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Association of diaphragmatic dysfunction with duration of mechanical ventilation in patients in the pediatric intensive care unit: a prospective cohort study

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Abstract

Background Mechanical ventilation (MV) can cause diaphragmatic injury and ventilator induced diaphragmatic dysfunction (VIDD). Diaphragm ultrasonography (DU) is increasingly used to assess diaphragmatic anatomy, function and pathology of patients receiving MV in the pediatric intensive care unit (PICU). We report the poor contractile ability of diaphragm during ventilation of critically ill patients in our PICU and the association to prolonged length of MV and PICU stay.

Methods Patients who received MV within 24 h of admission to the PICU, expected to undergo continuous MV for more than 48 h and succeeded to extubate were included in the study. DU monitoring was performed daily after the initiation of MV until extubation. Diaphragm thickening fraction (DTF) measured by DU was used as an indicator of diaphragmatic contractile activity. Patients with bilateral DTF = 0% during DU assessment were allocated into the severe VIDD group ($n = 26$) and the rest were into non-severe VIDD group ($n = 29$). The association of severe VIDD with individual length of MV, hospitalization and PICU stay were analyzed.

Results With daily DU assessment, severe VIDD occurred on 2.9 ± 1.2 days after the initiation of MV, and lasted for 1.9 ± 1.7 days. Values of DTF of all patients recovered to > 10% before extubation. The severe VIDD group had a significantly longer duration (days) of MV [12.0 (8.0-19.3) vs. 5.0 (3.5–7.5), $p < 0.001$] and PICU stay (days) [30.5 (14.9–44.5) vs. 13.0 (7.0-24.5), $p < 0.001$]. The occurrence of severe VIDD, first day of severe VIDD and length of severe VIDD were significantly positively associated with the duration of MV and PICU stay. The occurrence of severe VIDD on the second and third days after initiation of MV significantly associated to longer PICU stay (days) [43.0 (9.0–70.0) vs. 13.0 (3.0–40.0), $p = 0.009$; 36.0 (17.0-208.0) vs. 13.0 (3.0–40.0), $p = 0.005$, respectively], and the length of MV (days) was

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significantly longer in those with severe VIDD on the third day after initiation of MV [16.5 (7.0–29.0) vs. 5.0 (2.0–22.0), $p = 0.003$].

Conclusions Daily monitoring of diaphragmatic function with bedside ultrasonography after initiation of MV is necessary in critically ill patients in PICU and the influences and risk factors of severe VIDD need to be further studied. (355 words)

Keywords Ventilator induced diaphragmatic dysfunction, Pediatric critical care, Diaphragmatic ultrasound, Diaphragm thickening fraction

Introduction

The diaphragm, as the main respiratory muscle in the human body, contributes to 3/5 to 4/5 of the respiratory effort. The diaphragm is an essential component of the human respiratory pump system. When the diaphragm contracts, the diaphragmatic dome descends, increasing the volume of the thoracic cavity, which generates negative pressure and leads to lung expansion, allowing air to enter the lung tissue and facilitating active inhalation. Decrease in the ability of the diaphragm contraction results in insufficient negative pressure in the thoracic cavity, thereby affecting inhalation function. The range from partial to complete loss of diaphragmatic contraction capability is referred to as diaphragmatic dysfunction (DD) [1]. Mechanical ventilation (MV) is a life-saving respiratory support therapy that is used for 63% of pediatric patients with respiratory failure or cardiopulmonary disease admitted to the pediatric intensive care unit (PICU) [2]. However, many recent studies have shown that in adults, MV can cause diaphragmatic dysfunction (ventilator-induced DD, VIDD), characterized as loss of the diaphragm's capacity to generate force, together with muscle injury and fiber atrophy [3]. The frequency of VIDD in adults was nearly 2/5, and numerous studies have demonstrated that VIDD has adverse effects on prognosis in critically ill adult patients, including prolonged MV and hospital stay, difficulty in weaning from ventilation, increased readmission rates, and mortality [4–6].

The diagnosis of VIDD is based on a combination of dynamic and static imaging techniques [7], including fluoroscopy or chest X-ray examination. Recently diaphragmatic ultrasound (DU) has become the mainstream modality [8], replacing fluoroscopy in many institutions, for dynamic monitoring and evaluating diaphragmatic function in patients with MV due to its noninvasiveness, bedside availability, real-time visualization, cost effectiveness, and ability for repeated monitoring, which is applicable in young children [9–11]. In adults, the thickness of the right hemidiaphragm and the diaphragmatic thickening fraction (DTF) are used to assess VIDD development, and the DTF is applied as a predictor of successful extubation from MV [12]. Despite growing interest in DU in PICU, there are no reference values for normal diaphragm dimensions, function, or quantitative parameters to define VIDD in children [13]. Since the first DU investigation of VIDD development in critically ill children [9], emerging evidences have shown that acute diaphragmatic atrophy and dysfunction also exist in mechanical ventilated pediatric patients [9–11, 14, 15]. Diaphragm atrophy was reported in 44% of pediatric patients with the onset occurring within 24 h to 4 days after the initiation of MV [9, 16], which could strongly associated with the use of MV and neuromuscular blockade [15]. After intubation, progressive reductions in end-inspiratory thickness of the diaphragm (Dtei) and DTF within 24 h of ventilation were observed even in extremely preterm infants [11]. Nevertheless, the studies of association of VIDD with the prognosis of critically ill pediatric patients are scarce [10, 13].

This study aims to prospectively observe the changes in diaphragmatic function in mechanically ventilated pediatric patients by daily bedside DU detection at the very acute period after intubation and dynamically monitored till extubation. The primary focus of current study is to examine whether the occurrence of VIDD is associated with the outcomes of critically ill children, including the duration of MV, length of PICU stay and total hospital stay. Furthermore, the study aims to identify the peak periods during which VIDD is more likely to occur in critically ill children and explore the significance of VIDD occurring at different time points for the association with clinical outcomes.

Methods

This prospective, observational, single-center cohort study was approved by the Ethics Committee of the Children's Hospital of Fudan University (CHFU) on March 26, 2019; approval number was (2018)266. Written informed consent was obtained from the legal guardians of all participants involved in the study. The study was conducted from June 2022 to December 2022 in the PICU of CHFU, following the Declaration of Helsinki and used the STROBE reporting guidelines [17].

Patient enrollment

Patients who received MV within 24 h of admission into the PICU and expected to be ventilated for more than

48 h were included as study subjects. All enrolled patients underwent DU prescreening within 24 h before intubation. Inclusion criteria included clear DU images, ability to cooperate with the study, age between 0 and 15 years, and body mass index (BMI) between 10 and 20 kg/m². Exclusion criteria included effusion, pneumoperitoneum or drainage in the pleural or abdominal cavities, previous thoracoabdominal surgery, restriction of the thoracoabdominal cavity, congenital diaphragmatic hernia, and unilateral or bilateral DP. Standardized strategies of MV and protocols of sedation and analgesia were used for all enrolled children [18]. Simply, pressure control ventilation (PCV) mode was used in the early and critical stage of the disease, synchronized intermittent mandatory ventilation (SIMV) mode was used in the recovery stage and pressure support ventilation (PSV) mode was used in the weaning stage. No patients included in the current study were treated with the trigger mode of neurally adjusted ventilator assist (NAVA). Midazolam (2–4 μg/kg/min) and fentanyl (1–2 μg/kg/h) were used for sedatives and analgesics, respectively. During MV, spontaneous breathing was maintained. No steroids or muscle blockers were used.

Group allocation

The diaphragmatic function was measured using ultrasound within 24 h after the initiation of MV and subsequently once daily until extubation. The DTF measured by DU was used as an indicator of diaphragm contractile activity (for details see "DU assessment" below). During the ultrasound assessment, the absence of bilateral diaphragmatic contraction which meant bilateral DTF equaling zero was defined as severe VIDD [3, 13]. Patients who experienced severe VIDD on one or consecutive days were classified into the severe VIDD group, while those who was never evaluated as bilateral DTF equaling zero by DU were classified into the non-severe VIDD group.

Data collection

In accordance with the diagnostic criteria for pediatric sepsis established during the 2005 International Pediatric Sepsis Consensus Conference [19], all enrolled patients had their sepsis status determined within 24 h before intubation. Data on sex, age, height, weight, underlying diseases, intubation reasons, Pediatric Risk of Mortality III (PRISM III) score, nutritional markers (hemoglobin, albumin) and drugs of sedation and analgesia were collected. Patients who were transferred to another hospital before extubation, withdrew from the study, or died before extubation were excluded. Data from patients who were successfully extubated were included in the analysis, including daily DTF detected by bedside DU before intubation until extubation from MV and length of PICU stay, hospitalization and MV.

DU assessment

Using a linear array transducer with a frequency range of 6–13 MHz, the bilateral diaphragm thickness was measured. The transducer was placed vertically on the mid-axillary line of the thoracic wall between the seventh and ninth intercostal spaces [20]. B-mode imaging was used to visualize the diaphragm. In this region, the diaphragm was divided into three layers, with the pleura and peritoneum considered the most highly echogenic structures and the middle layer consisting of low echogenic diaphragmatic fibers. Starting from the mid-axillary line, the transducer was gradually moved upward to the highest position of the diaphragm. After selecting the optimal image, the respiratory cycle could be recognized when the diaphragm contracted and relaxed, leading to a change in diaphragm thickness. These changes were recorded using M-mode and shown as DTF, representing the status of active diaphragmatic work. Measurements were performed on both sides of the diaphragm. The formula for calculating the DTF was as follows: DTF (%) = (Dtei - Dtee)/Dtee × 100% [21] (Dtei: diaphragm thickness at end-inspiration, Dtee: diaphragm thickness at end-expiration). The average DTF value for each patient was calculated over three respiratory cycles, and a bilateral DTF of 0% was considered as severe VIDD. All diaphragmatic ultrasound examinations were performed daily by one physician who had received specialized training, usually at 8–10 o'clock in the morning. All images were obtained by waiting for moments when the patient was maximally relaxed, adapting to the cold ultrasound coupling agents and the changes of diaphragmatic thicknesses were fixed, regardless of the level of consciousness of patients [22]. The physician has been conducting diaphragmatic ultrasound evaluations since 2018, and 72 cases of bilateral diaphragmatic ultrasound evaluations have been published in relevant articles [21], exceeding the threshold of at least 40 ideally bilateral examination for independent use in daily practice in a Delphi consensus statement on the measurement of diaphragm-derived parameters in a critical care setting [20]. Figure 1 shows the characteristic DU image, in which A-A and C-C represent Dtei, B-B and D-D represent Dtee.

Statistic analysis

For clinical characteristics, demographic data, and the sonographic results from the severe VIDD and non-severe VIDD groups, normally distributed continuous variables were compared using one-way ANOVA, and data are presented as the mean ± standard deviation (SD). Non-normally distributed continuous variables were compared using the Mann-Whitney U test, and data are

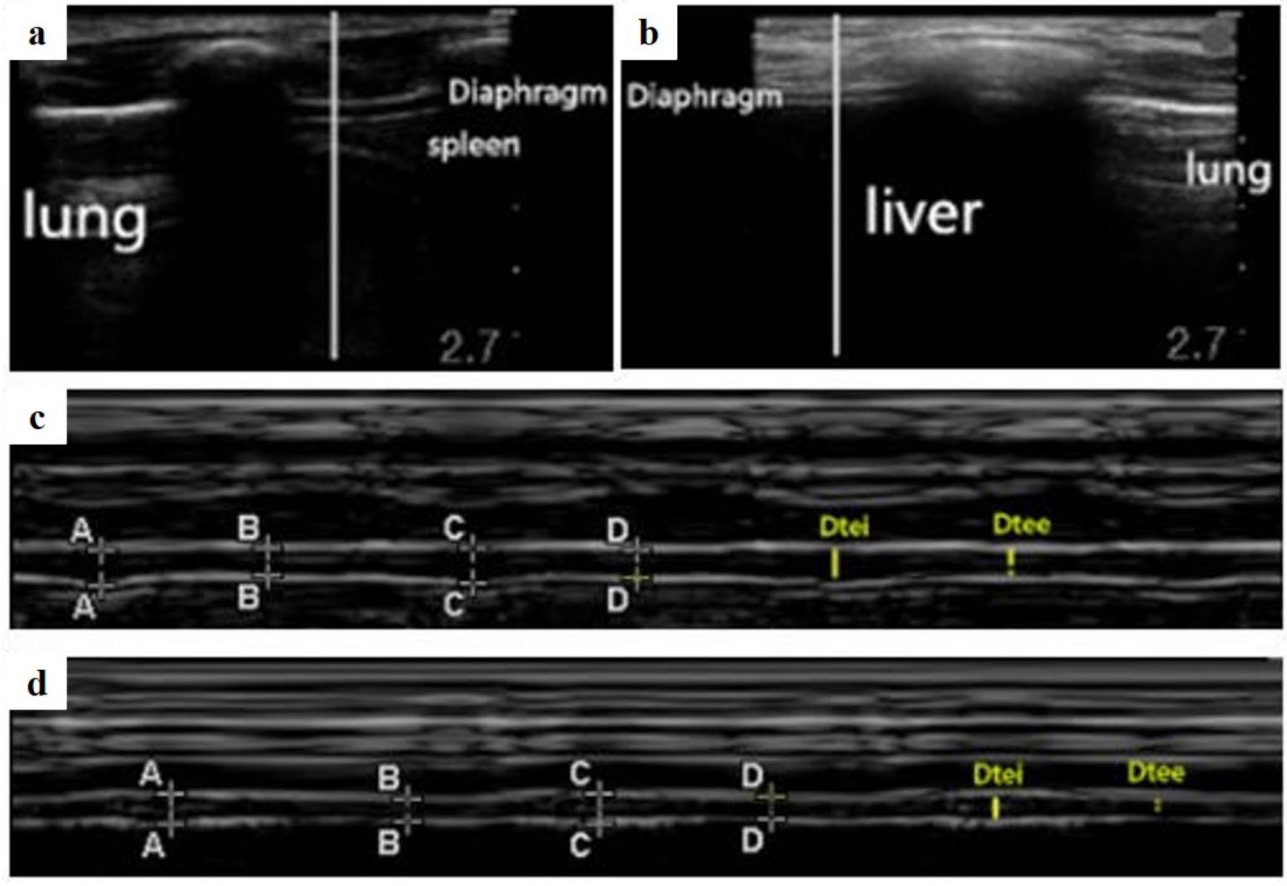

Fig. 1 Characterized image of diaphragmatic ultrasound. **A-A** and **C-C** represent Dtei: diaphragm thickness at end-inspiration; **B-B** and **D-D** represent Dtee: diaphragm thickness at end-expiration

presented as medians and interquartile ranges. When $n<10$, data are presented as median (minimum, maximum) values. Comparison of categorical variables was performed using Fisher's exact test or chi-square test, and descriptive statistics are presented as n (%). Multivariate linear regression model was conducted to identify the association of severe VIDD with lengths of PICU stay, hospitalization and MV. Four variables in the left column of Tables 1, 2, 3 and 4 were separately analyzed with co-variants in regression models. A p value <0.05 was considered as statistically significant, and Bonferroni correction was applied for pairwise comparisons. SPSS Statistics, version 22.0 (IBM Corp., Armonk, NY, USA) for Windows, was used for all data analyses.

Results

During the study period, a total of 105 patients received MV in PICU of CHFU, of which 15 were transferred into PICU with a ventilator, 16 were ventilated after 24 h of admission, four were successfully extubated within 48 h of MV and one was not cooperated with ultrasound examination. Totally 69 patients were eligible in the prospective study, of which three died before extubation, four were withhold/withdrawn of treatment by parents' requests and seven were transferred to another hospital with a ventilator, leaving 55 patients finally completed the weaning process and were included in the analysis. Based on the DU results, the eligible patients were divided into severe VIDD group ($n=26$) or non-severe VIDD group ($n=29$). The flowchart of the study is shown in Fig. 2. There were no significant differences in demographic characteristics between the severe VIDD and non-severe VIDD groups. The rates of underlying diseases and MV etiology were not significantly different between the two groups, nor were values of clinical feature, dosages of drugs of sedation and analgesia and DTF before intubation ($p>0.05$) (Table 1).

There were significant differences in the duration of MV [severe VIDD group: 12.0 (8.0-19.3) days vs. non-severe VIDD group: 5.0 (3.5–7.5) days, $p=0.000$] or length of PICU stay [severe VIDD group: 30.5 (14.8–44.5) days vs. non-severe VIDD group: 13.0 (7.0-24.5) days, $p=0.000$] between the two groups. However, there was no significant difference in the total length of hospital stay between the two groups (Table 2).

Table 1 Baseline characteristics of severe VIDD and non-severe VIDD group

Characteristics	Non-severe VIDD Group (*n* = 29)	Severe VIDD Group (*n* = 26)	*P* value
Age (months)	57.2 ± 49.8	53.0 ± 45.6	0.75
Male sex (%)	21 (72.4)	20 (76.9)	0.70
Height (cm)	102.7 ± 29.6	97.5 ± 29.2	0.51
Weight (kg)	18.0 ± 11.5	16.9 ± 11.0	0.71
BMI	15.7 ± 2.2	16.3 ± 1.6	0.27
Underlying diseases, n (%)			
Neuromuscular diseases	3 (10.3)	0	0.24
Laryngotracheal lesions	1 (3.4)	3 (11.5)	0.34
Mechanical Ventilation Etiology, n (%)			
Central nervous system	15 (51.7)	8 (30.8)	0.17
Pneumonia	4 (13.8)	9 (34.6)	0.11
Sepsis	4 (13.8)	5 (19.2)	0.72
Clinical Features			
Pediatric Risk of Mortality (PRISM III) score	5.1 ± 4.6	6.4 ± 5.9	0.37
Hemoglobin (g/L)	114.0 ± 21.0	110.6 ± 29.7	0.63
Albumin (g/L)	40.1 ± 5.9	37.5 ± 6.3	0.13
Drugs of sedation and analgesia			
Midazolam (ug/kg/min)	2.4 ± 1.1	2.7 ± 1.2	0.37
Fentanyl (ug/kg/h)	1.2 ± 0.7	1.2 ± 0.7	0.96
DTF before intubation (%)[1]	29.3 ± 11.9	23.1 ± 12.8	0.07

Values are mean ± standard deviation or n (%) where appropriate. *Abbreviations* BMI, body mass index; VIDD, ventilation induced diaphragmatic dysfunction; DTF, diaphragmatic thickening fraction. DTF was calculated as (diaphragm thickness at end-inspiration – diaphragm thickness at end-expiration)/diaphragm thickness at end-expiration × 100%. Severe VIDD was defined as bilateral DTF = 0 detected at any time after initiation of mechanical ventilation till extubation

[1] Values were calculated as averages of bilateral DTF by bedside sonography of individuals

Table 2 Comparison of lengths of PICU stay, hospitalization and mechanical ventilation between two groups

	Non-severe VIDD Group (*n* = 29)	Severe VIDD Group (*n* = 26)	*P* value
Length of PICU Stay	13.0 (7.0-24.5)	30.5 (14.8–44.5)	**0.000**
Length of hospitalization	26.0 (17.0–38.0)	33.0 (19.0-50.5)	0.107
Length of MV	5.0 (3.5–7.5)	12.0 (8.0-19.3)	**0.000**

Values are given in Median (IQR) in days. PICU, pediatric intensive care unit; MV, mechanical ventilation; VIDD, ventilation induced diaphragmatic dysfunction. *p* value < 0.05 was considered as statistically significant

All incidents of severe VIDD occurred within the first 5 days (2.9 ± 1.2 days) after initiation of MV, mostly on the second day. The condition of DTF = 0% lasted for 1.9 ± 1.7 (Means ± SD) days in severe VIDD group, and then the diaphragmatic function recovered gradually before extubation. One typical image of diaphragm by bedside ultrasound was shown in Fig. 3a, in which the breath rhythm could be recognized but the difference of diaphragmatic thickness vanished between end-inspiration (A-A or C-C in Fig. 3a) and end-expiration (B-B or D-D in Fig. 3a). The evolutions of DTF (%), Dtei (mm) and Dtee (mm) of two groups from the assessment before intubation to that on the 7th day of MV were presented in Fig. 3b, c and d. DTF in the severe VIDD group decreased from the 1st day after initiation of MV till the 3rd day of MV and increased gradually. From 1st to 7th day after initiation of MV, differences of DTF between severe VIDD group and non-severe VIDD group were significant (Fig. 3b). From 2nd to 7th day after MV initiation, the differences of Dtei (mm) between two groups were significant (Fig. 3c), but the differences of Dtee (mm) between the two groups were not significant within the 7 days. On the 7th day of MV, diaphragmatic atrophy represented by the percentage of Dtee (mm) reduction compared to that before intubation was 14.4% and 21.9% in non-severe VIDD and severe VIDD groups, and the rates of atrophy were −2.1% and −3.1% per day, respectively.

Multivariate linear regression analysis was conducted to explore the association of severe VIDD with length of PICU stay (Table 3A), hospitalization (Table 3B) and MV (Table 3C). The occurrence of severe VIDD, first day of severe VIDD and length of severe VIDD were significantly positively associated with the duration of MV and length of PICU stay. Only length of severe VIDD was significantly positively associated with the length of hospitalization (Table 3B). DTF before intubation had no significant association with any of the three lengths (Table 3).

Comparative analysis between the severe VIDD and non-severe VIDD groups at different time points after initiation of MV revealed that patients with severe VIDD occurred on the 2nd and 3rd days had significantly longer length of PICU stay, and patients with severe VIDD occurred on the 3rd day after MV initiation had significantly longer duration of MV (Table 4).

Table 3 Multiple linear regression analysis of the association of severe VIDD with length of PICU stay, hospitalization and mechanical ventilation

Variable	Regression coefficient	Standard error	Standardized regression coefficient	t	*p*
A. PICU stay					
DTF before intubation	0.003	0.354	0.001	0.009	0.993
Occurrence of severe VIDD [1]	25.168	7.552	0.429	3.333	**0.002**
First day of severe VIDD [2]	6.731	2.449	0.377	2.748	**0.009**
Length of severe VIDD [3], days	6.062	2.458	0.343	2.466	**0.018**
B. Hospitalization					
DTF before intubation	0.073	0.407	0.028	0.179	0.859
Occurrence of severe VIDD [1]	17.854	9.314	0.276	1.917	0.062
First day of severe VIDD [2]	3.498	2.996	0.178	1.168	0.249
Length of severe VIDD [3], days	6.382	2.854	0.328	2.236	**0.030**
C. Mechanical ventilation					
DTF before intubation	-0.206	0.134	-0.244	-1.544	0.130
Occurrence of severe VIDD [1]	8.842	2.989	0.418	2.958	**0.005**
First day of severe VIDD [2]	2.295	0.967	0.357	2.374	**0.022**
Length of severe VIDD [3], days	3.074	0.905	0.428	3.396	**0.001**

Values of the four variables were calculated with co-variants of underlying diseases, mechanical ventilation etiology, clinical features and drugs of sedation and analgesia in total population recruited in the analysis ($n=55$), respectively. *Abbreviations* and other definitions see legends of Tables 1 and 2. p value < 0.05 was considered as statistically significant

[1] It is a dichotomous variable, with individuals of severe VIDD group defined as 1 and those of non-severe VIDD group defined as 0

[2] It is a continuous variable, defined as the day of occurrence of DTF = 0% by bedside diaphragmatic ultrasonography examination, ranging from 1 to 5 of severe VIDD group and defined as 0 of non-severe VIDD group

[3] It is a continuous variable, defined as the total days lasted for DTF = 0% detected by bedside diaphragmatic ultrasonography, ranging from 1 to 7 days of severe VIDD group and defined as 0 of non-severe VIDD group

Table 4 Comparative analysis of outcomes based on the day of occurrence of severe VIDD after initiation of MV

		Day of occurrence of severe VIDD after initiation of MV				
Outcome	**Non-severe VIDD**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**
Number of cases	29	3	9	6	5	3
Length of PICU stay, Median (min-max)	13.0 (3.0–40.0)	30.0 (15.0–34.0)	43.0 (9.0–70.0)	36.0 (17.0-208.0)	15.0 (14.0–61.0)	18.0 (12.0–40.0)
*p		0.127	**0.009**	**0.005**	0.165	0.243
Length of hospitalization, Median (min-max)	26.0 (6.0–89.0)	37.0 (15.0–76.0)	45.0 (11.0-108.0)	36.0 (17.0-208.0)	31.0 (15.0–61.0)	19.0 (13.0–43.0)
*p		0.497	0.089	0.182	0.559	0.651
Length of MV Median (min-max)	5.0 (2.0–22.0)	11.0 (10.0–16.0)	10.0 (2.0–44.0)	16.5 (7.0–29.0)	9.0 (8.0–61.0)	10.0 (8.0–14.0)
*p		0.032	0.059	**0.003**	0.011	0.051

Abbreviations see legends of Tables 1 and 2. All p values reflect comparison with the non-severe VIDD group. *Bonferroni-corrected p values, corrected $p' = p/5 = 0.05/5 = 0.01$. The criteria for determining statistical significance in pairwise comparisons with the non-severe VIDD group were adjusted to $p < 0.01$

Bonferroni-corrected p values, $p' = p/5 = 0.05/5 = 0.01$ was determined as statistical significant

Discussion

To our knowledge, it is the first study reporting the condition of bilateral absence of DTF in breathe cycles in ventilated critically ill children assessed by daily bedside DU, and this condition is associated with prolonged duration of MV and stay in PICU. Absence or reduced DTF indicates lower contractile ability or activity of diaphragm, which could be induced by mechanical ventilator and reversely lead to weaning difficulties [23, 24]. The biopsy studies showed that MV adversely affect the diaphragmatic fiber architecture (decreased slow- and fast- twitch fibers, atrophied diaphragmatic fibers, and disrupted sarcomere structure) histologically, and the inactivity of the diaphragm caused by MV triggers a state of mitochondrial vulnerability that produces an enzymatic deficiency, generating excessive reactive oxygen species production, reducing antioxidant activity, activating apoptotic and proteolytic pathways and promoting the accumulation of lipids in diaphragm due to an excess of energy substrate [25]. It seems like that the cause of MV-induced diaphragm contractile dysfunction is multiplicative and includes oxidative modifications to contractile proteins resulting in depressed fiber sensitivity to

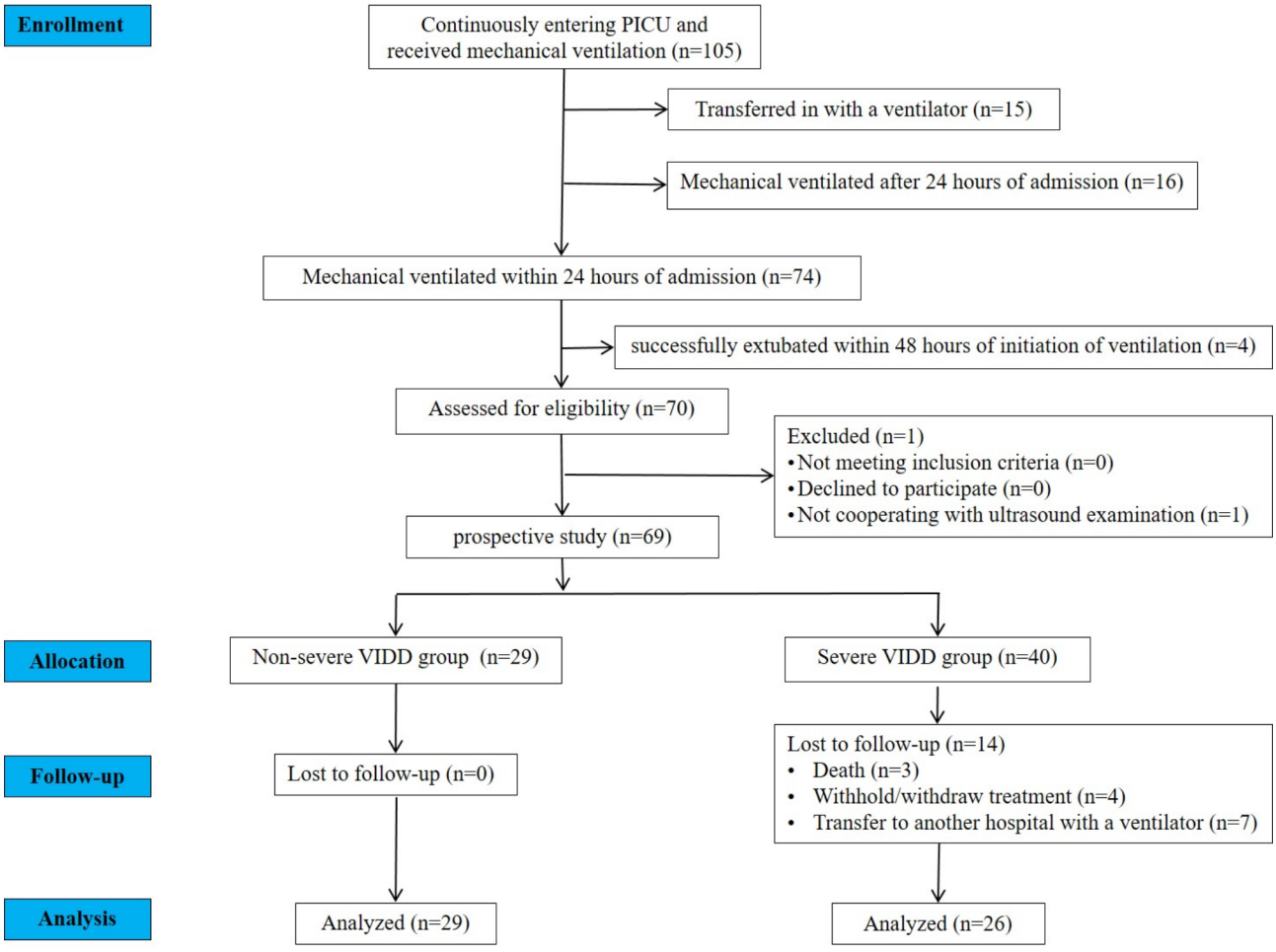

Fig. 2 Flowchart of the experiment. The non-severe VIDD group refers to patients who never experienced bilateral diaphragm thickening fraction (DTF) equaling zero by bedside ultrasonography monitoring after mechanical ventilation initiated till extubation. The severe VIDD group refers to patients who experienced bilateral DTF equaling zero at least once during bedside ultrasonography monitoring. The allocation time of patients were not simultaneous

calcium, protease activation leading to sarcomere disruption, and a loss of myosin heavy chain protein [26].

Currently, MV-related diaphragm dysfunction in pediatric research tends to be described as a phenomenon, and there is still a lack of diagnostic criteria. Traditionally, fluoroscopy has been considered the gold standard for assessing DD. However, the use of DU at the bedside has increased dramatically in critical care, providing quantitative, semi-quantitative and qualitative measurement of diaphragm for its quick response, convenience and non-invasiveness. DU assessment involves two parameters: mobility and thickness. Mobility represents the upward movement of the posterior diaphragm dome during the respiratory cycle, and it may passively occur due to the movement of thoracoabdominal viscera when DD occurs. Accordingly, it may not be suitable to use diaphragmatic excursion as a parameter to assess diaphragmatic function in patients receiving MV [26]. Diaphragmatic thickness examined in the region adjacent to the thorax during the respiratory cycle reflected both thickness and thickening ability of the diaphragm. During respiratory movements, the diaphragm contracts and relaxes, resulting in changes in thickness. Patient positioning has the greatest impact on diaphragm mobility but minimal influence on diaphragm thickness [27]. In sedated and mechanically ventilated patients, diaphragm thickening occurs only when the inhaled air volume exceeds 50% of the total lung capacity, which indicates passive inflation of the lung by the ventilator. Therefore, at lower lung volumes, DTF reflects the diaphragm's autonomous activity [12]. In a study on the diagnosis of DP during MV after neonatal cardiac surgery, it was found that diaphragm mobility was not suitable for diagnosing DP during positive pressure ventilation, and the use of the DTF was more appropriate [28]. In this present study, all included patients were mechanically ventilated, hence the use of the DTF as a parameter was more appropriate to evaluate the diaphragmatic function during MV.

In the diagnostic criteria for using ultrasound as a monitoring tool, the current cutoff value in adults is

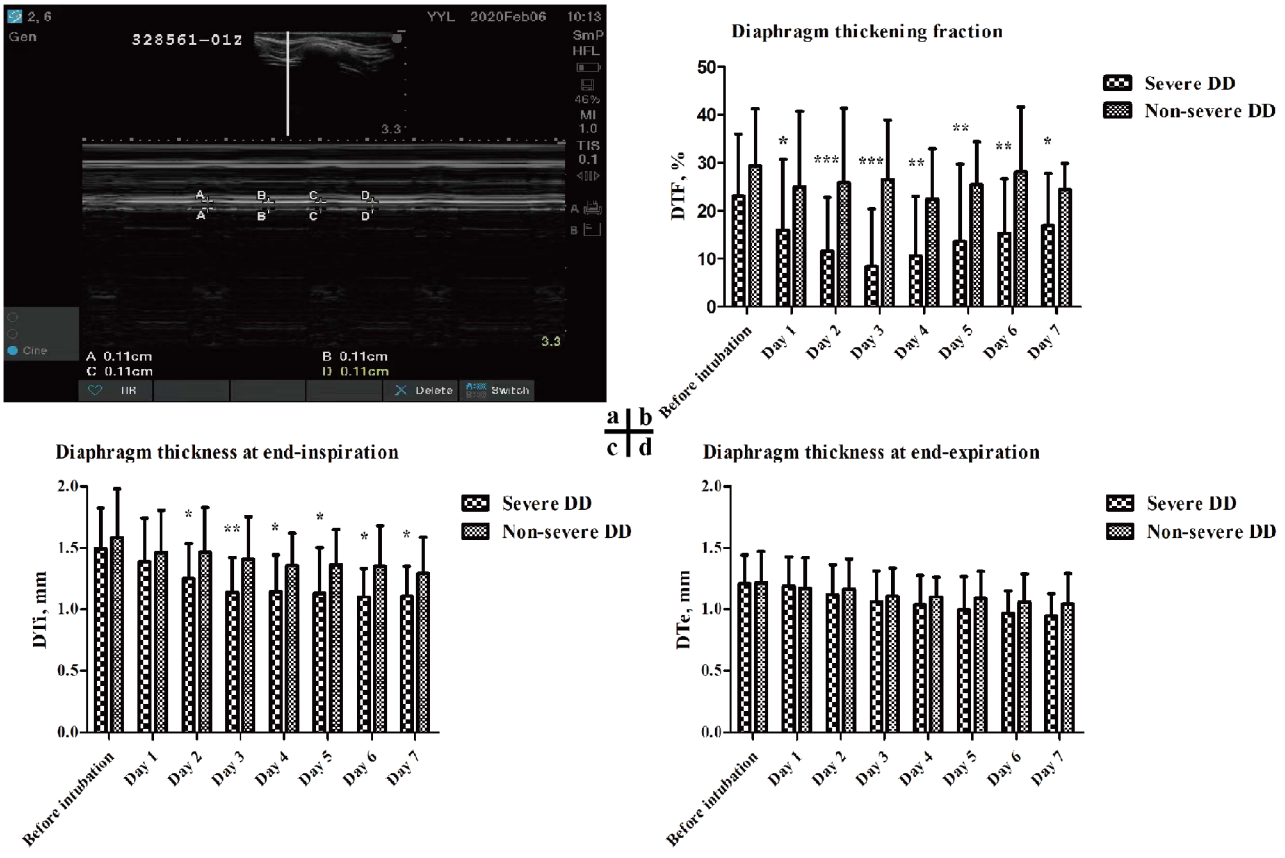

Fig. 3 One typical image of diaphragm ultrasound with severe VIDD (**a**) and the evolutions of functional parameters between groups (**b**-**d**). The breath rhythm could be recognized but the difference of diaphragmatic thickness vanished between end-inspiration (A-A or C-C) and end-expiration (B-B or D-D). *: $P<0.05$, **: $P<0.01$, ***: $P<0.001$ compared to non-severe VIDD group on the same day after initiation of MV

DTF < 20% [29]. However, this criterion has not been widely accepted by pediatricians, and several possible reasons explain why. The structure of the diaphragm differs between children and adults. In children, especially infants, the diaphragm is relatively flat rather than domed, as in adults. Most of the diaphragm muscle tissue in children is closely attached to the chest wall and runs horizontally in relation to the ribs [30]. Therefore, there may be a significant angular error in pediatric DU measurements. Unless there is extremely severe diaphragmatic dysfunction, such as complete diaphragmatic inactivity, using a DTF = 0% criterion would eliminate the influence of angular error. Furthermore, children may resist the DU examination procedure and generate breath-holding or deep breathing, and the reproducibility of diaphragm measurements may be low. Our clinical examinations indicated that even in some children with DTF < 20% who are not receiving oxygen, they can maintain a natural breathing state without any discomfort and can be successfully transferred out of the PICU and discharged, which was consistent with the findings of another pediatric study [9]. Therefore, we believe that it is unreasonable to apply the DTF < 20% of adult criterion for diagnosing VIDD in children, which may be attributed to the fewer presence of type 1 fibers (slow-twitch, high-oxidative) and poor resistance to diaphragmatic fatigue in children [9]. Based on these, in this study, a bilateral DTF = 0% cutoff point was considered as a better option, which would eliminate any associated errors and be operationally feasible, and we defined this phenomenon as severe VIDD, which was probably caused by diaphragmatic inactivity (lack of drive) after MV as those observed by electrical activity of diaphragm signal [31–33] and lack of contractile ability which may be associated with atrophy [15].

Previous studies have found that when using DTF < 20% as the criterion, VIDD can prolong the duration of MV and ICU stay in adult patients, but not suitable in pediatrician [34]. This study proposes for the first time DTF = 0% as the threshold, finding that the occurrence of VIDD was significantly associated with prolonged duration of MV and PICU stay. It was necessary to initiate continuous DU monitoring in PICU patients as soon as they were intubated. Moreover, the majority of VIDD incidents were detected within 5 days, with very few occurrences afterward. The second and third days were

the peak periods for the occurrence of VIDD, which is roughly consistent with previously studies [9, 16].

Finally, in this study, 26 children with severe VIDD were successfully extubated, and the evolution of DTF showed a gradually increase from 3rd to 7th day of intubation (Fig. 3b), but a steady and continous decrease in Dtee within the 7 days of MV (Fig. 3d). The occurrence of VIDD may be related to the interaction of multiple factors, such as the use of controlled MV mode [15, 25], sedative and analgesic drugs [33], and higher positive end-expiratory pressure (PEEP) levels [35, 36]. There is also strong evidence that processes other than VIDD, including sepsis and other systemic infections, senescence, intravenous medications such as neuromuscular blockers (NMB), and / or glucocorticoids are responsible for various forms of diaphragmatic myotrauma [26]. In particular, however, the spontaneous recovery of DTF from 3rd to 7th day of MV is speculated mainly related to the selection of ventilation mode of MV in our study, which is consistent with the findings of evolutions of peak inspiratory electrical activity of diaphragm [31]. Generally, the controlled ventilation mode is used first and then switched to the assisted ventilation mode after the critical stage of underlying diseases within several days. Human studies concluded that the decreased contractility was due to the effects of MV per se, but not attributed solely to NMB, though there was a synergistic effect of MV and NMB on depressing diaphragm contractility [25]. Other studies have shown that the controlled ventilation mode leads to the loss of diaphragmatic strength related to MV, while the assisted ventilation mode promotes the recovery of diaphragmatic strength [15]. It may give the explanation of the spontaneous recovery of DTF in the current study due to the switch of MV mode, and the continuously existing diaphragmatic atrophy may indicate existing diaphragmatic injury. However, the duration of VIDD that affects extubation remains a topic for further research. To avoid prolonged MV, improve extubation success rates, and reduce hospitalization time, efforts should be made to reduce diaphragmatic damage. This indicates that in clinical practice, timely intervention should be given once VIDD is detected to prevent continuous diaphragmatic damage [37]. The early diagnosis of VIDD and implementation of certain interventions, like medications (irisin [38], aminophylline [39], ruxolitinib [40], etc.) and phrenic nerve electrical stimulation [41], to reduce VIDD and improve outcomes, which should be investigated in the future.

This study has certain limitations, including its single center nature and the small size ($n=55$), which may limit the generalizability of the findings. Being conducted in a single PICU may introduce center-specific biases and limit the external validity. The study period (June 2022 to December 2022) is short, which might not capture seasonal variations in patient demographics and disease patterns. Future research should increase the sample size, investigated in multiple centers and a longer period. The aspects of inclusion criteria should include detailed values of MV modes, parameter settings and amounts of sedative and analgesic drugs matching each ultrasound assessment to identify factors influencing the occurrence of VIDD, the real impact of VIDD on the patients' prognosis, and explore interventions to prevent and reverse VIDD. In clinical practice, DU is not the gold standard for diaphragmatic function examination and may not represent the true level of diaphragmatic function [26]. But the non-invasiveness, repeatability, quick response and bedside availability make DU more and more popular in PICU and rigorous investigations concerning the prediction of non-invasive ventilation failure, assessment of diaphragmatic function during MV, guidance of parameters of MV titration and prediction of MV weaning are emerging.

In conclusion, VIDD has a significant association with the clinical outcomes of mechanically ventilated children, including longer PICU stays and MV duration. Therefore, it is necessary to continuously monitor diaphragmatic function using DU within the first 5 days of MV. In the future, once VIDD is identified clinically, efforts should be made to investigate the underlying causes and provide appropriate intervention measures to address it and improve prognosis. These intervention measures include shortening the duration of MV, minimizing the use of controlled MV mode, sedatives and analogic drugs, high PEEP levels, rapidly controlling sepsis and other systemic infections, reducing intravenous injection of NMB, and / or glucocorticoids, application of drugs and diaphragmatic nerve electrical stimulation to improve VIDD.

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Author contributions
YY and XG together completed data collection, statistical analysis and manuscript writing. JT and SW provided conception, design of the study, data interpretation and manuscript revision. WC and GL provided administrative support, patients and data interpretation. YL KL , and HY participated in data collection and assembly. All authors contributed to the article and approved the submitted version.

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Data availability
The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the ethics committee of Children's Hospital of Fudan University on March 26, 2019; approval number was (2018)266. Written informed consent was obtained from the legal guardians of all participants involved in the study. The study was conducted from June 2022 to December 2022 in the PICU of the Children's Hospital of Fudan University, following the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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