DOI: 10.1002/jpen.2627

ORIGINAL RESEARCH

Association between protein intake and muscle wasting in critically ill children: A prospective cohort study

Lyvonne N. Tume RN, PhD[1,2] | Christopher Simons BSc[2] | Lynne Latten RD, BSc (Hons)[2,3] | Chao Huang PhD[4] | Paul Comfort PhD[5] | Vanessa Compton Grad Dip Phys[2] | Anand Wagh MD[2] | Archie Veale BSc (Hons)[6] | Frederic V. Valla MD, PhD[7]

[1]Faculty of Health, Special Care & Medicine, Edge Hill University, Ormskirk, UK

[2]Pediatric Intensive Care Unit, Alder Hey Children's NHS Foundation Trust, Liverpool, UK

[3]Alder Hey Children's NHS Foundation Trust, Liverpool, UK

[4]Institute for Clinical and Applied Health Research and Hull York Medical School, University of Hull, Hull, UK

[5]Directorate of Psychology and Sport, University of Salford, Salford, Greater Manchester, UK

[6]Patient and Public Engagement Expert, Carlisle, UK

[7]Pediatric Intensive Care, Hospices Civils de Lyon, Lyon, France

Correspondence
Lyvonne N. Tume, RN, PhD, Edge Hill University, Ormskirk L39 4QP, UK.
Email: Lyvonne.tume@edgehill.ac.uk

Abstract

Background: Survival from pediatric critical illness in high-income countries is high, and the focus now must be on optimizing the recovery of survivors. Muscle mass wasting during critical illness is problematic, so identifying factors that may reduce this is important. Therefore, the aim of this study was to examine the relationship between quadricep muscle mass wasting (assessed by ultrasound), with protein and energy intake during and after pediatric critical illness.

Methods: A prospective cohort study in a mixed cardiac and general pediatric intensive care unit in England, United Kingdom. Serial ultrasound measurements were undertaken at day 1, 3, 5, 7, and 10.

Results: Thirty-four children (median age 6.65 [0.47–57.5] months) were included, and all showed a reduction in quadricep muscle thickness during critical care admission, with a mean muscle wasting of 7.75%. The 11 children followed-up had all recovered their baseline muscle thickness by 3 months after intensive care discharge. This muscle mass wasting was not related to protein ($P = 0.53$, $\rho = 0.019$) (95% CI: −0.011 to 0.049) or energy intake ($P = 0.138$, $\rho = 0.375$ 95% CI: −0.144 to 0.732) by 72 h after admission, nor with severity of illness, highest C-reactive protein, or exposure to intravenous steroids. Children exposed to neuromuscular blocking drugs exhibited 7.2% (95% CI: −0.13% to 14.54%) worse muscle mass wasting, but this was not statistically significant ($P = 0.063$).

Conclusion: Our study did not find any association between protein or energy intake at 72 h and quadricep muscle mass wasting.

KEYWORDS
child, intensive care, muscle mass, neonate, nutrition

CLINICAL RELEVANCY STATEMENT

Muscle mass changes can be seen in critically ill children, which can be assessed more objectively and over time using quadricep ultrasound.

BACKGROUND

In developed countries, most (>96%) children now survive critical illness[1]; therefore, optimizing their physical recovery is essential. Muscle mass wasting that occurs rapidly and that is severely associated with critical illness has been well described in adults[2] and increasingly described in children.[3–6] A recent narrative review revealed a prevalence of muscle mass loss was ~2% in critically ill children, lower than that in adults.[7] This muscle mass wasting persists in adults even 3 months after critical illness, hampering their rehabilitation.[8] Among interventions to potentially target this, in adults, protein intake was found to potentially ameliorate this rapid muscle loss,[9] but in children, this is largely unknown. Impairments in functional status after critical illness are being increasingly recognized in children, now described as postintensive care syndrome in pediatrics (PICs-P).[10] The consequences of which can impair recovery, results in developmental delays, and impact the child and family's quality of life.[11] Thus, ensuring effective physical rehabilitation after critical illness, is important and depends on muscle function and strength; thus, interventions that can prevent muscle mass wasting have the potential to promote a more rapid physical recovery. The primary aim of this study was to examine the relationship between muscle mass wasting (measured via ultrasound) with nutrition intake during and after pediatric critical illness using standard, readily available bedside equipment.

METHODS

A prospective cohort study was undertaken in a large mixed general and cardiac pediatric intensive care unit (PICU) and specialist extracorporeal membrane oxygenation center in Northwest England. The study is reported according to the STROBE Equator checklist,[12] and the study was registered on ISRCTN 81803039. UK Health Research Authority (ethical approval) was obtained from Liverpool Central Ethics Committee on April 8, 2021 (IRAS 301263), and informed parental consent was gained for all children.

Our primary study aim was to assess the relationship and determine any correlation between PICU muscle mass wasting and protein intake during critical illness. Our exposure of interest was protein intake defined as daily grams of protein intake. Our primary outcome was muscle mass wasting determined by quantitative assessment via thigh ultrasound using the technique described and validated by Valla et al.[13]

Secondary study outcomes were as follows:

1. To assess the relationship and determine any correlation between PICU muscle mass wasting and energy intake during critical illness.
2. To assess and further describe muscle mass wasting and function changes during PICU admission and from PICU discharge to 3 months after PICU discharge.
3. To describe and quantify other risk factors for PICU muscle mass wasting, including severity of illness (Pediatric Index of Mortality [PIM3]), exposure to intravenous steroids and neuromuscular blockade, inflammatory markers (C-reactive protein [CRP]), and admission diagnostic category.

We hypothesized that decreased protein intake would be associated with an increase in muscle mass wasting in PICU patients.

Study inclusion criteria were: Invasively ventilated children with a gestational age of ≥37 weeks to age16 years who were expected to stay >48 h in the PICU who were receiving some form of nutrition (enteral and/or parenteral). Children were excluded if they were extubated at PICU admission, they were expected to stay <48 h, they were not expected to survive or were undergoing palliative care, they had an existing muscle or neurological disease (with an expected abnormal baseline), we were unable to perform muscle ultrasound (not able to access either thigh or child isolated for infection and device could not be taken into the room), they had a previous PICU admission for >2 days in the last 2 years, or in cases in which 3-month follow-up was not possible.

Muscle mass wasting was quantitatively assessed by thigh ultrasound using the technique described and validated by Valla et al.[13] We assessed quadricep femoris muscle thickness as a surrogate of muscle mass, using the mean of four measurements (in two different incidences); and we also produced measurement of cross-sectional area (CSA). PICU muscle mass wasting was defined as a decrease in quadriceps muscle thickness of >10%. However, for the primary analysis we used a continuous scale for muscle thickness values instead of a cutoff. We also calculated the variability and measurement error at baseline so that we could determine if any observed changes were greater than the measurement error associated with this cohort. This measurement was performed at day 1, 3, 5, 7 and 10 of PICU stay when possible. Muscle function assessment was assessed using the Motor Function Measure of the Bayley scale (age <2 years) the muscle function score (MFM)-20 (age 2–6 years),[14] or the MFM-32 (age >6 years).[15] The scoring was performed by a trained operator (C. S.), if possible, at PICU discharge, hospital discharge, and 3 months later. Muscle mass wasting was represented by muscle thickness and muscle area. We used the day 1 muscle figures as the baseline and calculated the difference from day 1 as the muscle mass wasting (primary outcome). For example, for day 3, the muscle mass wasting is -(day 3 – day 1)/day 1, and we use the percentage of this figure as muscle mass wasting.

Assessment at 3-month follow-up after PICU discharge included the muscle assessment, described above, as well as functional status, quality of life, and feeding disturbances. These were assessed using the Functional Status Score (FSS)[16] and the generic pediatric quality of life score (PEDSQL) module. The FSS ranges from 6 to 30, with 6 being reference outcome and 30 being the poorest outcome. The PEDSQL Generic Core Scales items are represented on a 0–100 scale, with higher scores indicating better health-related quality of life.[17]

A typical week food diary (Nutritics) and activity diary were also completed by the parents/and or child within a week of the planned follow-up appointment. Analyses of these were done by the dietitian (L. L.) and the exercise specialist (P. C.); however, because of the lack of detail and inconsistent reporting from parents/carers, this was later excluded from further analysis.

Nutrition outcomes were assessed by weight (kilograms), height (meters) or length (centimeters), body mass index (weight in kilograms divided by height in meters squared), centiles, and weight-for-age z scores (WAZ). In addition, daily energy (kilocalories) and protein (grams) intakes were calculated by the dietitian (L. L.). This unit's protocol is that patients are fed within 6 h of PICU admission when possible, using a feeding protocol. Energy requirements were calculated using the Schofield predictive equation.[18] Protein requirements were estimated at 1.5 g/kg/day as per current recommendations.[19] The daily plasma CRP was used to assess inflammation.

Patient characteristics during critical illness were also recorded, including age, weight, sex, and severity of illness (using PIM3 and primary admission category). Patient outcomes (death, acquired infections, length of stay, mechanical ventilation duration) were also recorded daily up to day 10.

The original sample size calculation was based on regression approach to assess the association between PICU muscle wasting and protein intake during critical illness. With muscle wasting as dependent variable, a sample size of 50 allowed us to have protein intake as an independent variable, adjusting for two to three confounders.[20] As multiple measurements from each patient can enhance the statistical power of the analyses, we chose the repeated-measure mixed model. Because of the reduced sample size ($n = 34$) and limited patient data after day 5, we ran a repeated-measure mixed model with muscle wasting as the outcome and protein level as the independent variable, that is, with no adjustment for confounders.

Because of the reduced sample size, descriptive statistics were mainly used for analyses reporting. For formal statistical tests, 95% CIs and P values at 5% significance level are reported.

Baseline patient characteristics and outcomes were summarized with continuous data tested for normality and presented as mean (SD), mean (95% CIs), or median (IQR), whereas categorical data were presented as frequencies.

The primary analysis was undertaken via repeated-measure mixed model with muscle mass wasting as the outcome and protein level as the independent variable. Spearman rho correlation coefficients between energy target achievement by day 3, 5, and 7 and muscle mass change and protein intake and change in muscle mass were calculated. Correlations were interpreted as 0.00–0.10 (negligible correlation), 0.10–0.39 (weak correlation), 0.40–0.69 (moderate correlation), 0.70–0.89 (strong correlation), and 0.90–1.00 (very strong correlation).[21] Individual growth curves on changes in muscle mass and area over time are reported. In our planned analysis of secondary outcomes, we examined the association between muscle mass wasting and other variables: the severity of illness at PICU admission, highest CRP during the PICU stay, and exposure to intravenous steroids or neuromuscular blocking (NMB) drugs. Correlation was assessed between nonnormally distributed variables (highest CRP and PIM3) and muscle mass wasting using Spearman rho and between categorical variables (exposure to steroid drugs) using chi-square test.

Longer-term follow-up data (3 months after PICU discharge) were reported with descriptive statistics. All analyses were conducted by IBM SPSS version 28 and R language version 4.2.

RESULTS

Thirty-four children were recruited to the study (Figure 1 the study flowchart and Table 1 shows the patient characteristics). Over half of these children were discharged from PICU within a week. The flow of patients through the study is summarized in Figure 2 and illustrates patient numbers and measurements for each time point. Two patients out of 34 (5%) died in PICU, with one child dying after hospital discharge and before the 3-month follow-up. At day 10, there were only five patients available for muscle ultrasound (with muscle thickness mean [SD]: 1.11 [0.16]). This data sparseness means they are unlikely to be a representative general sample, and thus as it may introduce potential bias, we removed the data at day 10 from the analysis.

The percentage of the child's protein goal that was achieved increased over the PICU stay, with a median of 36% (15%–65%); 45% (13.2%–71%), 55% (20.2%–68.2%), and 64% (42%–112%) at day 3, 5, 7, and 10, respectively. Repeated-measure analysis, with muscle mass wasting at different time points as the dependent variable and protein level as the independent variable, showed that a 1% protein level change is associated with 0.03% (95% CI: −0.05% to 0.11%) muscle mass wasting, which is not statistically significant ($P = 0.46$). The median (IQR) of highest percentage of muscle mass wasting over 7 days of PICU stay was 3.0% (18.7%). Figure 3 show changes in muscle mass and CSA over time. In our 34 patients, 15 (44%) had a >10% decrease in muscle thickness. The median (IQR) in g/kg/day of cumulative protein deficit in patients with >10% muscle mass wasting was 0.80 (0.95) by day 3, 0.80 (0.78) by day 5, and 0.65 (0.88) by day 7. In terms of longer-term muscle mass wasting (from PICU discharge to 3 months later) we found muscle mass recovery was rapid, and of the children who we assessed at 3-month follow-up, all had fully recovered their baseline muscle mass.

The percentage of the child's energy goal achieved also increased over their PICU stay, with a median (IQR) of 34% (14%–60%); 36.5% (15.7%–57%), 49% (23.2%–65.7%), and 53% (35%–90%) at day 3, 5, 7, and 10, respectively. However, there was no significant Spearman correlation ($\rho = -0.271$, 95% CI: −0.629 to 0.182; $P = 0.233$) between energy target achievement by day 3 and the change in muscle mass. Spearman correlations by day 5 and day 7 were 0.600 (95% CI: 0–0.882) and 0.491 (95% CI: −0.054 to 0.810) but still not significant ($P = 0.06$ and 0.15). Similarly, we found no significant correlations between protein deficits and change in muscle mass by day 3 ($\rho = -0.414$, 95% CI: −0.717 to 0.022; $P = 0.06$), day 5 ($\rho = 0.115$, 95% CI: −0.521 to 0.669; $P = 0.74$), and day 7 ($\rho = 0.427$, 95% CI: −0.277 and 0.833; $P = 0.22$).

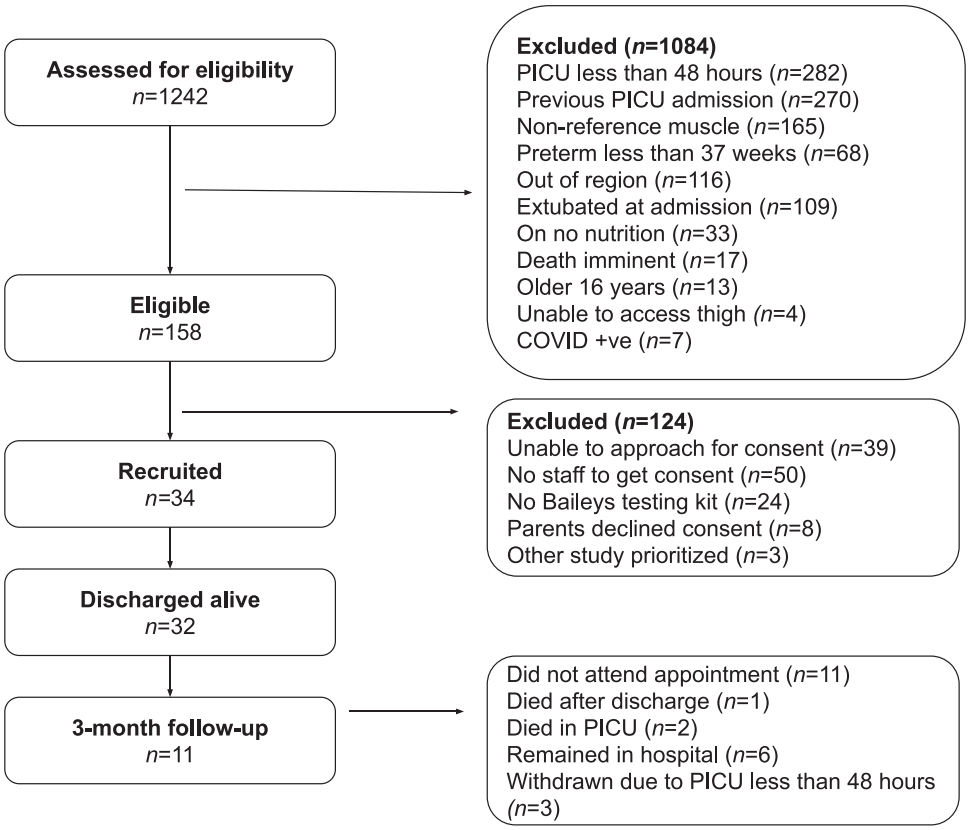

FIGURE 1 Study flowchart. PICU, pediatric intensive care unit.

The mean change in muscle during PICU stay between children exposed vs not exposed to NMB drugs and intravenous steroids vs no steroids are summarized in Table 2. We also examined other key variables likely to worsen muscle mass wasting. We found no significant correlations between severity of illness at PICU admission (PIM3) and muscle mass wasting (Spearman $\rho = 0.251$, $P = 0.316$) and between the highest CRP and exposure to intravenous steroids and muscle mass wasting ($\rho = 0.251$, $P = 0.505$). X^2 test showed no significant association between exposure to NMB drugs and muscle mass wasting ($P = 0.389$). In a linear regression as post hoc analysis, with the maximum percentage muscle wasting during PICU stay as dependent variable and the NMB/non-NMB grouping as independent variable, children exposed to NMB drugs (compared with children not exposed) had 7.2% (95% CI: −0.13% to 14.54%) more muscle mass wasting, but this was not statistically significant ($P = 0.063$).

Three children died, leaving 31 for possible follow-up. However, only 11 out of 31 (35.4%) had a follow-up assessment: 11 children did not attend the follow-up appointment, six children remained in hospital, and three were withdrawn from the study because they spent <48 h in the PICU (Figure 2). Most (26 out of 32) patients had a FSS assessed at critical care discharge. The mean FSS at PICU discharge was 10.6 (SD 5.28), but by hospital discharge, this was reference for all 21 out of 21 of patients assessed; and by 3 months, the mean score was 6.3 (SD 0.2) for the children assessed, with only one child scoring mildly abnormal at 9. In terms of age-appropriate motor scores, of the 11 children scored, all showed some improvement between hospital discharge and 3-month follow-up, with older children showing greater improvement. Twenty-three children in the study were older than 2 years (at which this tool can be used); of the 11 children at follow-up, only five PEDSQL scores were completed. Of these 5, the mean PEDSQL score was 67.2/100 7 (SD 71.12).

DISCUSSION

The results of our small single-center study have shown that children lose muscle mass over the course of their critical illness, consistent with other studies.[3,5,22–24] However, unlike adults, and earlier pediatric studies,[2,4,25] these children showed a rapid recovery of their muscle mass within 3 months of PICU discharge. In our study, we found no relationship between muscle mass wasting and protein or energy intake in the first 3 days in the PICU. This is different compared with other studies in children using ultrasound to assess muscle changes; however, it should be noted in these other studies, despite finding statistical significance, their associations were weak. Hoffman et al[22] showed that both percentage of goal energy and protein target in the 6 days prior impacted quadricep muscle thickness in the 36 children studied. They found that a 1% decline in goal protein intake over the prior 6 days was associated with a

TABLE 1 Patient characteristics and outcomes.

Patient characteristics	
Female sex (%)	11/34 (32%)
Age in months (median IQR)	6.65 (0.47–57.5)
Weight, kg (median IQR)	4.42 (3.4–22.8)
WAZ score (median IQR)	−0.74 (−1.59 to 0.087)
Mean (SD)	−0.92 (0.335)
PIM3 score (median IQR)	0.010 (0.005–0.038)
Cause of PICU admission, % (*n*/*N*)	
Cardiac surgery	38 (13/34)
Cardiac failure	15 (5/34)
Respiratory failure	18 (6/34)
Neurological failure/trauma	15 (5/34)
General surgery	6 (2/34)
Sepsis	3 (1/34)
Metabolic/endocrine	3 (1/34)
PICU therapies received	
Received neuromuscular blockade (%) and duration (days)	17/34 (50%) median 2 (1–2.25)
Received IV steroids (%) and duration (days)	(14.7%) median 5.5 (3.25–7.5)
Received ECMO (%) and duration ECMO (days)	3/34 (8.8%) median 9 (6.5–11.5)
Nutrition data	
Patients receiving parenteral nutrition, *n* (%)	2 (5.8)
Median (IQR) protein intake (g/kg/day)	
Day 3	36% (15%–65%)
Day 5	45% (13.2%–71%)
Day 7	55% (20.2%–68.2%)
Day 10	64% (42%–112%)
Energy intake (kcal/kg/day)	
Day 3	4% (14%–60%)
Day 5	36.5% (15.7%–57%)
Day 7	49% (23.2%–65.7%)
Day 10	53% (35%–90%)
Patient outcomes	
Length of ventilation days (median and IQR)	4 (3–5.37)
PICU length of stay (days) (median and IQR)	5 (3–7)
Healthcare-acquired infection while in PICU	0
Hospital length of stay (days) median and IQR	15.7 (8.87–25.75)
Survival to PICU discharge	32/34 (94%)
Survival to 3-month follow-up	31/34 (91%)
Patient outcomes	
Quality of life and motor function scores	
FSS at PICU discharge (*n* = 26)	mean 10.6 (SD 5.28)
FSS at hospital discharge (*n* = 21)	mean 6 (SD 0)
FSS at 3-month follow-up (*n* = 10)	mean 6.3 (SD 0.9)
Bayley's Motor Score at hospital discharge (*n* = 5)	mean 13.4 (SD 18.3)
Bayley's Motor Score at 3-month follow-up (*n* = 3)	mean 31.6 (SD 29.9)
MFM-20 score at hospital discharge (*n* = 3)	mean 43.3 (SD 7.3)
MFM-20 score at 3-month follow-up (*n* = 2)	mean 60 (SD 0)
MFM-32 score at hospital discharge (*n* = 2)	mean 76 (SD 2)
MFM-32 score at 3-month follow-up (*n* = 3)	mean 90 (SD 2.1)
PEDSQL at 3-month follow-up (*n* = 5)	mean 67.27 (SD 71.12)

Abbreviations: ECMO, extracorporeal membrane oxygenation; FFS, Functional Status Score; IQR, interquartile range; IV, intravenous; MFM, muscle function score; PEDSQL, pediatric quality of life score; PICU, pediatric intensive care unit; PIM3 score, Pediatric Index of Mortality Score version 3; SD, Standard Deviation; WAZ, weight-for-age *z* score.

0.17% decline in the quadricep muscle thickness. Similarly, in a study of 73 children in Singapore, Ong et al found that muscle mass wasting (also assessed by ultrasound but using a different technique) was associated with energy intake but not with protein.[23] The results of a further study of 119 children in Brazil noted a reduction in muscle mass (using ultrasound) between day 1 and day 7 and found this related to cumulative protein deficit but not related to energy.[24] We found a slightly lower protein deficit at day 5 compared with day 3. As time from ICU admission increases, feeds increase, and thus it is possible that some deficits reduce as feeds and protein delivery increases. Even though it may not reach the target, the deficit may reduce.

It is worth noting that despite these studies finding statistical significance, most of the associations were weak. We have hypothesized why we did not find a relationship between muscle mass wasting and energy or protein intake in our study. Our study is acknowledged to be underpowered, and this is more so in relation to follow-up. Furthermore, being proactive in feeding early using our nutrition protocol, we were still unable to achieve the child's target protein requirements, and this may have impacted on our findings. Although using standard pediatric enteral formulas, it is difficult to reach 1.5 g/kg/day protein without overshooting energy goals. It may also be that protein and energy are not the key factors affecting muscle mass wasting during critical illness but that of nonuse and immobility due to sedative and muscle relaxant drugs is a more

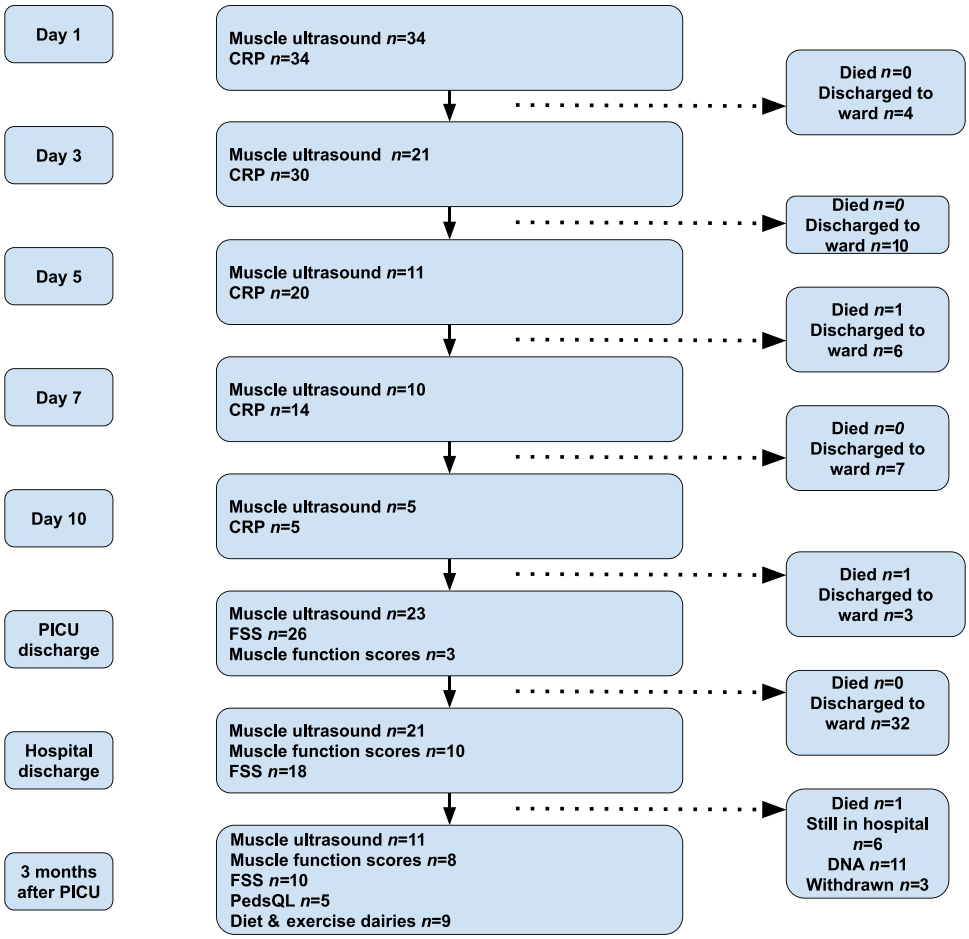

FIGURE 2 Patient flow diagram showing measurements at all timepoints. FFS, Functional Status Score; PICU, pediatric intensive care unit.

significant factor. Considering these inconsistencies among the observational studies (using quadricep ultrasound as the outcome), we suggest a systemic review and meta-analysis is now required.

Studies in adult critical care suggest that lower protein delivery in the acute phase of illness, promotes more muscle mass wasting.[9] A randomized pilot study of higher enteral protein in 22 critically ill children showed that increased enteral protein supplementation was safe and well tolerated and that a larger randomized controlled trial was feasible[26] but could not show any impact on outcomes.

The rapid recovery of muscle mass in critically ill patients after hospital discharge is different from that in adult patients. We suggest a possible reason for this in our study might be that a significant proportion (38%) were admitted for elective cardiac surgery. These children often have significant morbidity prior to their planned critical illness, often with limited exercise tolerance and poor weight gain and nutrition due to heart failure. Following a definitive cardiac surgical procedure, for many resulting in higher peripheral oxygen saturations, less outflow obstruction, and less heart failure, this may result in significant physiological improvements leading to better appetite, weight gain, and activity or exercise ability. Ong et al[23] also had a large cardiac population in their study, although it's unclear how many were cardiac surgical, and they also showed improvement in muscle mass and function at longer-term follow-up.

In terms of other factors associated with greater muscle mass wasting, we did not find that severity of illness, inflammatory markers (CRP), or exposure to steroid drugs correlated with muscle wasting, unlike that in critically ill adults.[25,27,28] However, we found that exposure to NMB drugs tended to worsen muscle mass wasting, consistent with adult studies.[25,28] We suggest that future research should focus on using more objective measures of post–critical care discharge movement and activity levels.

There are several limitations that need to be acknowledged in our study, most notably the small sample size, limiting our analysis and even smaller number of children at follow-up, limiting our ability to draw strong conclusions at this time point. The poor completion and lack of detail in the diet and exercises diaries prevented further detailed analysis and prevented any conclusions from these. The low follow-up rate of 35% may have impacted on the follow-up findings, biasing them toward less sick children and families. Our exclusion criteria around reference muscle and neurology at baseline impacted on our recruitment, and, in retrospect, may have been too rigid. Despite these limitations, using repeated measures of the outcome increased the power of this study, and this is the first study

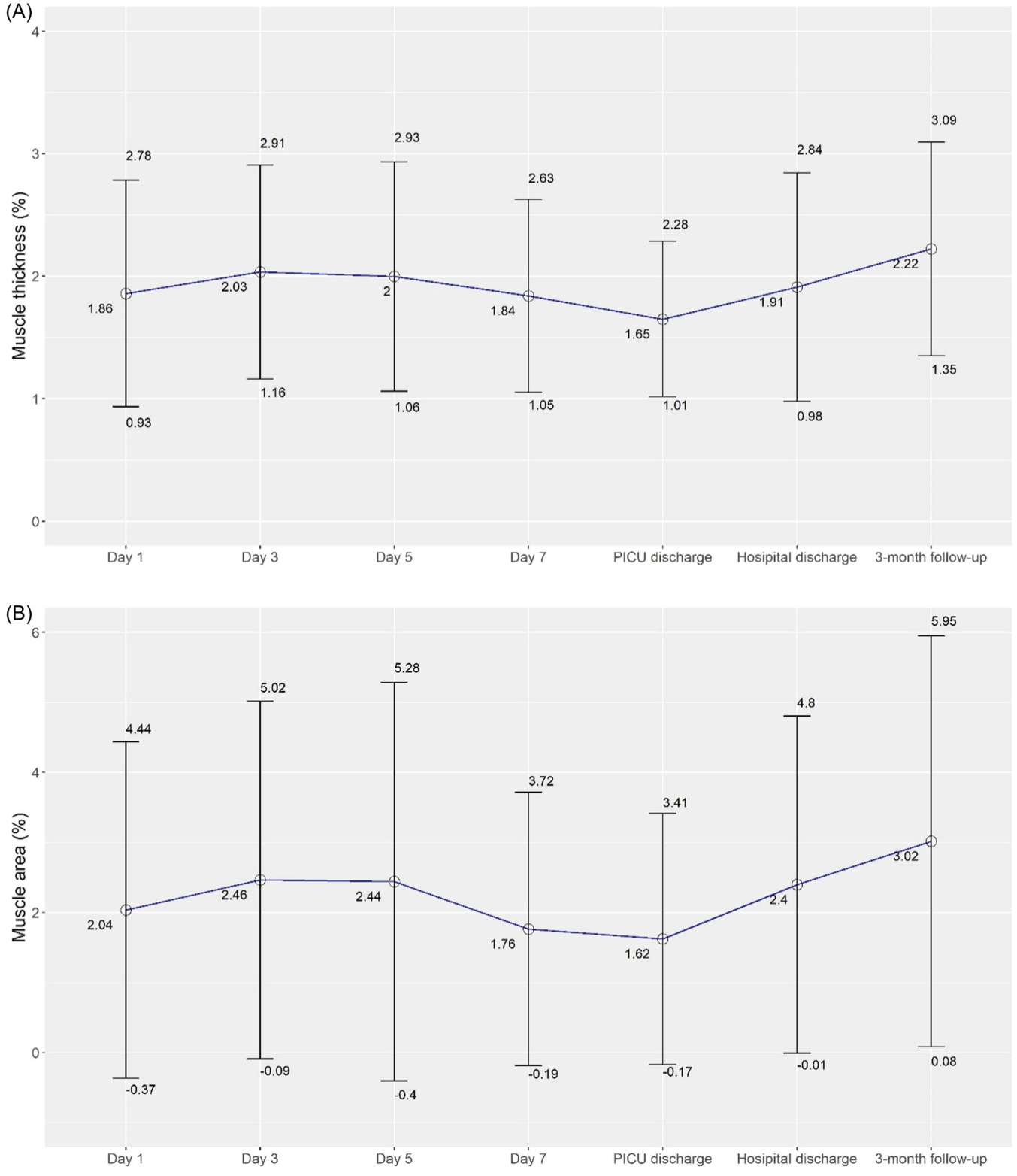

FIGURE 3 (A) Muscle thickness over time with error bars at each time point (day 10 excluded). (B) Muscle area over time with error bars at each time point (day 10 excluded). PICU, pediatric intensive care unit.

TABLE 2 Mean change in muscle mass during PICU stay for children exposed vs not exposed to Neuromuscular blockade (NMB) and IV steroids.

	Exposed to NMB (n = 17)	Not exposed to NMB (n = 17)
% mean muscle wasting: median (IQR)	1.504 (4.202)	0 (6.039)
	IV steroids (n = 5)	**Not exposed to steroids (n = 29)**
% mean muscle wasting: median (IQR)	0 (3.431)	0.665 (4.202)

conducted in the United Kingdom, providing useful feasibility data for future studies in this field.

CONCLUSIONS

Our study contributes to the increasing evidence of acute muscle mass wasting during critical illness in children. All children followed-up had recovered their baseline muscle 3 months after PICU. We found no relationships between either protein or energy intake by 72 h after PICU admission and muscle mass wasting. However, muscle ultrasound is a reliable and useful tool to assess physical recovery after pediatric critical illness, even in neonates.

AUTHOR CONTRIBUTIONS

Lyvonne N. Tume and Frederic V. Valla conceived the study; Lyvonne N. Tume and Frederic V. Valla designed the study; Christopher Simons led the acquisition of data; Vanessa Compton undertook data collection; Archie Veale contributed throughout the study design, analysis, and interpretation from a patient perspective; Lyvonne N. Tume, Chao Huang, and Lynne Latten analyzed the data; Lyvonne N. Tume, Frederic V. Valla, Paul Comfort, Chao Huang, Lynne Latten, and Anand Wagh contributed equally to the interpretation of the data; Lyvonne N. Tume drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

ACKNOWLEDGMENTS

We thank all the parents who allowed their children to participate in this study. This study was funded by the National Institute of Health Research (NIHR) under its Research for patient benefit (RfPB) programme (reference number NIHR202171). The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ORCID

Lyvonne N. Tume http://orcid.org/0000-0002-2547-8209
Lynne Latten http://orcid.org/0000-0003-1620-0114
Chao Huang http://orcid.org/0000-0002-3627-7218
Paul Comfort http://orcid.org/0000-0002-1131-8626
Frederic V. Valla http://orcid.org/0000-0001-5285-1104

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How to cite this article: Tume LN, Simons C, Latten L, et al. Association between protein intake and muscle wasting in critically ill children: a prospective cohort study. *J Parenter Enteral Nutr*. 2024;1-9. doi:10.1002/jpen.2627