40-100%; and flow 2-3 L/kg.min. The inhaled gas temperature of each group was 37°C, and the oxygen was inhaled for 24 h without interruption.The parameters were adjusted according to the blood gas analysis results, and the arterial partial oxygen pressure (PaO_2) was maintained at 60-80 mmHg (8.0-10.67 kPa), the arterial partial carbon dioxide pressure ($PaCO_2$) was maintained at 40-50 mmHg (5.33-6.67kPa), and the percutaneous oxygen saturation (SpO_2) was maintained above 90%. When the target SpO_2 was maintained and the condition of the patients improved, FiO_2 was gradually lowered to 21-25%, HFNC was withdrawn on the condition that was stable for 4-6 h.

2.2 Comparisons between the HFNC success group and the HFNC failure groups to analyze the risk factors for HFNC failure

2.2.1 HFNC 48 h failure risk factor analysis

(1)Comparisons of General Clinical Data

349 patients with acute respiratory insufficiency suffered from severe pneumonia 155 cases(44.4%), Sepsis 59 cases(16.9%), Shock 34 cases(9.7%), Multiple organ dysfunction syndrome 31 cases(8.9%), Intracranial hypertension syndrome 38 cases(10.9%), Bronchopulmonary dysplasia(BPD) with pulmonary infection 26 cases(7.4%), Acute respiratory distress syndrome 3 cases(0.9%), or Chemotherapy-induced myelosuppression with infection 2 cases(0.6%) and Pneumorrhagia 1 case(0.3%), and the distributions of disease types were no significant differences between the HFNC success group and the 48 h failure group(P >0.05). There also were no significant differences in age, sex or weight between the two groups (P >0.05), as shown in Table 1.

(2) Common clinical indexes and blood gas analysis affecting the respiratory support mode

The clinical indexes and blood gas analysis results of the two groups of patients are shown in Table 2. The GCS score, pH value and PaO_2/FiO_2 ratio of the HFNC 48 h failure group were lower than those of the success group, and the PRISM III score, PCT, $PaCO_2$ and $PaCO_2/PaO_2$ ratio were higher than those of the success group. The differences between the two groups were statistically significant (P <0.05). However, there was no significant difference in SpO_2, CRP, LAC or PaO_2 between the two groups (P >0.05).

(3) Multi-factor Logistic Analysis Results (shown in additional file 1)

The PRISM III score (OR=4.064, 95% CI=1.989 8.302) and $PaCO_2$ (OR=4.516, 95% CI=2.272 8.976) were risk factors for 48 h failure.

2.2.2 HFNC 24 h failure and 2 h failure risk factor analysis (shown in additional file 2)

The analysis results for the HFNC 24 h failure group were almost identical to those for the preceding 48 h, except that the CRP level in the 24 h failure group was also found to be higher than that in the HFNC success group (P <0.05). After multivariate logistic regression analysis, PCT (OR=2.794, 95% CI=1.390˜5.614)and $PaCO_2$ (OR=3.152, 95% CI=1.480˜6.713) were risk factors for HFNC 24 h failure.

The analysis results for the HFNC 2 h failure group were roughly the same as those for the preceding 48 h and 24 h. The PRISM III score, CRP and $PaCO_2/PaO_2$ ratio in the 2 h failure group were all higher than those in the success group (P <0.05). The PRISM III score (OR=27.977, 95% CI=3.693 211.961) and $PaCO_2/PaO_2$ ratio (OR=64.366, 95% CI=7.320 566.008) were risk factors for HFNC 2 h failure.

2.3 The Prediction Function of the Change Trend in Clinical Indexes before and after HFNC Treatment for Early Failure of HFNC

2.3.1 Zhang's research suggests that[12] evaluation of the effectiveness of non-invasive respiratory support therapy 1-2 h after initial treatment plays an important role in subsequent treatment decisions. Therefore, this study dynamically observed the before-and-after data of 67 patients who suffered acute respiratory insufficiency and received HFNC, among which 55 therapies were successful and 12 failed. There were no significant difference in age, sex or weight between the two groups (P >0.05) (shown in additional file 3). The PEWS scores of the success group before and after HFNC treatment were lower than those of the failed groups, while the oxygen saturation index and PaO_2/FiO_2 ratio were higher than those of the failed groups. PaO_2 after 2 h of HFNC treatment in the success group was higher than that in the failed groups, but the $PaCO_2/PaO_2$ ratio in the success group was lower than that in the failed groups. For these data, there were statistically significant differences between the two groups (P <0.05). There was no significant difference in heart rate, respiration, GCS score or $PaCO_2$ between the two groups before and after HFNC treatment (P >0.05). The range of decrease in PEWS scores for the success group was greater than that for the failed groups, while the changes in pH value, oxygen saturation index and PaO_2/FiO_2 ratio before and after HFNC treatment showed an upward trend in the success group and a downward trend in the failed group. The comparison had statistically significant differences (P <0.05) (see table 3).

2.3.2 Multi-factor Logistic Analysis Results (shown in additional file 4)

The $^{P}aO_2/FiO_2 ratio\%(OR = 5.875, 95\%CI = 1.51222.830) was a warning indicator for early HFNC failure.$

2.4 HFNC Failure Analysis with Respect to Residents (shown in additional file 5)

The rotation of residents into the PICU is usually carried out in the 1st half of the month, we compared HFNC failure rate between the 1st half and the 2ndhalf of each month in order to identify whether the failure was caused by the inexperience of residents, but there was no significant difference(P >0.05).

2.5 Analysis of Failed Outcomes for HFNC (shown in additional file 5)

Although there were no significant differences in the PICU stay time, hospitalization cost and in-hospital mortality, the patients that upgraded from HFNC to invasive respiratory support has a longer invasive mechanical ventilation time than that of patients who received invasive respiratory support directly (P <0.05).

Discussion

Respiratory support technology is the main means of treating children with critical and severe conditions. Because invasive respiratory support has been noticed to have many disadvantages, such as ventilator-induced lung injury (VILI), in recent years, more attention has been paid to non-invasive respiratory support, which could alleviate the pain of endotracheal intubation and reduce complications. However, studies have confirmed that the failure of non-invasive respiratory support is related to an increase in mortality[13]. Therefore,

if the focus is only on non-invasive respiratory support, invasive respiratory support via endotracheal intubation may be delayed, accompanied with poor prognosis for patients. As an emerging form of non-invasive respiratory support, high-flow nasal cannula oxygen therapy (HFNC) is even more comfortable than traditional non-invasive mechanical ventilation, with a lower incidence of complications such as head shaping, nasal injury, pneumothorax, and abdominal distension[14,15], to which more and more clinicians attached importance.Several clinical studies have shown that HFNC has achieved good clinical effects in the treatment of respiratory diseases, such as respiratory failure, respiratory distress syndrome (RDS), sleep paroxysmal apnea symptoms, and reduced the rate of endotracheal intubation in children [16-18].The study by Wing et al[19] also found that early HFNC used in children with acute respiratory insufficiency would reduce their possibility of endotracheal intubation and invasive mechanical ventilation. However, there is no uniform standard for HFNC indications and contraindications in pediatric applications, and few studies have focused on its relevant risks. Furthermore, the study by Ischaki and Gaunt et al[2,20] found that if the patient's condition did not improve within 48 h after HFNC, the respiratory support mode should be upgraded; otherwise, it led to further deterioration in respiratory function and increased mortality. Therefore, we suspected that the failure to HFNC in critically ill children would also have adverse consequences.

Considering that the earlier the failure time was, the lower the possibility was that failure was caused by disease progression, we compared the HFNC success group with the 48 h failure group, 24 h failure group and 2 h failure group, and the results were almost consistent. Among the 349 pediatric patients who were included in this study, the GCS score, PRISM III score, pH value, $PaCO_2/PaO_2$ ratio and PaO_2/FiO_2 ratio were significantly different between the HFNC success and failure groups (P <0.05). By multivariate logistic regression analysis, PRISM III score and $PaCO_2/PaO_2$ ratio were considered as risk factors for HFNC failure.

C-reactive protein (CRP) is an acute phase reactant synthesized in response to inflammation and in closely correlated with severity of infection[21], while Procalcitonin (PCT), the prehormone of calcitonin and is released in response to proinflammatory stimuli, has been widely proved to be an important biomarker in severe infection and more frequently used as an indicator of sepsis than CRP[22]. Normally when PCT and CRP were significantly increased, inflammation or organ damage was often more severe in pediatric patients. In this study, we have found that neither CRP nor the PCT, which suggested inflammatory reactions exist, were higher in each failure group compared with success group, but their differences between the 24 h failure group and the success group were statistically significant(P <0.05).When PCT>0.67 ng/ml, the risk of HFNC failure within 24 h increased by more than 2 times.Some studies observed that PCT concentrations were associated well with organ dysfunction, high PCT levels may reflect multiple organ dysfunction according to uncontrollable inflammation[23-25].Therefore, PCT and CRP are supposed to be a risk factor for HFNC failure. Further study is needed to expand the sample size and conduct hierarchical analysis for the inconsistent results. At same time when PCT or CRP significantly increase, HFNC as a support treatment should be closely monitored.

The pediatric risk of mortality (PRISM III) is currently the most widely used as pediatric critical assessment tool worldwide, which was positively correlated with organ failure[26].The study of Pollack et al reported that the increase in PRISM III score is positively significantly associated with increase in mortality[27]. In addition, some study observed that the older age, higher PRISM III score and faster respiratory rates were predictors for HFNC failure[28,29]. Similarly, our study also found that the PRISM III score was higher in each failure group than in the success group (P <0.05). Multivariate logistic regression showed that when the PRISM III score was¿4 points, the risk of HFNC failure within 48 h was over 4 times higher, while a PRISM III score¿6.5 points was associated with an over 27 times higher risk of HFNC failure within 2 h. The higher the score, the higher the risk of failure was. Therefore, for critically ill children, especially those with PRISM III scores¿6.5 points, HFNC should be closely monitored. But PRISM III score involves 14 physiological parameters and 23 parameter ranges[26], such as blood gas, blood sugar, electrolytes, liver and kidney function, and coagulation function, so it would take longer time to get PRISM III score than some warning scores for example PEWS score, which limits the value of PRISM III score to early predict the failure to HFNC and need more research to find more valuable scoring system.

There is no established guideline for the use of HFNC in hypercapnic respiratory failure. Physiologically, HFNC can provide not only a constant oxygen concentration but also a certain positive end-expiratory pressure in the airway with high-flow gas, thus improving oxygenation, in the meantime, HFNC can reduces the anatomical dead space and improves carbon dioxide wash-out[30], suggested that HFNC might be beneficial to not only hypoxemic but also acute hypercapnic respiratory failure as well, that have been confirmed by several studies[31-33]. In contrast, the study by Benjamin Sztrymf et al found that moderate $PaCO_2$ heightened after HFNC treatment[34], illustrating that HFNC application in hypercapnia is controversial.PaO_2 is an index of respiratory function, while $PaCO_2$ is a better index to pulmonary ventilation function[35]. Therefore, the $PaCO_2/PaO_2$ ratio could indicate pulmonary ventilation and diffusion function. In this study, it was found that the difference of $PaCO_2$ between the 24 h or 48 h failure group and success group was statistically significant (P <0.05), while $PaCO_2/PaO_2$ ratio was statistically different between all the failure groups and the success group (P <0.05). Moreover, the higher $PaCO_2$and the $PaCO_2/PaO_2$ ratio, the shorter failure time is. Multivariate logistic regression showed that when $PaCO_2$¿43 mmHg, the risk of HFNC failure within 24 h and 48 h was over 3 times and 4 times higher, respectively. When the ratio of $PaCO_2/PaO_2$ was¿0.67, the risk of HFNC failure within 2 h was over 64 times higher. Therefore, for pediatric patients with abnormal ventilation, HFNC should be carefully selected. More research on how to combine $PaCO_2$ and the $PaCO_2/PaO_2$ ratio to judge the failure risk of HFNC is needed.

It is noteworthy that HFNC might postpone invasive ventilation which should have been implemented, which would be harmful to peadiatric patients with respiratory instability; however, there is no unified standard or consensus on when giving up HFNC and upgrading respiratory support. Expert guidelines for clinical practice with non-invasive positive pressure ventilation(NIPPV)[12] indicated that evaluation about the effectiveness of non-invasive respiratory support therapy after 2 h initial treatment played an important role in subsequent treatment decisions. Adult studies suggest patients with effective response to the treatment be generally observed an improvement in oxygenation after the 1-2 h of HFNC, and low arterial oxygen saturation(SaO_2) and high respiratory rate should be considered as predictors of HFNC failure[34,36,37].In our study, we found that the decline in PEWS scores for the success group was significantly greater than that for the failed groups. Furthermore, the changes in pH value,oxygen saturation index and PaO_2/FiO_2 ratio before and after HFNC showed an upward trend in the success group and a downward trend in the failed group (P <0.05).The study by Lu Ye et al[38] found that HFNC seems effective for treating children with mild to moderate respiratory failure and the PaO_2/FiO_2 ratio is the optimal index to evaluate the success of HFNC application. Several studies showed HFNC treatment effective usually accompanying an increase of PaO_2/FiO_2 ratio alongside with relief of respiratory failure after 1 h of treatment[32,33].We found when the PaO_2/FiO_2 ratio decreased by¿28% after 2 h of HFNC treatment, the risk of early HFNC failure increased by more than 5 times, that is almost similar to these studies.Therefore, the change of the PaO_2/FiO_2 ratio was a warning indicator for early HFNC failure, if which was downward after 2 h of HFNC treatment, there was a high possibility of failure to HFNC and close monitoring required.

As there are no unified indication and contraindication for pediatricians to choose HFNC, the decision of respiratory support modes is dependent on the experiences of the physician. To determine whether increased HFNC failure is linked to improper choice by inexperienced physicians,we compared the HFNC failure rates between the 1st half and the 2nd half of each month and found that there was no significant difference (P >0.05), which means no reason to attributes the failure to inexperienced new residents, suggesting current training and working modes reasonable.

An earlier study on NIPPV reported that, of Intensive Care Unit(ICU) patients with acute respiratory failure, those who underwent invasive mechanical ventilation from the beginning had lower in-hospital mortality than those who just got invasive mechanical ventilation after non-invasive respiratory support failure[39].And Ozyilmaz et al[40] found non-invasive respiratory support failure was strongly associated with poor prognosis. Similarly, in our study,the PICU stay time, hospitalization cost and in-hospital mortality were greater in the group that respiratory support upgraded from HFNC to invasive than the group that was synchronously admitted to the PICU and directly received invasive respiratory support, but not statistically different, while the invasive mechanical ventilation time was statistically longer (P <0.05).So adverse consequences of HFNC

failure should be highly concerned.

Our study has some limitations. First, the sample size might not be large enough to determine the consistency of the predictors for HFNC failure, and studies with larger sample size are needed. Second, some instantaneous evaluating indicators were not taken into account in the initial study design, such as PEWS score; however, the comparison of before and after HFNC treatment found that PEWS score was very valuable, more prospective studies are therefore needed to validate a more valuable evaluating system in judging the failure risk of HFNC.

HFNC is an effective treatment for critically ill children, but some crucial questions remain to be determined, such as the indications of HFNC and the standards for timing the beginning of HFNC, for withdrawing HFNC, and for upgrading respiratory support.Taken together, our results indicate that the PRISM III score and the $PaCO_2/PaO_2$ ratio were risk factors for HFNC failure. When the PRISM III score¿6.5 points and the $PaCO_2/PaO_2$ ratio¿0.67, HFNC as a supportive treatment should be selected carefully. And the change in the PaO_2/FiO_2 ratio before and after HFNC is a warning indicator for early HFNC failure too. Early HFNC failure might lead to prolonged invasive mechanical ventilation. Therefore, in these conditions the choice of HFNC respiratory support should be made cautious.

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Figure 1 Analysis of the HFNC Failure Constituent Ratio

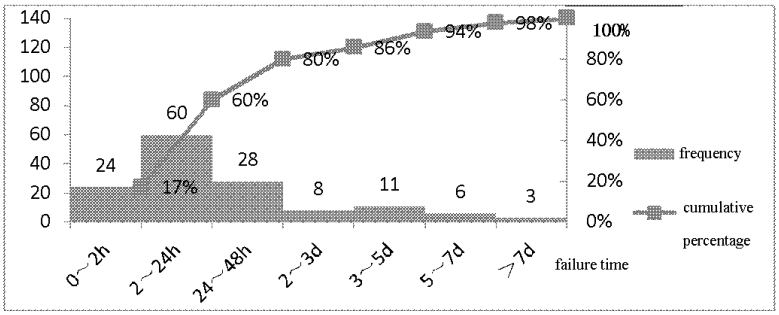

Figure 2 Patient Classification