ORIGINAL RESEARCH

Nutrition practices and outcomes in patients with pediatric acute respiratory distress syndrome

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Abstract

Background: Pediatric acute respiratory distress syndrome (PARDS) remains a significant cause of morbidity and mortality. Evidence suggests enteral nutrition (EN) may be protective in critically ill children.

Methods: This is a retrospective cohort study comparing intubated patients with PARDS who received EEN and those who did not. We included patients aged 2 weeks to 18 years who could receive full nutrition enterally prior to their disease and excluded patients with cyanotic heart disease. Disease severity was captured with oxygenation index (OI), oxygen saturation index (OSI), and pediatric logistic organ dysfunction (PELOD-2). EEN was defined as having received ≥25% of the calculated energy goal enterally within the first 48 h of PARDS diagnosis.

Results: We included 151 patients. Adjusted for age, OI, and OSI, the EEN group had a lower PICU mortality rate (adjusted odds ratio [aOR] = 0.071; 95% CI, 0.009–0.542; $P = 0.011$), had a higher likelihood of PICU discharge (adjusted risk ratio = 1.79; 95% CI, 1.25–2.55; $P = 0.001$), and was more likely to have at least one ventilator-free day (aOR = 3.96; 95% CI, 1.28–12.22; $P = 0.017$). Adjusted for age and PELOD-2, a statistically significant association between the EEN group and lower PICU mortality ($P = 0.033$), shorter PICU LOS ($P < 0.001$), and more ventilator-free days ($P = 0.037$) persisted.

Conclusion: Our study found that EEN was associated with superior mortality rates, PICU LOS, and ventilator-free days in patients with PARDS.

KEYWORDS
critical care, enteral nutrition, parenteral nutrition, pediatrics

CLINICAL RELEVANCY STATEMENT

Our retrospective cohort study showed that early enteral nutrition is associated with lower mortality rates, shorter pediatric intensive care unit length of stay, and more ventilator-free days in intubated children with pediatric acute respiratory disease. These findings continue to strengthen the argument for earlier introduction of enteral nutrition in the critically ill child, but prospective randomized controlled studies are needed to fully evaluate this association.

INTRODUCTION

Pediatric acute respiratory distress syndrome (PARDS) remains a significant cause of morbidity and mortality and only recently has a

pediatric-specific definition been established.[1–6] Despite this standardized definition, marked variation still persists in the management of PARDS.[4–6] Furthermore, very few studies have evaluated specific factors other than respiratory management that potentially mediate outcomes in the PARDS population.

Nutrition therapy in the pediatric intensive care unit (PICU) is one factor that has evolved significantly because of evidence demonstrating that enteral nutrition (EN) is associated with better outcomes in the critically ill child, even more so when initiated earlier in the disease course.[7–9] However, there remains a reluctance to start or a predilection to interrupt EN the more ill a child is despite studies demonstrating that EN is not associated with an increase in morbidity or mortality regardless of severity at the time of presentation.[10–12] Further evidence demonstrates that parenteral nutrition (PN), when started early, has been shown to be of no benefit in adults and is even harmful in critically ill children.[13–15] Ultimately, the severity of the child's clinical status seen in PARDS commonly leads to a delay in starting or interruptions in continuing EN, which can then influence the decision to start PN in the PICU. One study has shown improved mortality in PICU patients with PARDS who received adequate nutrition, but the timing of when nutrition was started in relation to PARDS was not directly addressed.[16]

Therefore, we conducted a retrospective cohort study to determine the association of nutrition delivery practices with outcomes in critically ill children with PARDS. We hypothesized that, in patients with PARDS, receiving early EN (EEN) would be associated with lower PICU mortality, shorter PICU length of stay (LOS), and more ventilator-free days than in patients who did not receive EEN.

METHODS

Study design

We received approval from our institutional review board to conduct a retrospective chart review. Electronic records were abstracted for pediatric patients aged 2 weeks to 18 years who were admitted the PICU between July 1, 2014, and October 31, 2019. We obtained demographic and severity of illness data from the Virtual PICU Systems (VPS, LLC) database and reviewed medical records for nutrition and clinical data. We included patients if they were intubated, met the criteria for PARDS based on the Pediatric Acute Lung Injury Consensus Conference (PALICC) guidelines, and had the capacity to receive full EN prior to their illness.[1] We excluded patients with cyanotic heart disease and those who could not receive full EN at baseline because of underlying chronic gastrointestinal (GI) conditions prior to their PARDS diagnosis. Baseline demographic and anthropometric data were obtained. PARDS severity was classified as mild, moderate, or severe based on the oxygenation index (OI) and/or the oxygen saturation index (OSI) and determined by the first OI/OSI score 6 h after the initial PARDS diagnosis.[1,3] Pediatric logistic organ dysfunction (PELOD-2) scores were also used to capture disease severity.[17]

We collected EN and PN data for 7 days following the diagnosis of PARDS and compared these data with daily nutrition goals. We used the Schofield equation to calculate basal metabolic rate, which was then modified based on the stress of the current illness and interventions to resting energy expenditure (REE). This institutional standard for calculating REE did not change during the period for this study. We recorded energy (kcal) and protein (g) intake from any enteral formula or supplements as well as PN. We also obtained lipid energy from propofol, which was added to the parenteral energy received.

A standardized definition for EEN does not currently exist. Our review of the literature found that EEN commonly varied between 10% and 33% of the energy goal and a timing of within 24 to 96 h of admission or onset of disease in the majority of studies.[7–12] Therefore, we chose to define EEN as previously defined by our research group as receiving 25% of the energy goal within 48 h of the initial PARDS diagnosis.

Data analysis

We calculated the total energy intake in the first 7 days after PARDS diagnosis based on the recorded intake of all enteral formula, supplements, and PN and compared that with the calculated nutrition goals. We categorized patients who received at least 25% of their calculated energy goal enterally within the first 48 h of PARDS diagnosis as having received EEN. We generated descriptive statistics using counts (percent) for categorical variables and medians (interquartile ranges [IQRs]) for continuous variables. For univariable analyses, we compared the EEN and non-EEN groups using the chi-square test or Fisher exact test for categorical variables and Mann-Whitney U test for continuous variables. We used multivariable analyses to adjust for age, PARDS severity (OI/OSI), and disease severity (PELOD-2). For PICU mortality, we utilized a logistic regression model in the multivariable analysis. We applied competing risk analysis to PICU LOS to adjust for mortality by treating PICU discharge and PICU mortality as competing risks, since occurrence of one can prevent the occurrence of the other. We then compared the cumulative incidences at days 50, 100, 150, and 200. For the 28-day ventilator-free days, since there was a large number of zeros, we used a zero-inflated Poisson model, which consist of two parts: a prediction of having at least one ventilator-free day and a prediction of the number of ventilator-free days for those with at least one ventilator-free day. SAS 9.4 and R 3.6.1 were used in the analysis, and $P < 0.05$ was considered statistically significant.

RESULTS

Of the 151 patients who met our inclusion criteria, 80 (53%) were female, 77 (51%) were White, and age ranged from 2 weeks to 18 years and 11 months old with a median age of 4.1 (IQR, 0.63–12.55) years. The median time between PICU admission and PARDS diagnosis was 6.93 h (IQR, 0.18–33.5 h). Forty-one (27%) patients received EEN. The EEN group was younger (median, 1.85 years) than the non-EEN group (median, 6.00 years), but this difference did not reach statistical significance ($P = 0.061$). Those in the EEN group weighed less (median, 10.7 vs 19.6 kg; $P = 0.024$) and were shorter (median, 82.2 vs 107.6 cm; $P < 0.001$). No difference was found between the groups

TABLE 1 Anthropometric, demographic, and PARDS severity of participants

Participant characteristics	All (n = 151)	EEN (n = 41)	Non-EEN (n = 110)	P-value
Gender, n (%)				0.40
• Male	71 (47.0)	17 (41.5)	54 (49.1)	
• Female	80 (53.0)	24 (58.5)	56 (50.9)	
Age, median (IQR), years	4.10 (0.63–12.55)	1.85 (0.53–10.13)	6.00 (1.07–13.70)	0.061
Weight, median (IQR), kg	16.30 (7.26–47.50)	10.70 (4.49–32.20)	19.55 (8.20–55.00)	0.024
Height, median (IQR), cm	102.20 (63.50–143.90)	82.20 (52.00–131.40)	107.60 (73.00–151.10)	<0.001
WFL/BMI,[a] n (%)				0.30
• Underweight	15 (10.0)	5 (12.2)	10 (9.2)	
• Normal	79 (52.6)	19 (46.3)	60 (55.0)	
• Overweight	22 (14.7)	4 (9.8)	18 (16.5)	
• Obese	34 (22.7)	13 (31.7)	21 (19.3)	
Race/ethnicity, n (%)				0.28
• White	77 (51.0)	24 (58.5)	53 (48.2)	
• African American	38 (25.2)	11 (26.8)	27 (24.5)	
• Others	31 (20.5)	5 (12.2)	26 (23.6)	
• Unknown	5 (3.3)	1 (2.4)	4 (3.6)	
PARDS severity				0.048
• Mild	86 (57.0)	29 (70.7)	57 (51.8)	
• Moderate	42 (27.8)	10 (24.4)	32 (29.1)	
• Severe	23 (15.2)	2 (4.9)	21 (19.1)	

Note: Data were compared between the EEN group and the non-EEN group by chi-square test or Fisher exact test for categorical variables and by the Mann-Whitney test for continuous variables.

Abbreviations: BMI, body mass index; EEN, early enteral nutrition; IQR, interquartile range; PARDS, pediatric acute respiratory distress syndrome; WFL, weight-for-length.

[a]WFL/BMI could not be calculated for one participant because of missing height information.

for gender, race or ethnicity, or weight-for-length or body mass index (Table 1).

Acute causes of PARDS and acute GI comorbidities were collected and compared between the EEN and non-EEN groups. Children within the EEN group were more likely to have pneumonia (61% vs 20.9%, $P < 0.0001$) and less likely to have had a cardiac arrest (2.4% vs 18.2%, $P = 0.013$) and shock (2.2% vs 69.1%, $P < 0.0001$) as the cause of their PARDS than the non-EEN group. No differences in the other acute conditions collected were seen, which included sepsis, near drowning, aspiration, pulmonary hemorrhage, trauma, anoxic brain injury, acute liver failure, or acute GI complications, which included hematemesis, hematochezia, intrabdominal hemorrhage, perforation, obstruction, or pancreatitis. Pertinent chronic pulmonary and GI comorbidities were also collected. The EEN group was more likely to have acyanotic congenital heart disease (19.5% vs 7.3%, $P = 0.039$) and chronic lung disease (26.8% vs 8.2%, $P = 0.003$) and be tracheostomy and ventilator dependent (14.6% vs 3.6%, $P = 0.025$) than the non-EEN group. No difference in the other chronic conditions was appreciated between

groups, which included cerebral palsy, hypoxic ischemic encephalopathy, scoliosis, leukemia, lymphoma, solid organ tumor, chronic liver failure, liver transplant, heart transplant, kidney transplant, bone marrow transplant, congenital or acquired immunodeficiency, home noninvasive positive pressure ventilation, tracheostomy dependence, gastrostomy tube, or gastrojejunal tube.

Daily enteral energy intake, quantified as a percentage of the total energy goal, was compared between survivors and nonsurvivors (Figure 1). A sharp increase in enteral energy intake was seen from the initial PARDS diagnosis to day 5 of PARDS illness in those who survived, whereas those who did not survive received minimal-to-no enteral energy. Daily enteral protein intake, quantified as grams (g) of protein per kilogram (kg) of body weight, was also compared between survivors and nonsurvivors and demonstrated the same findings (Figure 2).

Total nutrition (TN), defined as all EN and PN received, was compared between the EEN and non-EEN groups. A statistically significant difference in TN was seen on days 1–3 of PARDS diagnosis, with the EEN group receiving more TN on each of those days. There was no
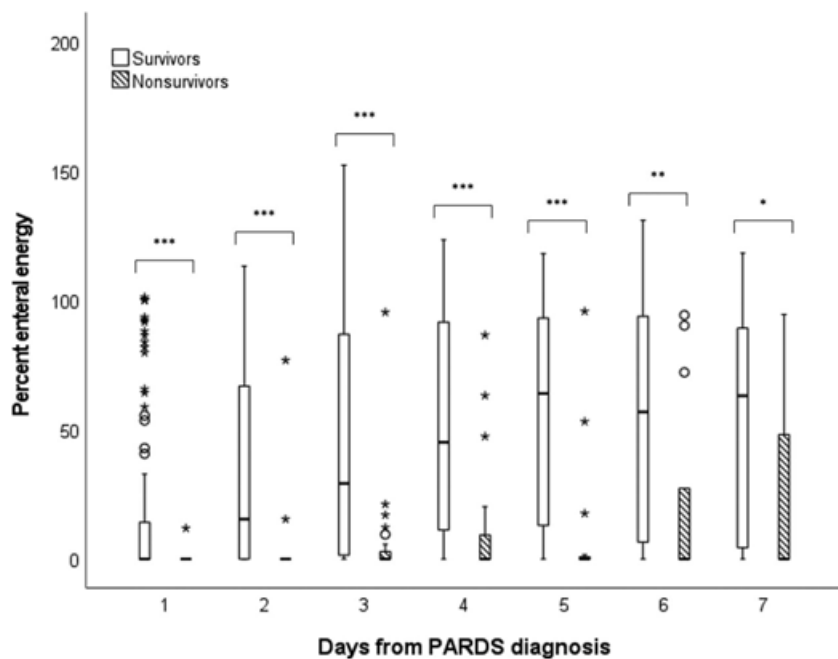
FIGURE 1 Enteral energy as a percent of the total daily goal starting from the diagnosis of PARDS. Circles (o) represent outliers and asterisks (*) within the whisker plots are extreme values. Asterisks above each whisker plot represent *P*-values comparing groups on that day of PARDS diagnosis: ***$P < 0.001$; **$P < 0.01$; *$P < 0.05$. PARDS, pediatric acute respiratory distress syndrome
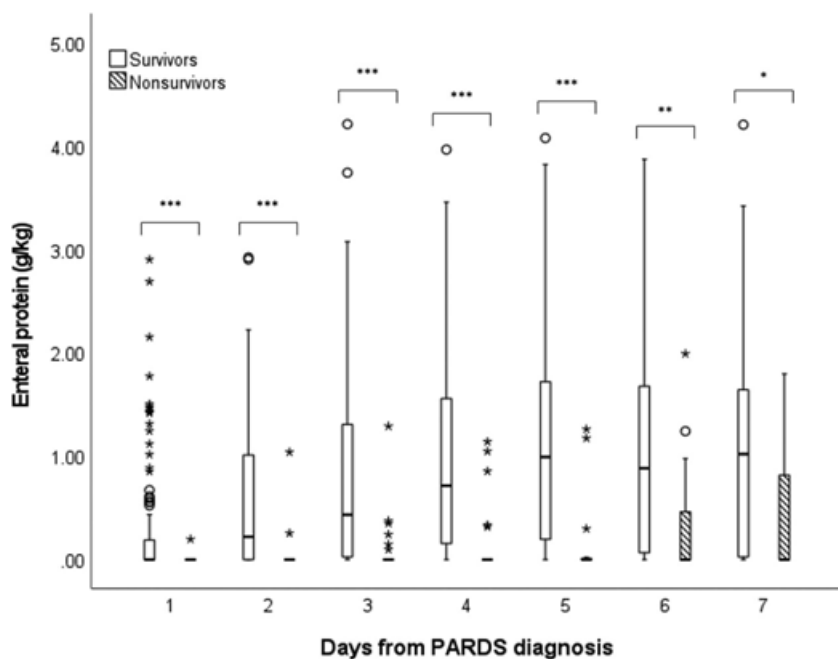
FIGURE 2 Daily enteral grams of protein per kilogram of body weight starting from the diagnosis of PARDS. Circles (o) represent outliers and asterisks (*) within the whisker plots are extreme values. Asterisks above each whisker plot represent *P*-values comparing groups on that day of PARDS diagnosis: ***$P < 0.001$; **$P < 0.01$; *$P < 0.05$. PARDS, pediatric acute respiratory distress syndrome

significant difference in TN between groups on days 4–7 (Table S1). EN and PN were further analyzed between groups. The EEN group had a significantly higher percentage of goal energy from days 1 to 6. There was no difference in the percentage of goal EN between groups on day 7 (Figure 3). There was no difference in the percentage of PN between groups on day 1. A significant difference in PN was seen on days 2–7, with the non-EEN group receiving more PN each day (Figure 4).

The PICU mortality rate was lower in the EEN group than in the non-EEN group, 2.4% compared with 30%, respectively (odds ratio [OR] = 0.058; 95% CI, 0.008–0.442; $P = 0.006$). After adjusting for age and PARDS severity, EEN continued to be associated with a lower PICU

mortality rate (adjusted OR = 0.071; 95% CI, 0.009–0.542; $P = 0.011$) compared with the non-EEN group.

The EEN group had a higher likelihood for PICU discharge ($P < 0.001$) (Figure 5). To more clearly quantify this relationship, cumulative probabilities were calculated at days 50, 100, 150, and 200 (Table 2). PICU discharge remained more likely in the EEN group after adjusting for age and PARDS severity (adjusted risk ratio = 1.79; 95% CI, 1.25–2.55; $P = 0.001$).

We excluded four patients who had either a tracheostomy or tracheostomy with ventilator dependence for the analysis of ventilator-free days within 28 days from PARDS diagnosis. Patients in the EEN

FIGURE 3 Enteral energy as a percent of the total daily goal between the EEN and non-EEN groups. Circles (o) represent outliers and asterisks (*) within the whisker plots are extreme values. Asterisks above each whisker plot represent *P*-values comparing groups on that day of PARDS diagnosis: ***$P < 0.001$; **$P < 0.01$; *$P < 0.05$. EEN, early enteral nutrition
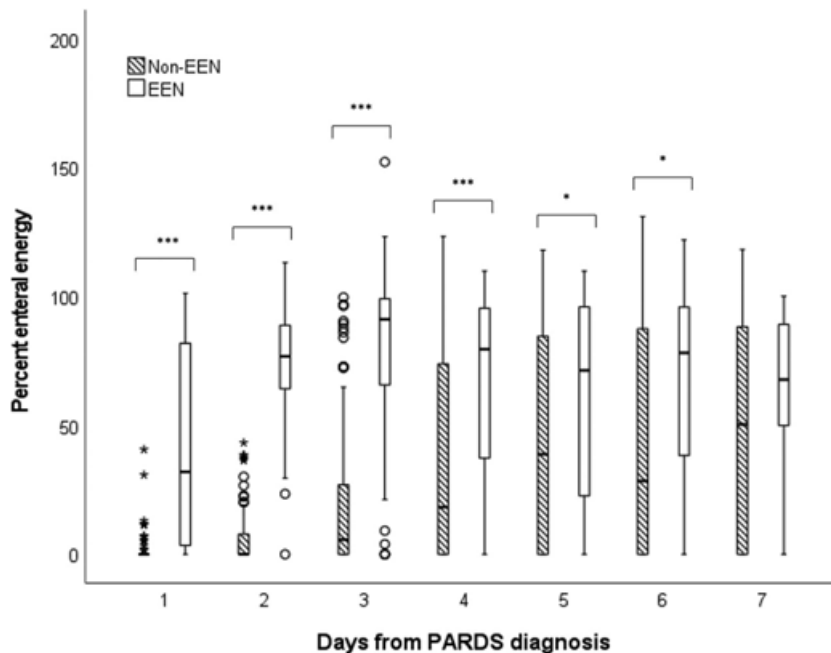
FIGURE 4 Parenteral energy as a percent of the total daily goal between the EEN and non-EEN groups. Circles (o) represent outliers and asterisks (*) within the whisker plots are extreme values. Asterisks above each whisker plot represent *P*-values comparing groups on that day of PARDS diagnosis: ***$P < 0.001$; **$P < 0.01$; *$P < 0.05$. EEN, early enteral nutrition
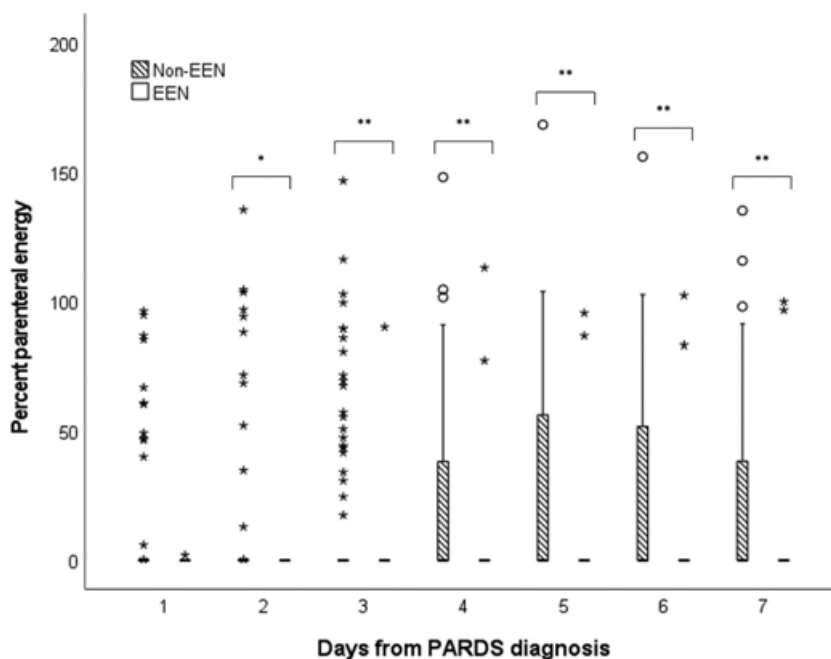
group had more 28-day ventilator-free days, with a median of 19.9 days, compared with patients in the non-EEN group, with a median of 13.8 days ($P = 0.017$). When controlling for age and PARDS severity, data were analyzed to predict the probability of having at least one ventilator-free day and to compare the number of ventilator-free days for those who had at least one. Patients in the EEN group were more likely to have at least one ventilator-free day than the non-EEN group (OR = 3.96; 95% CI, 1.28–12.22; $P = 0.017$). For those patients who had at least one ventilator-free day, there was no significant difference between groups for the number of ventilator-free days ($P = 0.68$).

PELOD-2 scores were also used to capture disease severity with scores calculated on the day of PARDS diagnosis. However, the PELOD-2 scores were highly correlated with OI/OSI scores, and so could not be included with the previously stated OI/OSI model so as not to introduce multicollinearity. Therefore, we ran a separate model using PELOD-2 while still controlling for age and continued to find a statistically significant association between EEN and lower PICU mortality ($P = 0.033$), shorter PICU LOS ($P < 0.001$), and more ventilator-free days ($P = 0.037$). We excluded four patients from this analysis because their admission to the PICU was >10 days prior to their PARDS
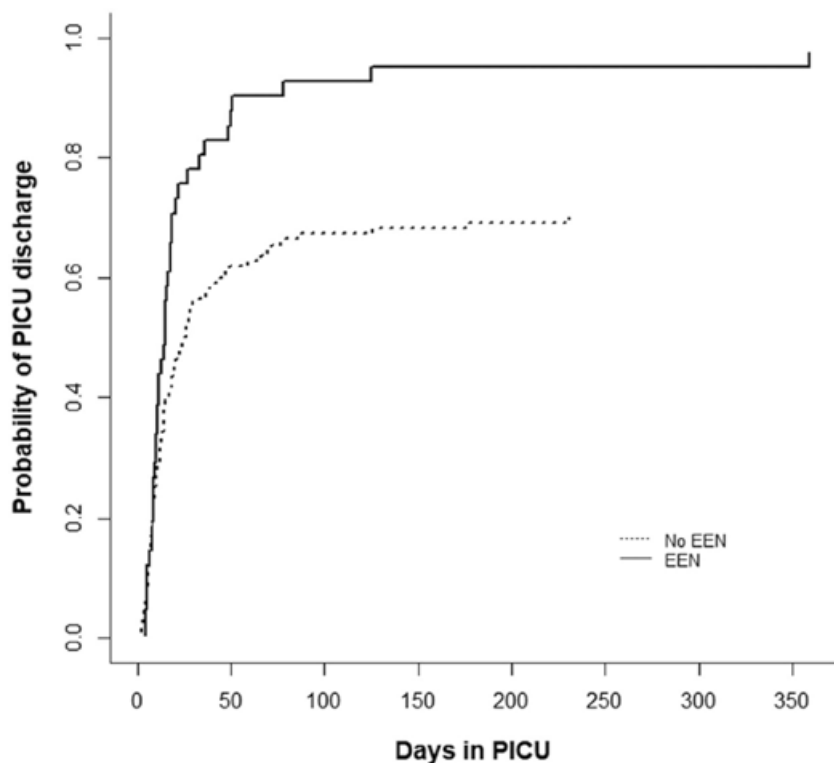
FIGURE 5 Plot of the cumulative probability of PICU discharge over time. EEN, early enteral nutrition; PICU, pediatric intensive care unit

TABLE 2 Cumulative probability of pediatric intensive care unit discharge with 95% CI

Cohort	Day 50	Day 100	Day 150	Day 200
EEN	87.8 (77.1–98.5)	92.7 (83.8–100)	95.1 (87.4–100)	95.1 (87.4–100)
Non-EEN	61.8 (52.6–71.0)	67.3 (58.3–76.2)	68.2 (59.3–77.1)	69.1 (60.2–78.0)

Abbreviation: EEN, early enteral nutrition.

diagnosis and they did not have a recorded PELOD-2 score at the time of PARDS diagnosis.

PARDS severity subgroups were analyzed. A statistically significant difference in mortality was seen in the mild PARDS cohort, as those who received EEN had a mortality rate of 0% whereas those in the non-EEN group had a mortality rate of 24.6% ($P = 0.002$). There was a tendency towards decreased mortality in the moderate and severe PARDS cohorts within the EEN group, but these did not reach statistical significance.

Lastly, secondary analysis of the relationship between protein received and mortality was completed. Early total protein (ETP) was defined as receiving 1.5 g/kg/day in the first 48 h from PARDS diagnosis in either enteral or parenteral forms. We were unable to compare early enteral protein intake alone as there were so few patients who received early enteral protein and none of them died. The ETP group was then compared with the non-ETP group. Compared with patients in the non-ETP group, patients in the ETP group were younger and shorter and weighed less. There was no significant difference in gender, race, or PARDS severity (data not shown). There was no significant difference in PICU mortality rate, with 20.0% in the ETP group compared with 22.8% in the non-ETP group ($P > 0.99$). No difference was appre-

ciated in PICU LOS ($P = 0.91$) or ventilator-free days within 28 days ($P = 0.98$) between the ETP and non-ETP groups.

DISCUSSION

Our study showed that receiving EEN was significantly associated with lower PICU mortality, shorter PICU LOS, and more ventilator-free days, which persisted after controlling for age and PARDS severity. Since the OI/OSI and PELOD-2 models were highly correlated, we were unable to control for both variables in the same model, as this would improperly introduce multicollinearity. We determined that attempting to control for disease severity only with OI/OSI may potentially confound our results by missing systemic disease severity not captured solely with OI/OSI. Therefore, a separate model was run, controlling for PELOD-2 scores and age, and a statistically significant association between EEN and lower mortality, shorter LOS, and more ventilator-free days was still appreciated. Overall, this provides evidence for an association between EEN and improved outcomes in the PARDS population and suggests the potential for a protective relationship.

This study is in agreement with previous literature that shows not only is EN safer than what was assumed historically, but, when introduced early, EN is associated with improved outcomes in critically ill children. Wong et al showed that adequate nutrition was associated with improved outcomes in children with PARDS, specifically.[16] However, they did not look at the timing of when adequate nutrition was reached as a marker for comparison. Therefore, our study strengthens the argument that the timing of when EN is started plays a role in the associations seen with improved outcomes.

We must also acknowledge that patients in the non-EEN group received a higher percentage of energy from PN than patients in the EEN group, which was statistically significant on days 2–7 (Figure 4). Given past literature showing that early PN is associated with poor outcomes in critically ill children,[14,15] a higher percentage of PN in the non-EEN group may have confounded the difference in poorer outcomes that goes beyond simply not receiving EEN. However, we cannot determine to what degree PN contributes to the poorer outcomes of the non-EEN group and does not appear to be clinically significant. First, there was no statistically significant difference on day 1, which, based on timing, is the most influential day for any association between EN or PN and outcomes. Second, 75% of both the EEN and non-EEN groups did not receive PN on days 2 and 3. Third, this study was not controlled for specific diseases or other patient factors that might influence the use of EN or PN.

We recognize the relationship between macronutrients and PICU outcomes is also being studied with evidence emphasizing protein delivery in the critically ill child.[18] Although we did not find any significant association between protein intake and clinical outcomes in our patients, protein intake was also not the focus of this study.

Finally, we performed a subcohort analysis between EEN and PICU mortality, our primary outcome, by PARDS severity group in order to better understand the significance and limitations of our results. We found a significant association in the mild PARDS group but not in the moderate and severe groups. We find this important for two reasons. First, although there was not a significant association in the moderate or severe categories, a tendency toward significance was appreciated. This may be due to inadequate sample size, and further studies with a larger number of patients may find EEN to be significantly associated with outcomes in patients with moderate and severe PARDS. Second, given that this study was not powered to find an association between EEN and mortality at the subcohort level, uncovering a statistically significant association with even fewer patients strengthens the relationship between EEN and mortality in mild PARDS. Furthermore, it argues for the prospective study of goal-directed EEN in PARDS to determine if this clinical significance extends to a causative and protective relationship.

There are limitations to our study. It is a single center, retrospective study, which limits the generalizability. Differences in patient population may alter PARDS presentation, or practice variations in management or differences in EN used could modify the association between EEN and PARDS outcomes found in our study. Our institution does not have a standardized guideline for EEN in PARDS, so clinical decisions were made on a patient-specific basis regarding which patients received EN or PN and when. Thus, our findings may be confounded by differences in clinical practice, which could not be ascertained in a retrospective study. However, our research group has previously used this definition of EEN, which conforms to a general precedent set by other studies that have also shown improved rates of morbidity and mortality when EN is initiated early in various disease states. Another limitation is our sample size. PARDS is a very heterogeneous disease state, both in severity and underlying cause. Although we were able to control for severity, controlling for each disease state was out of the scope of this study, given that our study sample consisted of 151 patients. Not being able to control for specific diseases that caused PARDS could have confounded our results. However, this should not take away from the clear association between EEN and mortality, PICU LOS, and ventilator-free days when controlling for severity in two different ways. Finally, it can be argued that having a larger study may uncover a potential association between EEN and moderate/severe PARDS. Conversely, the argument can also be made that the association and potential benefit of EEN in PARDS diminishes with increasing PARDS severity, thereby limiting the utilization of EEN in the most critically ill children.

CONCLUSION

Ultimately, a minimum dose of EN with specific recommendations on timing and macronutrient components that improves outcomes continues to be the goal but still has yet to be well defined. Our study showed a strong association between EEN, defined at 25% of the EN goal within the first 48 h, and improved PARDS outcomes that persisted after controlling for PARDS severity with OI/OSI and disease severity with PELOD-2. More studies are needed to determine if this association is strengthened in the setting of a larger sample size, and prospective, randomized control trials are needed to determine if the relationship between EEN and PARDS outcomes is a truly protective relationship.

CONFLICT OF INTERESTS

VPS data were provided by the VPS, LLC. No endorsement or editorial restriction of the interpretation of these data or opinions of the authors has been implied or stated. Theresa Mikhailov provides database consultation to VPS, LLC, but she receives no money for this activity. The Medical College of Wisconsin receives support for her services from VPS, LLC. The other authors have no financial relationships to disclose.

AUTHOR CONTRIBUTIONS

Matthew B. F. Powell, Prakadeshwari Rajapreyar, and Theresa A. Mikhailov equally contributed to the conception and design of the research. Matthew B. F. Powell contributed to the acquisition, analysis, and interpretation of the data. Jitsupa Sirinit contributed to the acquisition and analysis of the data. Prakadeshwari Rajapreyar, Ke Yan, and Theresa A. Mikhailov contributed to the analysis and interpretation of the data. Matthew B. F. Powell drafted the manuscript. All authors critically revised the manuscript, gave final approval, and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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SUPPORTING INFORMATION

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