Clinical outcomes and risk factors in critically ill children with diaphragmatic dysfunction: an prospective observational study

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Abstract

Background: Diaphragmatic dysfunction (DD) has a great negative impact on clinical outcomes, and it is a well-recognized complication in adult patients with critical illness. However, DD is largely unexplored in the critically ill pediatric population. The aim of this study was to identify risk factors associated with DD, and to investigate the effects of DD on clinical outcomes among critically ill children.

Methods: Diaphragmatic function was assessed by diaphragm ultrasound. According to the result of diaphragmatic ultrasound, all enrolled subjects were categorized into the DD group (n=24) and the non-DD group (n=46). Collection of sample characteristics in both groups include age, sex, height, weight, primary diagnosis, complications, laboratory findings, medications, ventilatory time and clinical outcomes.

Results: The incidence of DD in this PICU was 34.3%. The level of CRP at discharge (P=0.003) in the DD group was higher than the non-DD group, and duration of elevated C-reactive protein (CRP) (P<0.001), sedative days (P=0.008) and ventilatory treatment time (P<0.001) in the DD group was significantly longer than the non-DD group. Ventilatory treatment time and duration of elevated CRP were independently risk factors associated with DD. Patients in the DD group had longer PICU length of stay, higher rate of weaning or extubation failure and higher mortality.

Conclusion: DD is associated with poorer clinical outcomes in critically ill children, which include a longer PICU length of stay, higher rate of weaning or extubation failure and a higher mortality. The ventilatory treatment time and duration of elevated CRP are main risk factors of DD in critically ill children.

Background

The diaphragm is the primary respiratory muscle, generating approximately 60 to 80 percent of the inspiratory capacity\[1\]. Diaphragmatic dysfunction (DD) has a great negative impact on respiratory function, and it is a well-recognized complication in adult patients with critical illness, especially among patients with mechanical ventilation (MV)\[2\]. The study performed in adults found that diaphragm thickness decreases rapidly following intubation in nearly 50% of ventilated patients\[3\]. There is a wide variety of factors which can lead to DD in critically ill adult patients, including MV, sepsis, sedative, steroids, neuromuscular blockers, multiorgan dysfunction syndrome and preadmission injury\[2, 4, 5\]. MV is a leading cause of DD, the diaphragm atrophy can be significant in 18–69 hours under complete controlled ventilation\[6\], And MV is widely used in critical illness patients as a conventional treatment technology of PICU, approximately 30% of children in the pediatric intensive care unit (PICU) receive MV support\[7\], and 38% of them have DD\[8\]. Patients with DD are at higher risk for delayed, difficult weaning and extubation failure, together with an increased risk of longer ICU length of stay, poor functional outcomes, and death\[9\]. Mariani et al.\[10\] found that the ICU mortality is higher in patients with DD compared with absence of DD. The study conducted by Lu et al.\[11\] demonstrated that subjects with DD show longer mechanical ventilation durations and ICU stays.
A wide variety of adult studies have found the causes and clinical outcomes of DD in critically ill patients. However, DD is largely unexplored in the critically ill pediatric population. The studies on risk factors of DD and how it impacts clinical outcomes in children are limited\cite{12-14}. As a result, there are few clinical experience in the identification, appropriate intervention and improvement of prognosis of critically ill children.

The aim of this study was to identify risk factors associated with DD, and to investigate the effects of DD on short-term clinical outcomes in children and to test the hypothesis that DD is associated with poor clinical outcomes among critical illness children in the PICU.

**Methods**

**Subjects**

This study was conducted in an academic, 57-bed PICU of First Hospital of Jilin University in China. Study subjects including 70 consecutive patients younger than 18 years old who required invasive MV for more than 24 hours were enrolled between January 2019 and January 2020. The institutional ethics committee of the hospital approved the study protocol (ChiCTR1800020196). The parents or guardians of the eligible children provided written informed consent. An information sheet was provided for the parents or guardians of the participants.

All children met the standard criteria\cite{15} for weaning readiness (improvement in the cause of primary disease, PaO$_2$/FiO$_2$ > 200, positive end-expiratory pressure (PEEP) ≤ 5-10cm H$_2$O, FiO$_2$ ≤ 50%, and hemodynamically stable in the absence of vasopressors) were included in the study. Exclusion criteria include known neuromuscular disease (such as amyotrophic lateral sclerosis, Guillain-Barre, or myasthenia gravis), cervical spinal cord injury, pneumothorax, unwillingness of the parents or guardians to participate in the study.

**Study Design**

Enrolled subjects underwent a diaphragm assessment by using ultrasonography during the spontaneous breathing trial (SBT), which was performed using pressure support trials with a pressure support (8 cm H$_2$O) and 5 cm H$_2$O PEEP using a Drager Evita 4 ventilator for 30 min. Ultrasound measurements were taken at the fifth minute after the beginning SBT. All enrolled subjects were categorized into the DD group and the non-DD group according to the result of diaphragmatic echo. DD was defined as a diaphragmatic thickening fraction (DTF) of < 20% during tidal breathing\cite{16}.

**Diaphragm ultrasound measurement**

The diaphragm ultrasound was performed using a portable ultrasound machine (Mindray, M7 series, China) with a 10MHz linear probe by two experienced sonographers. Only the right hemidiaphragm was measured because the right hemidiaphragm was more feasible and repeatable compared with the left
hemidiaphragm\cite{12}. All subjects were placed in a semi-recumbent position with the head of the bed at a 30-degree angle. The probe was placed between the mid-axillary or antero-axillary line, in the 8th to 11th intercostal space, and positioned in a cranio-caudal direction and perpendicular to the skin to achieve the best view of the right hemidiaphragm\cite{17}. At this position, the diaphragmatic ultrasound image was a hypoechoic structure between two echoic lines (the pleural and the peritoneal membrane)(Fig 1). In the B-mode image, diaphragm thickness (Tdi) was measured from the inner edge of the pleural line to the inner edge of the peritoneal line at both end inspiration and end expiration. The calculation formula of DTF was (Tdi-inspiration – Tdi-expiration) / Tdi-expiration\cite{18}. Tdi and body weight (BW) have significant positive correlations in children\cite{19}. Therefore, Tdi was standardised by BW (DE/BW).

**Patient Characteristics and Clinical Outcomes**

We collected the basic demographic of all subjects, beside, primary diagnosis, medications, inflammatory factor levels at discharge and duration of elevated inflammatory factors were also collected, as the previous study demonstrated that systemic inflammation is associated with muscle atrophy in critically ill adult patients\cite{20}. The clinical outcomes we observed include delay or difficulty in weaning, extubation failure, total length of time on mechanical ventilation, length of PICU stay and mortality.

**Statistical analysis**

For comparisons of demographic, clinical characteristics and outcomes between DD and non-DD patient group, continuous variables were compared with Student t-test or Mann-Whitney U test. Categorical variables were compared with Chi-squared test or Fisher’s exact test. Data are presented as mean ± standard deviation for continuous variables with a normal distribution and as median with interquartile range for variables with a non-normal distribution. Categorical variables were described as n (%). To determine which factors are significantly associated with DD, logistic regression analysis was then performed. All analyses were carried out using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp, Armonk, NY). and a $p$-value less than or equal to 0.05 was considered statistically significant.

**Results**

**Sample characteristics**

One hundred and thirty-three children underwent mechanical ventilation support during the study period. Sixty-three cases were excluded, and seventy patients were included in this study eventually. Eligibles were divided into either the DD group (n=24) or non-DD group (n=46) according to the result of diaphragmatic echo (Fig 2).

All children characteristics were summarized in Table 1. The incidence of DD in this PICU was 34.3% (24/70). Comparison of characteristics between the two groups showed that the level of CRP at discharge (4.50[1.94-19.76] vs 1.81[0.73-5.54], $P$=0.003) in the DD group was higher than the non-DD group, and duration of elevated C-reactive protein (CRP) (18.50[7.25-28.00] vs 4.50[2.00-8.25], $P$<0.001), sedative
days (8.00[5.25-15.00] vs 6.00[4.00-8.00], P=0.008) and ventilatory treatment time (13.00[10.00-18.00] vs 5.50[5.00-7.00], P<0.001) in the DD group were significantly longer than the non-DD group. However, it should be noted that there were no difference in the proportion of patients with sepsis and methylprednisolone treatment time in the two groups, which are important factors associated with DD in adults.

**Risk Factors for the Development of DD**

The results of our multivariable logistic regression analysis are shown in Table 2. The independent risk factors associated with the development of DD included ventilatory treatment time (OR, 1.99; 95%CI, 1.18–3.38) and duration of elevated CRP (OR, 1.12; 95%CI, 1.01–1.24).

**Comparison of clinical outcomes between the DD group and the non-DD group**

It is clearly showd in Table 3. that patients in the DD group had poorer clinical outcomes including a longer PICU length of stay (26.50[15.00-35.50] vs13.00[10.00-18.00], P<0.001 ), a higher rate of weaning failure (37.5% vs 10.87%, P=0.008) or extubation failure (33.33% vs 8.7%, P=0.009) and a higher mortality (20.83% vs 2.17%, P=0.008) compared with the non-DD group.

**Discussion**

To our knowledge, this is the first study to investigate factors associated with the development of DD and clinical outcomes of patients with DD in the critically ill pediatric population. Our findings demonstrated that the incidence rate of DD to be 34.3% in children, we also found that ventilatory treatment time and duration of elevated CRP are associated with the development of DD. This shows that MV is not the only cause of DD, and the development of DD in critically ill children is caused by multiple factors. We also report for the first time that the duration of elevated CRP is associated with DD in critically ill children, which demonstrates that the body's inflammatory response is an important risk factor. In this study, we have also shown that children with DD are associated with poorer outcomes, including a longer PICU length of stay, a higher rate of weaning or extubation failure and a higher mortality.

Our results are similar to studies investigating DD among adult hospitalized patients. We found patients with DD had longer total ventilation time, higher rates of weaning or extubation failure and higher mortality than children without DD[8,21,22]. Limited studies on DD in critically ill children showed that respiratory weakness is independently associated with reintubation and longer ventilation time[23,24]. Our previous study also found that patients with failed weaning have worse diaphragmatic function[25]. This suggests that DD is closely associated with poorer clinical outcomes in both adults and children. The prevalence of diaphragm dysfunction diagnosed with ultrasound was found in 40%-60% of mechanically ventilated adults[10,26,27]. These reports are higher than our result. The main reasons for consideration are as follows: Firstly, the development of auxiliary inspiratory muscles in children are immature, diaphragm playe a greater role in ventilation than adults[28]. Therefore, the baseline function of
Diaphragm in children is higher than that in adults. Secondly, the majority of patients in adult studies are elderly chronic obstructive pulmonary disease (COPD) patients, whose diaphragmatic muscle fibres have a chronic oxidative remodelling process, leading to diaphragm compensatory ability weakness[29]. Thirdly, the average ventilatory treatment time in children with DD is shorter than in adults [360 (168–528) vs 576 (374–850) hrs][8,25]. Furthermore, our findings demonstrated that ventilatory time is the independent risk factor of DD in critically ill children, which is similar to adult studies[2,30]. Another important finding in this study is that duration of elevated CRP to be associated with development of DD. Inflammation is an important contributor to the pathology of diseases implicated in skeletal muscle dysfunction[31], some studies among adults found that systemic inflammation is the most significant risk factor for ICU-AW[20,32]. And inflammation is prevalent after critical illness and is associated with poor physical recovery[33]. However, the role of inflammation in respiratory muscle is largely unexplored, especially in the critically ill pediatric population. Therefore our findings demonstrated that duration of inflammatory response may be a main risk factor of DD. Nevertheless, our findings cannot definitively confirm causality, which can only be demonstrated in the context of a randomized control study (RCT).

This study has several limitations. Firstly, we studied a relatively small population, this might restrain the validity. Secondly, ultrasound diagnostic criteria (DTF < 20%) for DD comes from adult studies. Whether this reference value applies to children requires further study among pediatric population. Thirdly, our study included only CRP to represent inflammatory response of the patients, the reliability of our finding is limited. Therefore, more inflammatory factors such as interleukin 6 (IL-6), interleukin 8 (IL-8), and transforming growth factor (TGF) are needed to reflect the inflammatory response more precisely in further study, so that our findings can be confirmed. Fourthly, due to our small sample size, some important factors in adult research such as sepsis did not produce positive results in our study. This does not demonstrate that sepsis is not associated with DD, instead, we should expand the sample size and conduct the RCT. Finally, we only investigated the clinical outcomes of children with DD during their hospital stay, however, there was a lack of follow-up of the effects of DD on patients after discharge. The study conducted by Dres et al[4], demonstrated that DD is twice as frequent as limb muscle weakness. Limb muscle weakness is significantly associated with poorer physical function after discharge[34–36]. Therefore, it is critical to investigate the impact of DD on long-term prognosis of critically ill children.

**Conclusions**

DD strongly impacts clinical outcomes in critically ill children, which includes a longer PICU length of stay, a higher rate of weaning or extubation failure and a higher mortality. The ventilatory time and duration of elevated CRP are main risk factors of development of DD in critically ill children. It is important to identify DD earlier among critically ill children in order to protect the diaphragmatic functions. Due to the relatively inadequate research performed in children, more studies on DD among pediatric population need to be carried out to better guide clinical and respiratory rehabilitation.

**Abbreviations**
Declarations

Ethics approval and consent to participate

The study was approved by the institutional ethics committee of the hospital, the First Hospital of Jilin University (ChiCTR1800020196). The parents or guardians of the eligible children provided written informed consent. An information sheet was provided for the parents or guardians of all the participants.

Consent for publication

Not applicable.

Availability of data and materials:

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions:

Dr. YX conceived the study design and data collection. Dr. CF Y participated in the study design. Dr. YA performed statistical analyses. Dr. JQ participated in literature search. Dr. FY J reviewed the manuscript. All authors interpreted the data, contributed to the intellectual content, reviewed the manuscript, and approved the final version.

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**Tables**

Due to technical limitations, Tables 1 - 3 are only available for download from the Supplementary Files section.

**Figures**

**Figure 1**

Ultrasound B-mode using a 10 MHz probe in the zone of apposition.
Figure 2
Flow chart of this study.

Supplementary Files
This is a list of supplementary files associated with this preprint. Click to download.
- Table2.docx
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- CONSORTChecklist.doc
- Table3.docx