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Poor Adherence to Lung Protective Mechanical Ventilation in Pediatric Acute Respiratory Distress Syndrome

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Abstract

Objective—To determine the frequency of low tidal volume ventilation (LTVV) in pediatric acute respiratory distress syndrome (PARDS), and assess if any demographic or clinical factors improve LTVV adherence.

Design—Descriptive post-hoc analysis of 4 multicenter PARDS studies

Setting—26 academic pediatric intensive care units

Patients—315 PARDS patients

Measurements and Main Results—All patients who received conventional mechanical ventilation at hours 0 and 24 of PARDS who had data to calculate ideal body weight (IBW) were included. Two cutoff points for LTVV were assessed: ≤6.5mL/kg IBW and ≤8mL/kg IBW. Of 555 patients, we excluded 240 for other respiratory support modes or missing data. The remaining 315 patients had a median PF ratio of 140 (IQR 90–201), and there were no differences in

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demographics between those who did and did not receive LTVV. With TV cutoff of ≤6.5mL/kg IBW, the adherence rate was 32% at hour 0 and 33% at hour 24. A LTVV cutoff of TV ≤8mL/kg IBW resulted in an adherence rate of 58% at hour 0 and 60% at hour 24. LTVV use was no different by severity of PARDS nor did adherence improve over time. At hour 0, overweight children were less likely to receive LTVV ≤6.5mL/kg IBW (11% overweight vs 38% non-overweight, p=0.02); no difference was noted by hour 24. Furthermore, in the overweight group, using admission weight instead of IBW resulted in misclassification of up to 14% of patients as receiving LTVV when they actually were not.

Conclusions—LTVV is underused in the first 24 hours of PARDS. Age, PRISM-III, and PARDS severity were not associated with improved LTVV adherence, nor did adherence improve over time. Overweight children were less likely to receive LTVV strategies in the first day of illness.

Keywords

pediatric acute respiratory distress syndrome; acute lung injury; pediatric; ideal body weight; mechanical ventilation

Introduction

Acute Respiratory Distress Syndrome (ARDS) is associated with mortality rates of 18 to 35% in the pediatric population(1–3). In 2000, the ARDS Network showed significant reduction in mortality in patients who received lung protective mechanical ventilation with low tidal volume (TV), defined as 6–8mL/kg of predicted body weight (PBW), and low pulmonary airway plateau pressures(4). Since then both adult and pediatric intensivists strive to utilize this strategy in ARDS and pediatric ARDS (PARDS).

Observational studies in adults with ARDS reveal that implementation and adherence to lung protective mechanical ventilation is poor, with adherence rates as low as 13% when defined by TV <6.5mL/kg PBW to 50% when defined by TV <8ml/kg PBW(5–9). These studies report underutilization may be associated with lung injury severity(5, 7), refractory hypercapnia or hypoxemia(6, 10), patient discomfort, use of muscle relaxant medications(7), and under-recognition of ARDS(5, 10). There is a paucity of published data in the PARDS population reporting adherence rates of lung protective ventilation strategies.

The objective of this study was to determine the frequency of low tidal volume ventilation (LTVV) use in PARDS patients during the first 24 hours of illness and establish if any demographic and clinical factors were associated with improved LTVV adherence.

Methods and Materials

Design, Setting and Patients

Our cohort was developed from the combination of 4 prospective PARDS studies (1 clinical trial, 3 observational studies), via the collaboration of 26 academic hospitals within the Pediatric Acute Lung Injury and Sepsis Investigators Network. Two studies enrolled patients between 2000 and 2005, and the other two between 2007 and 2010. Pediatric ARDS

(PARDS) and pediatric acute lung injury (ALI) were identified based on the 1994 North American-European Consensus Conference criteria: a PaO2 to FiO2 ratio (PF ratio) of <300, bilateral infiltrates on chest radiograph, and no evidence of left atrial hypertension(11). The term ALI has since been replaced with the term mild ARDS(3) and any patient meeting the above criteria was said to have PARDS and included in the cohort. Details of the 4 studies are provided in an online data supplement.

We restricted analysis to all patients younger than 18 years old who were receiving conventional mechanical ventilation (CMV) at both hours 0 and 24 of study enrollment. Those with no documented PF ratio at disease onset, or no recorded admission height were excluded. This study received IRB exemption from UCSF Benioff Children's Hospital, Oakland.

Measurements and Data Collection

Ideal body weight (IBW) was calculated based on gender, age and admission height according to data tables provided by the National Center for Health Statistics(12). PARDS severity was defined by PF ratio calculated at time of diagnosis, with mild PARDS being a PF ratio of 201–300, moderate being a PF ratio of 101–200, and severe being a PF ratio of ≤100. Tidal volume was recorded from the ventilator at hours 0 and 24 of illness and divided by the patient's IBW to determine their hour 0 and hour 24 TV per kilogram of IBW. In 3 of the 4 studies used to create the combined cohort, the guidelines for the use of tidal volumes of 6–8mL/kg predicted body weight were provided to all study sites; the 4^{th} cohort was collected for epidemiologic reasons only and no guidelines for patient care were provided, although LTVV was the standard practice guideline for this facility. As mechanical ventilation strategy was not uniformly protocolized across parent studies, patients were treated with both pressure-cycled and volume-cycled ventilation; if a patient was on a pressure-cycled ventilation mode, the exhaled TV was recorded as the TV the patient received; these measurements were most frequently made at the end of the endotracheal tube. The cohort was divided into two groups; a low tidal volume ventilation (LTVV) group and a non-LTVV group based on TV recorded at hours 0 and 24 of study enrollment. Since the ARDSnet protocol for adult patients recommends a TV of 6 to 8ml/kg of PBW, we evaluated two cutoff points of LTVV: a tidal volume of ≤6.5mL/kg IBW, and secondly, a tidal volume of ≤8mL/kg IBW akin to previously published adult cut-offs.

Outcomes Measures and Statistical Analysis

The primary purpose was to determine the frequency of LTVV use and evaluate if any demographic and clinical factors were associated with improved LTVV adherence at hours 0 and 24 of PARDS. We calculated the proportion of mechanically ventilated PARDS patients receiving LTVV within the 2 TV limits, ≤6.5mL/kg IBW and ≤8mL/kg IBW. Clinical and demographic factors analyzed included age, gender, PARDS severity, PRISM-III (a severity of illness score determined in the first 24 hours of admission)(13), positive end expiratory pressure (PEEP) requirement, and resultant peak inspiratory pressures (PIP). To evaluate if frequency of LTVV use changed over time, we dichotomized patients by year of study enrollment, either before or after 2006. The comparisons between the LTVV group and the non-LTVV group were performed by chi-square test for categorical variables and by

Student's t-test for normally distributed continuous variables or Wilcoxon rank sum test for non-normally distributed variables. Multivariate analyses were performed to determine the odds of receiving LTVV and included clinically relevant variables as well as those with a p-value of <0.1 on univariate analysis.

In children older than 2 years in which a BMI z-score could be calculated, we analyzed whether an association between being overweight, defined by Center for Disease Control criteria, and use of LTVV existed. Anticipating that the difference between admission weight and IBW would be less in children of normal weight than in the overweight, we performed a sub-analysis in patients older than 2 years with BMI data. TV by admission weight was subtracted from TV by IBW to determine the difference in TV per kilogram between the 2 weight measurements. We then compared the difference between the overweight and non-overweight by Wilcoxon rank sum test. A p-value of <0.05 was accepted as being statistically significant in all analyses. All analyses were performed using STATA software, version 13.1 (StataCorp, College Station, Texas).

Results

555 unique patients were identified from the 4 parent studies. We excluded 110 patients for no height recorded, 39 without a PF ratio noted, and 91 who were receiving other modes of respiratory support at hour 0 or hour 24 of illness, leaving 315 patients for analysis. There was no difference in age, gender PRISM-III score or ICU length of stay between those included and those excluded from analysis. Table 1 reports the demographics and clinical data of the cohort. There were 80 (25%) children with mild PARDS, 138 (44%) with moderate PARDS and 97 (31%) with severe PARDS. Forty-six patients (15%) died from their illness.

At hour 0 of study entry, 231 (73%) were utilizing conventional mechanical ventilation; of these 167 (72%) had a tidal volume recorded in the database. The median TV was 7.4mL/kg IBW (IQR 6.3–9.4). At hour 24 of PARDs, 275 (87%) patients were requiring conventional mechanical ventilation, of which 234 (85%) had a TV recorded in the database. The median TV was 7.4mL/kg IBW (IQR 6.2–8.9) at hour 24.

LTVV defined as tidal volume ≤6.5mL/kg IBW

With LTVV defined as TV≤6.5mL/kg IBW, 31% (n = 53) of the patients were adherent to LTVV at hour 0 and 33% (n = 77) at hour 24 (Figure 1). Table 2 compares the LTVV and non-LVV groups when LTVV was defined TV≤6.5mL/kg IBW. At both time points, there were no differences between the LTVV and non-LTVV groups by PARDS severity, age, gender, race, PRISM-III score, PEEP required, PIP, or whether the study was performed before or after 2006. Interestingly, when evaluating patients >2 years old with a BMI recorded (n = 82), at hour 0 the overweight patients were much less likely to be adherent to LTVV ≤6.5mL/kg IBW, with 11% (n=3) of the overweight utilizing LTVV ≤6.5mL/kg IBW compared to 38% (n=21) of the non-overweight, p = 0.02. By hour 24, however, there was no difference in proportion receiving LTVV by weight classification, 26% (n=7) of the overweight vs. 24% (n=13) of the non-overweight. Multivariate analyses, adjusting for PRISM-III, gender, time of enrollment (before or after 2006), and weight status revealed

similar results to the univariate analyses with the exception that at hour 0, males were less likely to receive LTVV (OR 0.26, 95%CI 0.08–0.83, p=0.02), and those with higher PRISM-III scores were more likely to receive LTVV (OR 1.09 for 1-unit increase in PRISM-III score, 95%CI 1.02–1.17, p=0.01).

LTVV defined as tidal volume <8mL/kg IBW

When LTVV was defined by TV <8mL/kg IBW, 58% (n = 97) of the patients met LTVV criteria at hour 0, and 60% (n = 139) met LTVV criteria at hour 24 (Figure 1). Table 3 compares the LTVV and non-LTVV groups when LTVV was defined as TV <8mL/kg IBW. Similar to the stricter LTVV definition, there were no differences between the LTVV and non-LTVV groups with regard to age, gender, PRISM-III score, PARDS severity, PEEP requirements and timing of study enrollment (before or after 2006) at either the hour 0 or hour 24 time point. The difference in proportion of overweight patients receiving LTVV <8mL/kg IBW (41%, n=11) and the non-overweight patients receiving LTVV<8mL/kg IBW (64%, n = 35) was statistically significant, p = 0.05 at hour 0, but again this difference was not present by hour 24, with 52% (n = 14) of the overweight receiving LTVV and 40% (n = 22) of the non-overweight receiving LTVV, p = 0.3. Multivariate analysis revealed the same results; however, the odds of LTVV between the overweight and non-overweight at hour 0 were no longer statistically significant (OR 0.44 for the overweight, 95%CI 0.2–1.2, p=0.1).

Comparison of tidal volumes by admission weight and ideal body weight

In the 181 children with calculable BMI z-scores, 70 (39%) were deemed overweight. Eighty-two (45%) had TV reported at hours 0 and 24. At hour 0, the median difference between TV calculated with admission weight and TV calculated with IBW was −0.3mL/kg (IQR −1 to 0.3) in the non-overweight group and 2.6mL/kg (IQR 1.7 to 3.5) in the overweight, p<0.001. This can be seen in Figure 2, which reports the median TV per kilogram admission weight (white box) and per kilogram IBW (grey box) at hour 0 comparing the overweight and the non-overweight. When admission weight was used 10 (14%) overweight patients were misclassified as receiving LTVV ≤6.5mL/kg when they truly were not. Similar results were seen at hour 24, with a median difference of −0.3mL/kg (IQR −0.9 to 0.3) in the non-overweight group compared to a median difference of 2mL/kg (IQR 1.2 to 2.7) in the overweight group, p<0.001. When admission weight was used instead of ideal body weight, 7 (10%) overweight patients were misclassified as receiving LTVV ≤6.5mL/kg when they truly were not.

Discussion

Pediatric Acute Respiratory Distress Syndrome (PARDS) is associated with mortality rates as high as 18–35%(1–3), although lower mortality rates are often reported in clinical trials(14, 15). High mortality rates are also noted in adults with ARDS and as a result, many research endeavors have evaluated the pathobiology and modes of treatment and prevention in ARDS. Despite such great interest, we have limited understanding of methods to prevent ARDS, reverse damage incurred during the illness or methods to accelerate healing. We have, however, found evidence that limiting further injury to the lungs can reduce disease progression and improve outcomes.

The use of mechanical ventilation in patients with ARDS and PARDS can reverse life-threatening hypoxemia and alleviate work of breathing, providing time for the injured lungs to heal. Unfortunately, mechanical ventilation, itself, can induce lung injury, even in individuals with healthy lungs(16, 17). With this understanding, in 2000, the ARDS Network randomly assigned patients to receive mechanical ventilation with either a conventional TV of 12mL/kg PBW or a low TV of 6mL/kg of PBW while maintaining an appropriate pulmonary airway plateau pressure. The trial was stopped early after interim analysis revealed a 22% lower mortality rate in the low tidal volume group(4). Since then both pediatric and adult intensivists strive to utilize this low tidal volume mechanical ventilation strategy in ARDS and PARDS patients.

In this study, we quantified frequency of low tidal volume ventilation (LTVV) use in PARDS patients and evaluated several factors that may influence the rate of adherence to LTVV. We found that at hours 0 and 24 of PARDS, only 30% of PARDS patients who were utilizing conventional mechanical ventilation were doing so with a strict LTVV strategy in place. When the definition of LTVV was expanded to include tidal volumes up to 8mL/kg IBW, the frequency of LTVV use increased to only 58–60%, leaving a large proportion of patients receiving tidal volumes higher than the ARDSNet recommended cut-off. Furthermore, we found that adherence to LTVV was not affected by age of the patient or by severity of illness, nor did adherence improve over time. Notably, children who were overweight were less likely to receive LTVV immediately upon recognition of PARDS but no significant difference in adherence rates between the overweight and non-overweight patients was apparent by 24 hours of illness.

The finding that a large proportion of patients are not ventilated at lung protective tidal volumes is similar to adherence patterns noted in adult ARDS. In 2000 to 2002, Kalhan and colleagues performed a prospective observational study and noted that in 88 patients, 24% were receiving LTVV defined as TV <6.5mL/kg PBW(5), with no association between LTVV adherence and any demographic or clinical factors, except that those with better oxygenation and lung compliance were less likely to receive LTVV. In 2008, Umoh et al. prospectively studied 150 ARDS patients and found that on the day after diagnosis 46% of patients were adherent to LTVV ≤6.5mL/kg PBW. No demographic factors were associated with adherence in this study(6). Lastly, Chen and colleagues published their prospective study of 111 ARDS patients enrolled in 2010 and 2011. Defining LTVV as TV ≤7.5mL/kg PBW, they found a 44% adherence frequency during the first 2 days with increased odds of adherence associated with worse lung injury and with use of muscle relaxant medications(7). To the best of our knowledge there is little published data of LTVV adherence in the pediatric PARDS population.

Our study reveals that adherence patterns to LTVV are not dependent on severity of PARDS nor did they improve over time, and it behooves us to postulate other possible clinical or systematic obstacles that may be impacting adherence rates. While the ARDSNet study showed clear benefit to LTVV, an analogous pediatric randomized control trial has never been completed. Observational studies evaluating tidal volume impact on PARDS outcomes have been mixed. Two retrospective studies have shown reduced mortality with lower tidal volumes in pediatric patients(18, 19), while both Khemani et al. and De Jager and colleagues

found no correlation between tidal volumes and outcome(20, 21). Perhaps this lack of definitive proof has translated into lower adherence to LTVV.

Such uncertainty in the unique care of PARDS patients led to several experts in the field of PARDS joining forces to re-evaluate the diagnosis and treatment strategies of PARDS in order to set forth a collaborative consensus regarding diagnosis, management and future research directions for the field. The Pediatric Acute Lung Injury Consensus Conference (PALICC) group found little evidence regarding benefit of one ventilator strategy over another and concluded sparse pediatric data was available. As a result, guidelines were created based on adult data with consensus based pediatric modifications. They recommend that in patients in controlled mechanical ventilation modes, using tidal volumes in or below the physiologic range for age and body weight; that is 5–8mL/kg IBW. Furthermore, tidal volume should be adjusted with disease severity, with even lower volumes of 3–6mL/kg IBW for patients with poor respiratory system compliance(22). Both these recommendations received approximately 80% agreement between the consensus members, with all members calling for more robust research to evaluate the impact of tidal volume on outcomes in children with PARDS.

The prevalence of obesity in children is increasing and physicians must adjust clinical management in the setting of this chronic condition reaching epidemic proportions. As shown in this analysis, the frequency of LTVV use is significantly less in overweight children than non-overweight children, at least in the first day of illness. A likely reason for this lower adherence rate is the prescription of tidal volumes based on admission weight instead of ideal body weight, and we have shown in this study, doing so in overweight children can lead to significantly higher tidal volumes exerted on the pulmonary system, up to 2 to 3ml/kg more volume per breath, leading to misclassification of 10–14% of overweight patients as receiving LTVV when they actually are not. It is also possible that clinicians are concerned of higher risk of atelectasis at lower tidal volumes because of worse chest wall compliance in overweight patients. This concern would be mitigated, however, will optimal PEEP use and is certainly an area for future research endeavors.

Our study has some limitations. We performed a secondary analysis of data not initially designed to determine LTVV adherence or test for factors that may impact LTVV adherence. As such, confounding by unmeasured covariates may have occurred, including valuable data points such as baseline lung function or airway plateau pressures; variables integral to implementation and maintenance of lung protective mechanical ventilation. Additionally, our conclusion is dependent on the completeness of the data collected, yet several patients were excluded because of missing tidal volume data. However, the demographic data between those excluded and those included was not significantly different. Further, our cohort had no unified ventilation strategy and it is unclear if all or only part of the subjects had exhaled tidal volumes measured at the endotracheal tube or at the ventilator itself, a factor that may cause discrepancy in tidal volume measurements. Additionally, with some of the patients utilizing pressure controlled ventilation modes, one would speculate that the tidal volumes achieved in these patients are dictated by the peak inspiratory pressures, which likely resulted in lower tidal volumes (and subsequently better adherence to LTVV) in those with more severe disease. Of note, however, there was no difference in mean tidal volume by

disease severity (PF ratio) at 0 or 24 hours in those on pressure control modes. These limitations speak to the need to standardize ventilator set up and ventilation strategies in future prospective studies; a point greatly emphasized in the recent PALICC guidelines.

In conclusion, the low tidal volume ventilation (LTVV) strategy is underused in children with PARDS in the first 24 hours of illness. Age, PRISM-III, and PARDS severity were not associated with improved LTVV adherence, nor did adherence improve over time. Notably, children who are overweight are less likely to receive LTVV strategies in the first day of illness and basing tidal volumes on admission weights instead of ideal body weight in this group can lead to false reassurance that patients are receiving lung protective mechanical ventilation. Although no robust, prospective, multicenter trials have proven clear benefit of low tidal volume ventilation in children with PARDS, given the great impact of this strategy in adults, such protocols must be greatly considered until proven otherwise; a conclusion shared by the Pediatric Acute Lung Injury Consensus Conference (PALICC). These data indicate the need for more rigorous implementation strategies for lung protective ventilation in PARDS patients, and further investigation of pediatric specific ventilator strategies and parameters.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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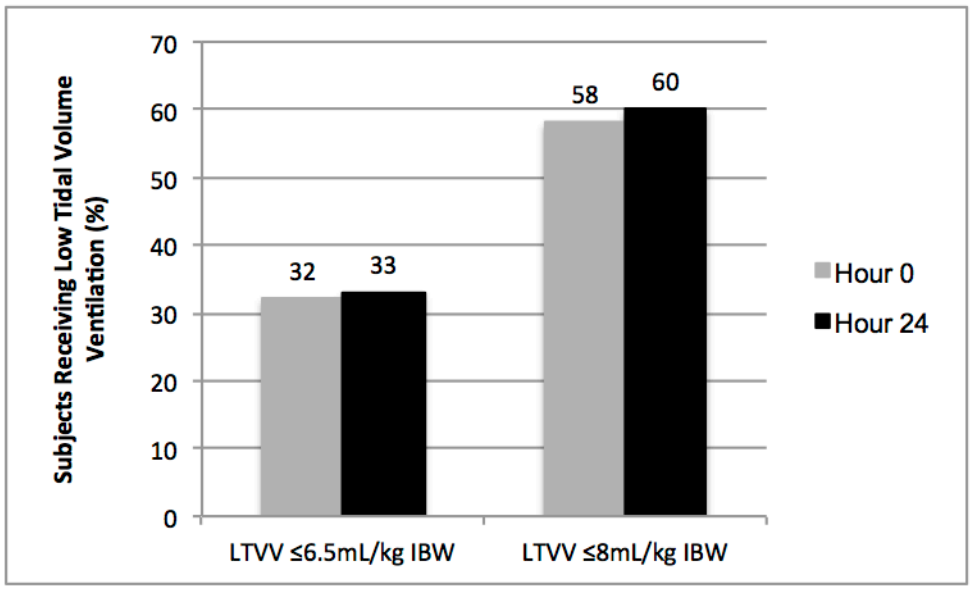

Figure 1. Frequency of Patients Receiving Low Tidal Volume Ventilation at Hours 0 and 24 of PARDS

The frequency of patients receiving low tidal volume ventilation (LTVV) at hours 0 and 24 of pediatric acute respiratory distress syndrome (PARDS) with LTVV defined by tidal volumes ≤6.5mL/kg ideal body weight (left bars) and by tidal volumes <8mL/kg ideal body weight (right bars).

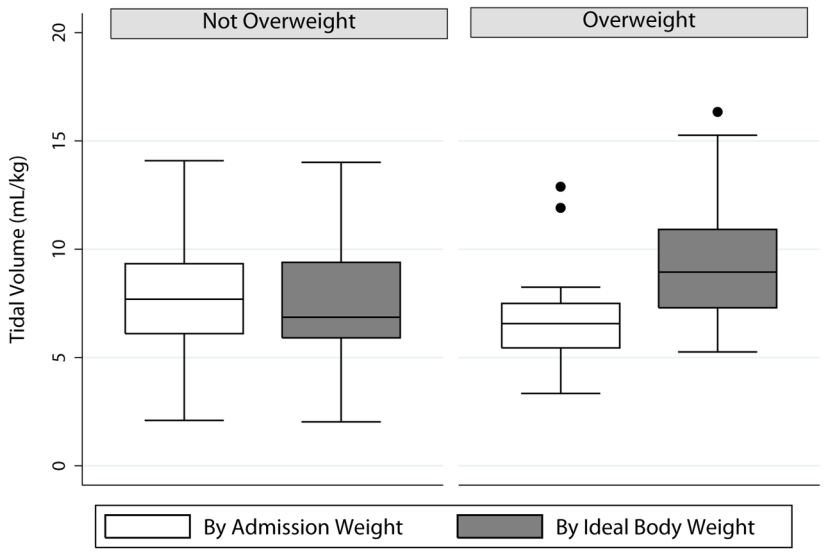

Figure 2. Comparison of Tidal Volumes When Assessed by Admission Weight and Ideal Body Weight

Boxplot graphs of tidal volumes divided by admission weight (white) and by ideal body weight (grey). $p < 0.001$ for the comparison of the difference between values calculated by admission weight and ideal body weight in the overweight vs. non-overweight individuals.

Table 1

Baseline Demographics and Clinical Characteristics of the Whole Cohort

Clinical Variables	Whole Cohort n = 315
Age, median, years (IQR)	3.3 (0.4–10.8)
Male, n (%)	173 (55)
Race/Ethnicity, n (%)	
Caucasian, non-Hispanic	171 (54)
African American	40 (13)
Asian/Pacific Islander	18 (6)
Hispanic/Latino	60 (19)
Other	26 (8)
Any Past Medical History, n (%)	162 (51)
Immunocompromised, n (%)[a]	24 (8)
PF Ratio at Diagnosis, median, (IQR)	141 (90–203)
PRISM-III Score, median (IQR)	9 (4–14)
In-hospital Mortality, n (%)	46 (15)
ICU Length of Stay, days, median (IQR)	10 (7–19)
Hospital Length of Stay, days, median (IQR)	18 (11–28)
Ventilator Free Days, days, median (IQR)[b]	20 (6–23)

[a] May be less than expected as entity was an exclusion criteria for one or more studies combined to form this cohort

[b] Defined as the number of days out of 28 from day of PARDS diagnosis that the patient did not require invasive mechanical ventilation, all who died receive a value of 0 days.

Table 2

Comparison of Demographic and Clinical Factors between LTVV and non-LTVV groups with LTVV defined as TV ≤6.5mL/kg IBW

	Hour 0			Hour 24		
Factor	**≤ 6.5mL/kg**	**>6.5mL/kg**	**p-value**	**≤ 6.5mL/kg**	**>6.5mL/kg**	**p-value**
Gender, n (%)			0.16			0.16
Male	25 (27)	67 (73)		37 (29)	89 (71)	
Female	28 (37)	47 (63)		40 (38)	65 (62)	
Age, median (IQR), years	1.7 (0.2–6.3)	2.3 (0.3–10)	0.6	2 (0.3–8)	4 (0.5–11)	0.5
Weight Classification[a]			**0.02**			0.8
Not Overweight	21 (38)	34 (62)		13 (24)	42 (76)	
Overweight	3 (11)	24 (89)		7 (26)	20 (74)	
PEEP[b], median (IQR), cmH_2O	6 (5–10)	6 (5–10)	0.6	6 (5–8)	6 (5–10)	0.6
PIP[b], median (IQR), cmH_2O	28 (23–32)	27 (24–34)	0.85	28 (23–34)	28 (24–32)	0.6
ARDS Severity, n (%)			0.9			0.96
Mild	16 (33)	32 (67)		21 (33)	43 (67)	
Moderate	22 (32)	46 (68)		36 (34)	69 (66)	
Severe	15 (29)	36 (71)		20 (32)	42 (68)	
PRISM-III Score, median (IQR)	10 (4–15)	8 (3–13)	0.5	8 (4–14)	8 (4–14)	0.5
Study Period, n (%)			0.18			0.16
Before 2006	52 (33)	106 (67)		49 (37)	83 (63)	
After 2006	1 (11)	8 (89)		28 (28)	71 (71)	

[a] Weight Classification in patients >2 years old based on admission weight and height

[b] PEEP = positive end expiratory pressure; PIP = peak inspiratory pressure

Table 3

Comparison of Demographic and Clinical Factors between LTVV and non-LTVV groups with LTVV defined as TV ≤8mL/kg IBW

	Hour 0			Hour 24		
Factor	**≤ 8mL/kg**	**>8mL/kg**	**p-value**	**≤ 8mL/kg**	**>8mL/kg**	**p-value**
Gender, n (%)			0.16			**0.03**
Male	49 (53)	43 (47)		37 (40)	55 (60)	
Female	48 (63)	27 (37)		43 (57)	32 (43)	
Age, median (IQR), years	1.8 (0.2–8.2)	2.4 (0.3–10)	0.44	1.7 (0.2–7.7)	2.4 (0.3–10.3)	0.16
Weight Classification[a]			**0.05**			0.3
Not Overweight	35 (64)	20 (36)		22 (40)	33 (60)	
Overweight	11 (41)	16 (59)		14 (52)	13 (48)	
PEEP[b], median (IQR), cmH_2O	5.5 (5–8)	6 (5–10)	0.4	5 (5–8)	6 (5–10)	0.09
PIP[b], median (IQR), cmH_2O	27 (23–32)	29 (25–33)	0.3	27 (23–34)	28 (24–32)	0.85
ARDS Severity, n (%)			0.28			0.91
Mild	32 (67)	16 (33)		38 (59)	26 (41)	
Moderate	39 (57)	29 (43)		65 (61)	40 (39)	
Severe	26 (51)	25 (49)		36 (58)	26 (42)	
PRISM-III Score, median (IQR)	9 (4–14)	10 (3–15)	0.74	7 (3–12)	10 (4–16)	0.1
Study Period, n (%)			0.13			**<0.01**
Before 2006	94 (59)	64 (41)		89 (67)	44 (33)	
After 2006	3 (33)	6 (67)		50 (51)	49 (49)	

[a] Weight Classification in patients >2 years old based on admission weight and height

[b] PEEP = positive end expiratory pressure; PIP = peak inspiratory pressure