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Association of Patient Weight Status with Plasma Surfactant Protein D, a Biomarker of Alveolar Epithelial Injury, in Children with Acute Respiratory Failure

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Abstract

Aims and Objectives: Alveolar epithelial injury is a key determinant of acute respiratory failure (ARF) severity. Plasma surfactant protein-D (SP-D), a biomarker of alveolar epithelial injury, is lower in obese adults with ARF compared to their lean peers. We aimed to determine if children with ARF have similar variance in plasma SP-D associated with their weight status on admission.

Methods: Plasma SP-D was measured on days 0, 1 or 2 in children (1–18 years) with ARF enrolled in the Genetic Variation and Biomarkers in Children with Acute Lung Injury (*BALI*) and *RESTORE* studies. Weight classification (underweight, normal, overweight, obese) was based on

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body mass index or weight-for-height z-scores. Associations between weight group and SP-D on each day were tested.

Results: Inclusion criteria were met in 212 subjects, 24% were obese. There were no differences among weight groups in SP-D levels on days 0 and 1. However, on day 2, there was a statistically significant linear trend for lower SP-D levels as weight increased in both the univariate analysis (p=0.02) and when adjusting for age, ethnicity, and diagnosis of PARDS (p=0.05).

Conclusions: Obesity was associated with lower plasma SP-D levels on day 2 of ARF. This finding may be explained by altered ARF pathogenesis in obese individuals or a reduced incidence of ventilator induced lung injury.

Keywords

acute respiratory distress syndrome; acute respiratory failure; pediatric; obesity; mechanical ventilation; surfactant protein D; body mass index; children; alveolar epithelial injury

Introduction

Pediatric acute respiratory failure and its most severe form, pediatric acute respiratory distress syndrome (PARDS), include some of the most critically ill children cared for in the pediatric intensive care unit (PICU). Mortality is high in children with ARF, particularly in those with PARDS(1–3). PARDS survivors also face significant morbidity, with approximately one third of survivors having abnormal pulmonary function testing and reduced quality of life up to 1 year after illness(4). Obesity is an increasing epidemic that poses a multitude of health risks; however, in ARDS/PARDS, the relationship between obesity and outcomes is more complex. Obese adults and children with ARDS/PARDS paradoxically have similar, or better, survival compared to lean patients, despite often requiring longer periods of mechanical ventilation(5–8). This weight focused variability in outcomes may be due to either the pathogenesis of acute respiratory failure or the interaction of the patient with mechanical ventilation support, or both.

Surfactant protein D (SP-D), produced primarily by alveolar type II cells in the lung epithelium, participates in pulmonary immunity and homeostasis and has been used to detect short-term changes in lung integrity(9,10). Its expression is upregulated in response to lung injury or infection(11), congruent with increased epithelial permeability. As a result, SP-D levels in the blood are elevated when lung epithelial injury is present(12,13). Plasma SP-D levels have been widely used as a biomarker of lung injury, particularly alveolar epithelial injury(14,15). In adults and children with acute lung disease, plasma SP-D levels increase with the severity of lung injury and are higher in those with worse outcomes, including longer duration of mechanical ventilation and death(16–21). Additionally, plasma SP-D levels increase over time in ARDS/PARDS patients with peak levels between days 3 and 7 of illness(13,17,18,22).

The objective of this study was to evaluate whether the plasma SP-D levels on days 0, 1 and 2 of acute respiratory failure differed among underweight, appropriate weight, overweight, and obese children. We hypothesized that patients who were overweight or obese would have lower levels of plasma SP-D than those who were lean.

Methods and Materials

Design, Setting and Patients:

This was a secondary analysis of children enrolled in the *Genetic Variation and Biomarkers in Children with Acute Lung Injury* (*R01HL095410*, *BALI*) study, an ancillary study to the *Protocolized Sedation vs Usual Care in Pediatric Patients Mechanically Ventilated for Acute Respiratory Failure* (*RESTORE*, HL086622/HL086649) clinical trial(17,23). *RESTORE* was executed at 31 U.S. Pediatric Intensive Care Units (PICUs) from 2009 to 2013. Twenty-two of the 31 *RESTORE* participating PICUs also participated in *BALI*. All participating institutions obtained institutional review board approval and informed consent from the legal guardian of participating patients. *RESTORE* enrolled 2,449 children 2 weeks to 17 years old receiving invasive mechanical ventilator support for at least 24 hours for acute airways and/or parenchymal lung disease; 549 of these subjects were co-enrolled in the *BALI* study. *BALI* was designed to examine the association of specific plasma protein biomarkers or genetic variants with the development of PARDS. A patient's weight status did not affect inclusion or exclusion in these studies.

Surfactant Protein D (SP-D) was measured in the first plasma sample taken after *BALI* enrollment. Plasma SP-D was assayed in duplicate by an ELISA (Yamasa Corporation) which is highly specific for SP-D (<0.3% cross-reactivity with human mannose binding lectin or SP-A)(24). For this analysis we included those with an SP-D measurement taken on either the day of intubation (day 0), or on one of the following 2 days. We included all children ages 1 through 17 years from the *BALI* cohort. Those <1 year of age were excluded *a priori* because of growth variability associated with prematurity and variable feeding schedules (e.g. timing of solid food initiation). Subjects without an admission height and weight were also excluded.

Measurements and Data Collection

Weight-for-height (ages 1 to <2 years) or body mass index (BMI, ages 2–18 years) z-scores were calculated using hospital admission height and weight and corrected for age and gender based on the Center for Disease Control (CDC) (25). To define our four weight groups we utilized the published 2006 CDC weight group definitions in order to align with current practice within the nutrition/obesity discipline: underweight (z-score <−1.89, ≤3rd percentile), appropriate weight (z-score −1.89 to +1.04, 4th to 84th percentile), overweight (z-score +1.05 to +1.65, 85th–95th percentile), and obese (z-score ≥ +1.65, >95th percentile) (26). Patients with z-scores less than −5 or greater than +5 were excluded as z-scores outside of this range either represent pathology for which regular growth charts cannot be used (e.g. dwarfism) or measurement error.

Other data collected included age, gender, race, ethnicity, prior pulmonary disease, immune compromised status, pediatric risk of mortality-III (PRISM-III) score(27) and presence of PARDS during the admission. PARDS was defined using oxygenation index (OI) or oxygen saturation index (OSI) as described by the Pediatric Acute Lung Injury Consensus Conference(28) except that all patients defined as having PARDS also had bilateral infiltrates as described in the primary *BALI* analyses(29,30).

Outcomes Measures and Statistical Analysis

Baseline characteristics and clinical outcomes of the subjects in each weight group were compared. Chi-square comparison was used for categorical variables. For evaluation of continuous variables across the weight groups, both a Kruskal-Wallis test with a post-hoc Dunn's test for multiple pairwise comparisons(31), and a Kruskal-Wallis non-parametric trend test were used(32). Because SP-D levels were not normally distributed, log transformed plasma SP-D levels were used for all analyses. Two subjects in the cohort had a value of 0 for their SP-D concentrations, therefore, 0.1 ng/mL was added to all subject's SP-D values to allow for log transformation. Baseline characteristics and clinical outcomes were evaluated for association with SP-D levels on any of the study days using a Student's t test or analysis of variance (ANOVA) for categorical variables and by linear regression for continuous variables.

To determine if there was an association between a subject's weight status and the concentration of plasma SP-D on any day within the first 3 days of acute respiratory failure, we first evaluated the presence of an interaction between weight group and day of SP-D measurement by linear regression. Secondly, for each blood collection time point (day 0, 1 or 2) we examined the plasma SP-D levels across the four weight groups using a linear regression with a post-regression linear trend test. Multivariate linear regression was used to determine whether associations between plasma SP-D levels and subject weight group were confounded by age, ethnicity, or diagnosis of PARDS. These confounders were selected *a priori* because of known associations with BMI and/or etiology of lung injury. A p-value of ≤ 0.05 was considered as being statistically significant in all analyses. All analyses were performed using STATA software, version 15.1 (StataCorp, College Station, Texas).

Results

Of the 549 subjects, 212 met the age inclusion criteria, had weight and height measurements, and had a plasma SP-D measurement between days 0–2. Those excluded were 173 subjects who were less than 1 year old, 46 subjects with insufficient data to calculate a weight-for-height or BMI z-score, 8 with likely erroneous height or weight measurements , and an additional 110 subjects that had weight and height measurements but did not have a SP-D measurement on any of the first 3 study days. Supplemental Table e-1 reports the demographic data of those with SP-D measurements within the first three days (included in subsequent analyses) and those without an SP-D measurement during this period of time; there were no statistically significant differences between these two groups. The distribution of subjects in the cohort examined was 9% in the underweight, 54% in the appropriate weight, 13% in the overweight, and 24% in the obese group. The proportion of subjects in each weight group remained the same independent of whether SP-D was measured on study day 0, 1 or 2 (p=0.46).

Table 1 compares patient characteristics between the weight groups. The overall in-hospital mortality for the cohort was 11%. PARDS was diagnosed in 155 (77%) of subjects; 137 (64%) met PARDS criteria on the day of intubation (study day 0) and 150 (70%) met PARDS criteria by day 2. There were no statistically significant differences between weight groups with regard to age, gender, race, ethnicity, prior pulmonary disease, immune

compromised status, etiology of acute respiratory failure, diagnosis of PARDS, or death. Duration of mechanical ventilation and hospital length of stay differed across the weight groups (Kruskal-Wallis, p = 0.04 and p = 0.05, respectively). Obese patients had longer durations of mechanical ventilation (median 13 days, IQR 5–24 days) compared to the underweight (median 5 days, IQR 4–14 days, p=0.01, Dunn's test), the appropriate weight (median 7 days, IQR 4–12 days, p=0.006), and the overweight (median 8 days, IQR 4–11 days, p=0.03). The hospital length of stay was also longer in the obese (median 27 days, IQR 15–38 days) compared to the underweight (median 15 days, IQR 10–29 days, p=0.04), the appropriate weight (median 16 days, IQR 10–31 days, p=0.005), and the overweight (median 15 days, IQR 10–24 days, p=0.02).

SP-D levels were significantly different across days (Kruskal-Wallis, p < 0.001). Dunn's post hoc test revealed that SP-D levels were higher on day 2 (median 16 ng/mL, IQR 11–27 ng/mL) compared to day 0 (median 11.3 ng/mL, IQR 6–26 ng/mL, p = 0.01) and day 1 (median 10 ng/mL, IQR 5–19 ng/mL, p = 0.0001). This was consistent with a nonparametric trend test indicating a statistically significant trend for higher SP-D levels later in the illness course (p < 0.001), Figure 1. Subjects with early SP-D measurements (day 0 or 1) were no different from those with measurements on day 2 with regard to demographics, etiology of respiratory failure, or PRISM-III score. Evaluating each study day separately, SP-D measurements were not associated with age, gender, a history of prior or chronic lung disease, immune compromised state or PRISM-III score on any study day. For those with SP-D measured on day 2, SP-D measurements were lower in Hispanic/Latino subjects (median SP-D of 11.0 ng/mL, IQR 5.3–15.9 ng/mL, n=15 vs. 17.0 ng/mL, IQR 11.7–32.8 ng/mL, n=70 in non-Hispanic/Latinos, p=0.01). SP-D measurements were not different between those with and without a PARDS diagnosis on or before the day of SP-D measurement.

Analysis using linear regression demonstrated a statistically significant interaction between day of SP-D measurement and weight group (p=0.005). Figure 2 shows the SP-D measurements for each study day stratified by the weight groups. The median plasma SP-D on days 0 and 1 was not statistically significantly different between the weight groups (Fig. 2A, 2B). On day 2, however, SP-D levels were significantly different across the weight groups (Figure 2 C, Kruskal-Wallis, p=0.03). Dunn's post hoc test revealed that SP-D levels in the overweight (median 11 ng/mL, IQR 10–12 ng/mL) and the obese (median 14 ng/mL, IQR 6–21 ng/mL) were significantly lower than those who were underweight (median 34 ng/mL, IQR 20–50 ng/mL, p = 0.006 and p=0.009, respectively). Compared to those of appropriate weight, SP-D levels in the overweight group (median 11 ng/mL, IQR 10–12 ng/mL) were significantly lower than those in appropriate weight group (median 16 ng/mL, IQR 12–28 ng/mL, p = 0.04). While the obese group had lower SP-D levels (median 14 ng/mL, IQR 6–21 ng/mL) compared to the appropriate weight group, this comparison did not reach statistical significance (p=0.06). The linear regression trend test indicated that there was a statistically significant trend for lower SP-D levels as weight increased (Table 2, p=0.02).

In multivariate linear regression analysis adjusted for age, ethnicity, and diagnosis of PARDS, there remained a statistically significant interaction between weight group and day

of SP-D measurement (p = 0.01). In addition, on day 2 weight group continued to have a statistically significant linear trend for decreasing SP-D levels as weight category increased, despite covariate adjustment (p = 0.05 by post linear regression trend test, Table 2).

Discussion

The degree of alveolar epithelial cell injury is a key determinant of severity as well as short- and long-term outcomes in acute respiratory failure and also in its most severe form, ARDS/PARDS(33). SP-D, a protein secreted by type II alveolar cells(9), is one of the best characterized markers of alveolar epithelial injury in adults and children with acute respiratory failure and ARDS/PARDS(13,17). In this study, we found that in children with acute respiratory failure, plasma SP-D levels are higher on day 2 of illness compared to the day of intubation, and this elevation of SP-D is at least partially dependent on an individual's weight status. While plasma SP-D levels did not differ between weight groups on days 0 or 1, plasma SP-D levels on day 2 decreased with increasing weight, with the highest concentrations in the underweight and the lowest levels observed in obese patients.

To our knowledge this is the first evaluation of the association of weight status with biomarkers of acute lung injury in children. Our finding of lower SP-D levels in obese children later in the disease course is consistent with adult findings. Stapleton et al. evaluated biomarkers of lung injury in over 1,400 adult ARDS patients. They found that increasing BMI was associated with lower levels of plasma SP-D and that those with higher BMI had a blunted rise in SP-D over time compared to those of normal weight(34). These data suggest that obese patients with ARDS exhibit reduced alveolar epithelial injury that persists over time.

One hypothesis to explain the difference in alveolar epithelial injury between obese and non-obese patients is the interaction between the patient and the mechanical ventilator. Lung inflation is dependent on transpulmonary pressure, defined as the difference between airway pressure and pleural pressure(35). The obese individual has increased chest wall mass which leads to elevated pleural pressures(36,37). For obese patients with acute respiratory failure, a greater percentage of ventilator work is used to overcome the elevated pleural pressure, subsequently reducing the pressure exposure at the alveolar level, and mitigating alveolar overdistension, one of the leading contributors to poor outcomes in ARDS(38). Our finding of lower plasma SP-D levels in obese children with acute respiratory failure supports this potential explanation for the finding of reduced mortality in obese ARDS/PARDS subjects. As such, our work underscores the vital need to investigate the interaction of weight with mechanical ventilation mechanics and the risk of ventilator induced lung injury in children. While this cohort did not provide ventilator parameters, such as tidal volume, future studies evaluating ventilator induced lung injury and the association with biomarkers of injury should include ventilator data at the same time as biomarker measurement to inform high quality analysis and reduce confounding.

Interestingly, several animal and human adult studies have found an association between the level of SP-D expression and BMI (39–41), and there is evidence which suggests a genetic link between weight and SP-D expression (39). In a mouse model, SP-D deficient mice are

overweight and have higher fat deposition compared to wild type mice(39,42). In studies of healthy human adults, plasma SP-D levels are negatively correlated with BMI of the subjects (39–41,43). In one of these studies, however, this relationship was age dependent and most prevalent in the elderly(39). In our study, the association between weight and SP-D levels was only present on day 2 of illness. However our study examines SP-D levels during an acute phase of illness and it is possible the impact of BMI on SP-D levels may have been obscured by the acute response to illness on days 0 and 1. Our study also found that SP-D levels were lower in patients of Hispanic/Latino ethnicity on day 2. Although the number of patients of Hispanic/Latino ethnicity in our group was small this finding suggests that future studies using SP-D as a surrogate biomarker of lung injury should account for race and ethnicity in addition to weight status. The association between plasma SP-D level and weight group on day 2 of illness observed in this study remained statistically significant even when accounting for ethnicity.

This study has some limitations. BMI and weight-for-height z-scores may be inaccurate in patients who are critically ill because of fluid resuscitation or erroneous measurements of height in patients who were supine. In this study, we utilized hospital admission weight to minimize the impact of fluid resuscitation. Secondly, while this is the first evaluation of the association of weight with a biomarker of alveolar epithelial injury in pediatric acute respiratory failure, our results would have benefitted from a larger sample size. Since our cohort was sub-divided into 4 weight groups and SP-D levels were measured only once per patient and across 3 different study days, the proportions of subjects in each evaluation were too small for robust multivariate analyses. Lastly, with each subject only having SP-D measured once, we lack the ability to evaluate rate of change of SP-D between the weight groups, which may be quite informative. Further prospective studies evaluating biomarkers of lung injury over time and with more detailed data on mechanical ventilation strategies utilized would likely enhance our knowledge of weight associated pathogenesis of pediatric acute lung injury.

Conclusion

In children with acute respiratory failure, the elevation in plasma SP-D, a biomarker of alveolar epithelial injury, is dependent, at least in part, on the weight of the patient, particularly later in the illness course. Two days after intubation, the underweight demonstrate the highest concentration of plasma SP-D, with the lowest SP-D levels found in the obese. Our findings indicate that weight may play a role in the pathogenesis of acute lung injury or in the patient-ventilator interaction, or both. In order to reduce the morbidity and mortality of ARDS/PARDS, prospective studies utilizing bedside measurements of lung and respiratory system mechanics, such as esophageal manometry and electrical impedance tomography, combined with biomarkers of lung injury may be necessary. Improved understanding of the pathogenesis of acute lung injury and how mechanical ventilation supports, or possibly harms, patients with different body habitus, chest wall and lung mechanics will allow more personalized care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References:

1. Flori HR, Glidden D, Rutherford G, Matthay MA. Pediatric Acute Lung Injury: Prospective Evaluation of Risk Factors Associated with Mortality. Am J Respir Crit Care Med. 2005;171:995–1001. [PubMed: 15618461]
2. Erickson S, Schibler A, Numa A, Nuthall G, Yung M, Pascoe E, et al. Acute lung injury in pediatric intensive care in Australia and New Zealand—A prospective, multicenter, observational study. Pediatr Crit Care Med. 2007;8(4):317–23. [PubMed: 17545931]
3. Khemani RG, Smith L, Lopez-Fernandez YM, Kwok J, Morzov R, Klein MJ, et al. Paediatric acute respiratory distress syndrome incidence and epidemiology (PARDIE): an international, observational study. Lancet Respir Med. 2019;7(2):115–28. [PubMed: 30361119]
4. Ward SL, Turpin A, Spicer AC, Treadwell MJ, Church GD, Flori HR. Long-Term Pulmonary Function and Quality of Life in Children After Acute Respiratory Distress Syndrome: A Feasibility Investigation. Pediatr Crit Care Med. 2017;18(1):e48–55. [PubMed: 28060170]
5. Gong MN, Bajwa EK, Thompson BT, Christiani DC. Body mass index is associated with the development of acute respiratory distress syndrome. Thorax. 2010 1;65(1):44–50. [PubMed: 19770169]
6. Morris AE, Stapleton RD, Rubenfeld GD, Hudson LD, Caldwell E, Steinberg KP. The association between body mass index and clinical outcomes in acute lung injury. Chest. 2007 3;131(2):342–8. [PubMed: 17296631]
7. O'Brien JM, Phillips GS, Ali N a., Lucarelli M, Marsh CB, Lemeshow S. Body mass index is independently associated with hospital mortality in mechanically ventilated adults with acute lung injury. Crit Care Med. 2006 1;34(3):738–44. [PubMed: 16521268]
8. Ward SL, Gildengorin V, Valentine SL, Sapru A, Curley MAQ, Thomas N, et al. Impact of Weight Extremes on Clinical Outcomes in Pediatric Acute Respiratory Distress Syndrome. Crit Care Med. 2016;44(11):2052–9. [PubMed: 27355525]
9. Crouch EC. Structure, biologic properties, and expression of surfactant protein D (SP-D). Biochim Biophys Acta - Mol Basis Dis. 1998;1408(2):278–89.
10. Kishore U, Greenhough TJ, Waters P, Shrive AK, Ghai R, Kamran MF, et al. Surfactant proteins SP-A and SP-D: Structure, function and receptors. Mol Immunol. 2006;43(9):1293–315. [PubMed: 16213021]
11. Foo S-S, Reading PC, Jaillon S, Mantovani A, Mahalingam S. Pentraxins and Collectins: Friend or Foe during Pathogen Invasion? Trends Microbiol. 2015;23(12):799–811. [PubMed: 26482345]
12. Ju C-R, Liu W, Chen R-C. Serum Surfactant Protein D: Biomarker of Chronic Obstructive Pulmonary Disease. Dis Markers. 2012;32:281–7. [PubMed: 22674408]
13. Eisner M, Parsons P, Matthay M, Ware L, Greene K. Plasma surfactant protein levels and clinical outcomes in patients with acute lung injury. Thorax. 2003 11;58(11):983–8. [PubMed: 14586055]
14. Calfee CS, Janz DR, Bernard GR, May AK, Kangelaris KN, Matthay M a., et al. Distinct Molecular Phenotypes of Direct Versus Indirect ARDS in Single and Multi-Center Studies. CHEST J. 2014;147(6):1539–48.

15. Park J, Pabon M, Choi AMK, Siempos II, Fredenburgh LE, Baron RM, et al. Plasma surfactant protein-D as a diagnostic biomarker for acute respiratory distress syndrome: validation in US and Korean cohorts. BMC Pulm Med. 2017;17(1):204. [PubMed: 29246207]
16. Todd DA, Marsh MJ, George A, Henderson NG, Barr H, Sebastian S, et al. Surfactant phospholipids, surfactant proteins, and inflammatory markers during acute lung injury in children. Pediatr Crit Care Med. 2010;11(1):82–91. [PubMed: 19550365]
17. Dahmer MK, Flori HR, Sapru A, Kohne J, Weeks HM, Curley MAQ, et al. Surfactant Protein D is Associated with Severe Pediatric Acute Respiratory Distress Syndrome, Prolonged Ventilation, and Death in Children with Acute Respiratory Failure. CHEST J. 2020;In press.
18. Determann RM, Royakkers AANM, Haitsma JJ, Zhang H, Slutsky AS, Ranieri VM, et al. Plasma levels of surfactant protein D and KL-6 for evaluation of lung injury in critically ill mechanically ventilated patients. BMC Pulm Med. 2010;10(1):1–9. [PubMed: 20051135]
19. Ware LB, Koyama T, Billheimer DD, Wu W, Bernard GR, Thompson BT, et al. Prognostic and Pathogenetic Value of Combining Clinical and Biochemical Indices in Patients With Acute Lung Injury. Chest. 2010 2 26;137(2):288–96. [PubMed: 19858233]
20. Calfee CS, Ware LB, Glidden DV, Eisner MD, Parsons PE, Thompson BT, et al. Use of risk reclassification with multiple biomarkers improves mortality prediction in acute lung injury. Crit Care Med. 2011 4;39(4):711–7. [PubMed: 21283009]
21. Jensen J-US, Itenov TS, Thormar KM, Hein L, Mohr TT, Andersen MH, et al. Prediction of non-recovery from ventilator-demanding acute respiratory failure, ARDS and death using lung damage biomarkers: data from a 1200-patient critical care randomized trial. Ann Intensive Care. 2016;6(1):114. [PubMed: 27873291]
22. Greene KE, Wright J, Steinberg K, Ruzinski J, CaldwellL E, Wong W, et al. Serial Changes in Surfactant-associated Proteins in Lung and Serum before and after Onset of ARDS. Am J Respir Crit Care Med. 1999 12 1;160(6):1843–50. [PubMed: 10588595]
23. Curley M, Wypij D, Watson R. Protocolized sedation vs usual care in pediatric patients mechanically ventilated for acute respiratory failure: A randomized clinical trial. JAMA. 2015 1 27;313(4):379–89. [PubMed: 25602358]
24. Nagae H, Takahashi H, Kuroki Y, Honda Y, Nagata A, Ogasawara Y, et al. Enzyme-linked immunosorbent assay using F(ab′)2 fragment for the detection of human pulmonary surfactant protein D in sera. Clin Chim Acta. 1997;266(2):157–71. [PubMed: 9437544]
25. Kuczmarski RJ, Ogden CL, Guo SS, Grummer-Strawn LM, Flegal KM, Mei Z, et al. 2000 CDC Growth Charts for the United States: methods and development. Vital and health statistics. Series 11, Data from the national health survey. 2002. 1–190 p.
26. Barlow SE. Expert Committee Recommendations Regarding the Prevention , Assessment , and Treatment of Child and Adolescent Overweight and Obesity : Summary Report. Pediatrics. 2007;120:S164–92. [PubMed: 18055651]
27. Pollack MM, Patel KM, Ruttimann UE. The pediatric risk of mortality III— Acute physiology score (PRISM III-APS): A method of assessing physiologic instability for pediatric intensive care unit patients. J Pediatr. 1997 10;131(4):575–81. [PubMed: 9386662]
28. Khemani R, Smith LS, Zimmerman JJ, Erickson S. Pediatric Acute Respiratory Distress Syndrome: Consensus Recommendations From the Pediatric Acute Lung Injury Consensus Conference. Pediatr Crit Care Med. 2015;16(5):428–39. [PubMed: 25647235]
29. Dahmer MK, Quasney MW, Sapru A, Gildengorin G, Curley MAQ, Matthay MA, et al. Interleukin-1 Receptor Antagonist Is Associated With Pediatric Acute Respiratory Distress Syndrome and Worse Outcomes in Children With Acute Respiratory Failure. Pediatr Crit Care Med. 2018;19(10):930–8. [PubMed: 30095747]
30. Flori H, Sapru A, Quasney MW, Gildengorin G, Curley MAQ, Matthay MA, et al. A prospective investigation of interleukin-8 levels in pediatric acute respiratory failure and acute respiratory distress syndrome. Crit Care. 2019;23(1):128. [PubMed: 30995942]
31. Dinno A Nonparametric pairwise multiple comparisons in independent groups using Dunn's test. Stata J. 2015;15(1):292–300.
32. Cuzick J A wilcoxon-type test for trend. Stat Med. 1985 Jan 1;4(1):87–90.

33. Matthay MA, Zemans RL, Zimmerman GA, Arabi YM, Beitler JR, Mercat A, et al. Acute respiratory distress syndrome. Nat Rev Dis Prim. 2019;5(1):18. [PubMed: 30872586]
34. Stapleton RD, Dixon AE, Parsons PE, Ware LB, Suratt BT. The association between BMI and plasma cytokine levels in patients with acute lung injury. Chest. 2010 9;138(3):568–77. [PubMed: 20435656]
35. Mead J, Takishima T, Leith D. Stress distribution in lungs: a model of pulmonary elasticity. J Appl Physiol. 1970;28(5):596–608. [PubMed: 5442255]
36. Behazin N, Jones SB, Cohen RI, Loring SH. Respiratory restriction and elevated pleural and esophageal pressures in morbid obesity. J Appl Physiol. 2010 1 6;108(1):212–8. [PubMed: 19910329]
37. Davidson WJ, Mackenzie-Rife KA, Witmans MB, Montgomery MD, Ball GDC, Egbogah S, et al. Obesity negatively impacts lung function in children and adolescents. Pediatr Pulmonol. 2014;49(10):1003–10. [PubMed: 24167154]
38. The Acute Respiratory Distress Syndrome Network. Ventilation With Lower Tidal Volumes As Compared With Tradtional Tidal Volumes For Acute Lung Injury And The Acute Respiratory Distress Syndrome. N Engl J Med. 2000;342(18):1301–8. [PubMed: 10793162]
39. Sorensen GL, Hjelmborg J v. B, Leth-Larsen R, Schmidt V, Fenger M, Poulain F, et al. Surfactant Protein D of the Innate Immune Defence is Inversely Associated with Human Obesity and SP-D Deficiency Infers Increased Body Weight in Mice. Scand J Immunol. 2006 12 1;64(6):633–8. [PubMed: 17083619]
40. Zhao XM, Wu YP, Wei R, Cai HX, Tornoe I, Han JJ, et al. Plasma Surfactant Protein D Levels and the Relation to Body Mass Index in a Chinese Population. Scand J Immunol. 2007 7 1;66(1):71–6. [PubMed: 17587348]
41. Jawed S, Mannan N, Qureshi M. Association of Surfactant Protein-D with Obesity. J Ayub Med Coll Abbottabad. 2016;28(3):489–92. [PubMed: 28712219]
42. Stidsen JV, Khorooshi R, Rahbek MKU, Kirketerp-Møller KL, Hansen PBL, Bie P, et al. Surfactant Protein D Deficiency in Mice Is Associated with Hyperphagia, Altered Fat Deposition, Insulin Resistance, and Increased Basal Endotoxemia. PLoS One. 2012 4 11;7(4):e35066. [PubMed: 22509382]
43. Ortega FJ, Pueyo N, Moreno-Navarrete JM, Sabater M, Rodriguez-Hermosa JI, Ricart W, et al. The lung innate immune gene surfactant protein-D is expressed in adipose tissue and linked to obesity status. Int J Obes. 2013;37(12):1532–8.

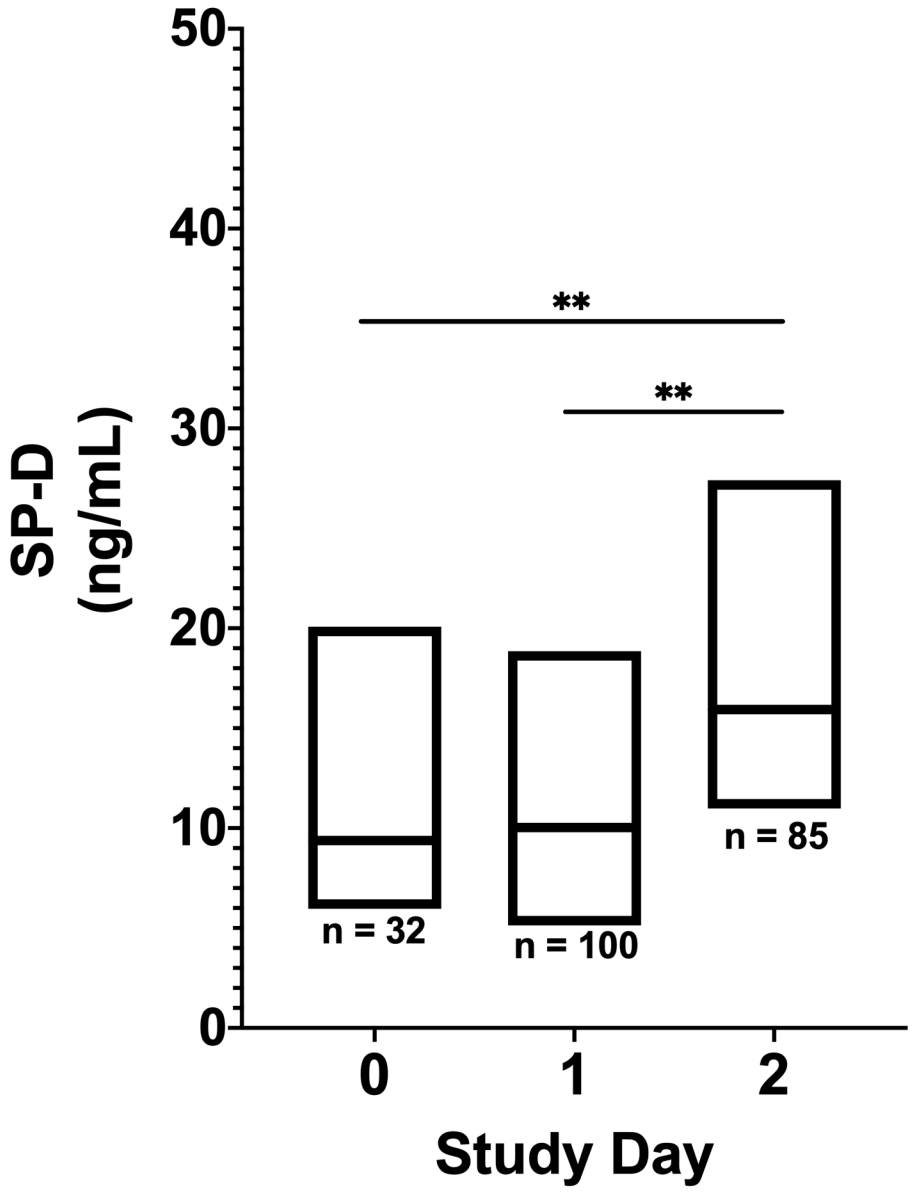

Figure 1: Plasma SP-D levels measured on study days 0, 1 or 2

Plasma SP-D levels were measured once per subject. Boxes represent the median and interquartile range. Measurements on day 2 were statistically significantly higher than those measured on prior days (** $p \leq 0.01$, Dunn's post-hoc multiple pairwise comparisons).

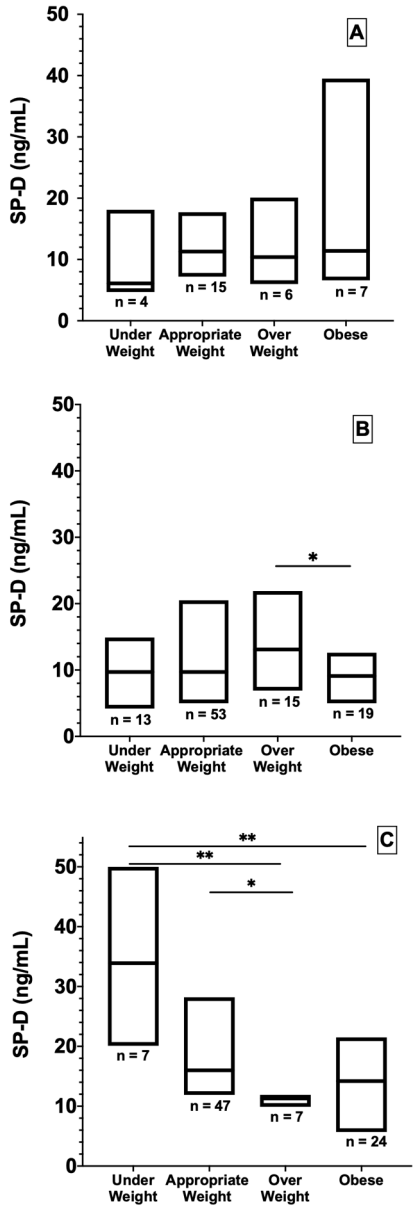

Figure 2: SP-D levels stratified by weight group.

Plasma SP-D measured on study day 0 (panel A), study day 1 (panel B), or on study day 2 (panel C). Plasma SP-D levels were not different among the weight groups on study days 0 or 1. On study day 2 the plasma SP-D levels are different between weight groups ($p = 0.03$, Kruskal-Wallis) with the highest level in the underweight group and lower in the overweight and obese (** $p \leq 0.01$, * $p \leq 0.05$, Dunn's post-hoc multiple pairwise comparisons).

Table 1:

Patient Characteristics by Weight Group

	Whole Cohort n = 212	Underweight n = 19	Appropriate Weight n = 115	Overweight n = 28	Obese n = 50
Age, years, median (IQR)	8.3 (4–14)	10.1 (4–16)	8.3 (3–14)	7.7 (4–14)	8.1 (4–14)
Male, n (%)	119 (54)	8 (42)	58 (50)	19 (68)	30 (60)
Race, n (%)					
Caucasian	152 (72)	10 (53)	89 (77)	18 (64)	35 (70)
African American	31 (15)	4 (21)	13 (11)	6 (21)	8 (16)
Asian/Pacific Islander	12 (6)	2 (10)	8 (7)	2 (7)	2 (4)
American Indian	2 (1)	1 (5)	0 (0)	0 (0)	1 (2)
Multiracial	11 (5)	1 (5)	5 (4)	2 (7)	3 (6)
Other/ Declined to report	2 (1)	1 (5)	0 (0)	0 (0)	1 (2)
Hispanic/Latino, n (%)	46 (22)	2 (11)	21 (18)	9 (32)	14 (28)
Any Past Medical History, n (%)	126 (59)	10 (53)	64 (55)	18 (64)	34 (68)
Prior Pulmonary Disease, n (%)	70 (33)	7 (37)	35 (30)	10 (36)	18 (36)
Immune compromised, n (%)	10 (5)	2 (11)	4 (3)	1 (4)	3 (6)
Respiratory Failure Etiology, n (%)					
Pneumonia	84 (40)	5 (26)	51 (44)	7 (25)	21 (42)
Sepsis	52 (25)	5 (26)	23 (20)	11 (39)	13 (26)
Reactive Airway Disease	28 (13)	3 (16)	15 (13)	4 (14)	6 (12)
Aspiration	15 (7)	1(5)	7 (6)	4 (14)	3 (6)
Bronchiolitis	11 (5)	2 (11)	8 (7)	0 (0)	1 (2)
Other[a]	22 (10)	3 (16)	11 (10)	2 (7)	6 (12)
ARDS Diagnoses, n (%)	155 (73)	12 (63)	81 (70)	19 (68)	37 (74)
PRISM-III Score, median (IQR)	10 (5–14)	10 (4–15)	10 (5–14)	10 (6–15)	11 (6–16)
Duration of Mechanical Ventilation, days, median (IQR)[b]	8 (4–15)	5 (4–11)	7 (4–12)	7 (4–12)	13 (5–24)
PICU Length of Stay, days, median (IQR)	11 (7–19)	11 (7–18)	10 (7–17)	11 (5–15)	18 (9–26)
Hospital Length of Stay, days, median (IQR)	18 (10–34)	16 (10–29)	16 (10–31)	15 (10–24)	27 (15–38)
Died, n (%)	24 (11)	3 (16)	12 (10)	3 (11)	6 (12)

[a]Other includes croup, thoracic trauma, acute chest syndrome, pulmonary edema, bone marrow transplant related injury, transfusion related injury, and pulmonary hemorrhage

[b]Duration of mechanical ventilation was capped at 28 days such that any subject still intubated at 28 days received a value of 28 and any subject who died received a value of 28

Table 2:

Linear Regression for Day 2 Plasma SP-D levels

Variable	Univariate Analysis[ℱ] Coefficient (95% CI)	Multivariate Analysis[§] Coefficient (95% CI)
Weight Group		
Underweight	Ref	Ref
Normal Weight	−0.52 (−1.3 to 0.3)	−0.38 (−1.2 to 0.4)
Overweight	−0.84 (−1.9 to 0.2)	−0.67 (−1.7 to 0.3)
Obese	−0.94 (−1.8 to −0.1)	−0.73 (−1.6 to 0.1)
Age (years)	-	0.04 (0.01 to 0.1)
Hispanic/Latino	-	−0.78 (−1.3 to −0.2)
PARDS diagnosis	-	−0.02 (−0.5 to 0.5)

[ℱ] p = 0.02 for linear trend with SP-D levels declining as weight group increases.

[§] p = 0.05 for linear trend with SP-D levels declining as weight group increases.