Nutrition in Clinical Practice
Volume 36 Number 2
April 2021 449–455

DOI: 10.1002/ncp.10541
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Clinical Outcomes in Critically Ill Children With Excess Weight: A Retrospective Cohort Study

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Abstract

Background: Because of its high prevalence and negative impact on quality of life and longevity, overweight in childhood and adolescence is a major public health concern. The objective of the present study was to determine whether excess weight is associated with clinical outcomes in critically ill children and adolescents admitted to the pediatric intensive care unit (PICU). *Method:* This retrospective cohort study was performed with children and adolescents admitted to a PICU over 3 years. Nutrition status was classified based on the body mass index *z*-score for age, following World Health Organization (WHO) criteria. The following outcomes were assessed: mortality, need for mechanical ventilation, length of admission, and multiple organ dysfunction syndrome. *Results:* Of 1468 patients admitted during the study period, 1407 were included in the study: 956 (68.0%) had adequate weight, 228 (16.2%) were overweight, and 223 (15.8%) were underweight. Associations were detected between most variables and all nutrition categories (underweight, adequate weight, and overweight). In the descriptive analysis, mortality was more prevalent in nutrition status extremes (extremely underweight or overweight). An independent association between nutrition status and mortality was not detected in any category. *Conclusion:* Nutrition status was not independently associated with poor outcomes. However, overweight should be considered a potential risk factor for adverse clinical outcomes in PICU admissions. (*Nutr Clin Pract.* 2021;36:449–455)

Keywords

body mass index; critical illness; mortality; overweight; pediatric intensive care units; pediatrics

Introduction

Because of its high prevalence and negative impact on quality of life and longevity, overweight in childhood and adolescence is a major public health concern.[1] A study performed by the Imperial College London in partnership with the World Health Organization (WHO), published in 2017, estimated a 10-fold increase over a period of 40 years in the prevalence of overweight in children older than 5 years.[2]

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Financial disclosure: The present study was supported by Brazilian funding agency CAPES (*Coordenação* de Aperfeiçoamento de Pessoal Nível Superior), award code 001.

Conflicts of interest: None declared.

This article originally appeared online on July 3, 2020.

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Studies evaluating nutrition status have usually focused on underweight as predictor of risk; a more recent trend, however, is the investigation of overweight in hospitalized children.[3] Around the year 2000, the first studies focusing on overweight and obese children and adolescents in hospital settings were published.[4-7] According to the latest Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Pediatric Critically Ill Patient, issued by the Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition (ASPEN), *z*-scores for body mass index for age (BMI/A; weight for length < 2 years) should be used to screen patients at extremes of these values on pediatric intensive care unit (PICU) admission. Thus, overweight patients are included in the risk range together with underweight/low-height individuals.[8]

Overweight pediatric patients may experience complications in various organs and systems, which may be more severe in the presence of critical illness.[9] A possible explanation for that refers to the likely exacerbation of inflammatory response.[10-12] An association has been proposed between overweight and pediatric PICU mortality[13]; however, the literature so far shows heterogeneous studies producing conflicting results.[14-16]

The objective of the present study was to determine whether excess weight is associated with clinical outcomes in critically ill children and adolescents admitted to the PICU.

Methods

The present retrospective study was reported following the guidelines described in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist.[17]

Study Population

Patients aged 1 month to 18 years, admitted to a PICU from June 1, 2013, to January 31, 2017, were eligible for the study. Patients who did not have their anthropometric data recorded with extreme prematurity and those with admission duration of <8 hours or >90 days were not included. Admission duration of >90 days was chosen as a cutoff because these patients do not represent the population under study. In patients with multiple admissions, all admissions were considered. Data were collected from the unit's database, hospital information system, and patient charts.

Variables

The following demographic variables were studied: age (months), gestational age at birth (for patients with age ≤24 months), and sex. Admission was categorized in to medical or surgical.

To determine the severity of health status at admission, the Pediatric Index of Mortality 2 (PIM2) score was used.[18] PIM2 was expressed as a categorical variable for analysis: patients with a PIM2 score >75th percentile of the sample's median score were stratified as having the "most unfavorable prognosis."

The presence of complex chronic conditions (CCCs) was evaluated to characterize the sample and for severity adjustment. Patients were classified as with/without CCCs on admission, according to the criteria proposed by Feudtner et al and updated in 2014.[19] The number of CCCs was determined. Associated CCCs were defined as 2 or more co-occurring chronic disorders in 1 single patient.

The biochemical parameters C-reactive protein (CRP) and lactate levels within 24 hours of admission were collected, and values >4 mg/dL and mmol/L, respectively, were considered increased.[20-22]

Mortality was analyzed as a categorical variable (death/survival) for assessment of association with nutrition status. Mortality was also adjusted by PIM2 score using the standardized mortality ratio (SMR) for the comparison of clinical outcomes in different nutrition status categories. SMR is obtained by dividing observed mortality by expected mortality (according to the sample's PIM2 scores). A comparative descriptive analysis was performed for all nutrition status categories.

Additional outcomes were as follows: length of PICU admission (in days; for analysis purposes, prolonged length of PICU admission was defined as admission duration corresponding to the 75th percentile of sample median length); need for mechanical ventilation during admission; presence of infection during admission; development of respiratory, cardiac, renal, hematologic, hepatic, or neurologic dysfunction during admission. The presence of multiple organ dysfunction syndrome (MODS), defined as the presence of at least 2 organ dysfunctions during admission, was also recorded.[23]

Nutrition Status Assessment and Classification

Nutrition status was assessed based on weight and height. Data on anthropometric measurements were obtained from the patients' medical records. These measurements were performed within 24 hours of PICU admission by the nursing team. If anthropometric measurements could not be performed, the patient's most recent data were extracted from hospital records or vaccination cards. For evaluation, 2006/2007 WHO BMI/A and height for age (H/A) standards for children aged 0 to <5 years and from 5 to 19 years were used.[24,25] Both parameters cover all the age ranges in the present study. For patients with gestational age at birth <37 weeks, defined as premature births, age correction was performed before nutrition status assessment. To calculate BMI/A and H/A, the software WHO Anthro 3.2.2 was used for the group aged 0 to <5 years[26] and WHO Anthro Plus 1.0.2 for the group aged 5–19 years,[27] with values expressed as *z*-scores for later classification of nutrition status. Classification was performed according to WHO cutoff points. BMI/A was used as a parameter to classify nutrition status for assessment of association with the outcomes. H/A was used as a complementary analysis to characterize the sample by identifying patients with low and very low H/A. The sample was grouped into 3 nutrition categories (BMI/A) for analysis: adequate/normal weight, underweight, and excess weight. Adequate weight included children classified as adequate/normal weight for age or at risk of overweight. Underweight included children classified as thin or very thin. Excess weight included children classified as overweight, obese, and severely obese.

Statistical Analysis

Because the distribution of continuous variables was asymmetric, these variables were expressed as medians (interquartile range). Categorical variables were expressed as absolute and relative frequency. The χ^2 test for categorical variables and the Kruskal-Wallis test for continuous, asymmetric variables were used to compare nutrition status categories. Bonferroni correction was used in both cases. Poisson regression analysis was used to evaluate an independent association between nutrition status (category) and mortality. Four models were tested, starting with the raw model including only nutrition status and followed by stepwise inclusion of variables with adjustments suggested by the diagram. Causal diagrams were used to guide the selection of variables for the multivariate models. Diagrams are directed acyclic graphs that encode hypotheses about the causal processes that generate Dice. Four models were tested, starting with the crude model, including only nutritional status, followed by inclusion of the variable suggested by the diagram (CCC) and afterwards, inclusion of the other variables. In our study, based on a literature review and the investigators' expertise, the following variables were identified and are presented in Figure 1: age, presence of CCC, MODS, increased CRP and lactate levels, and PIM2.[28-30] Data processing and analysis were performed using SPSS 18.0. A 5% significance level ($P < .05$) was adopted. All the patients admitted to the PICU over the study period were included.

Ethics

The study project was approved by the Institutional Review Board (protocol no. 2.061.931).

Results

Of 1468 admissions during the study period, 61 patients were not eligible based on predefined criteria, and 1407 patients were included in the study. The patient selection process is described in Figure 2.

Inadequate nutrition status was observed in 451 (32%) of the 1407 patients, according to BMI/A. Of these, 228 (16.2%) were classified as excess weight. H/A was considered inadequate in 354 (25.1%) patients. The clinical profile of patients on admission is described in Table 1.

Comparison of nutrition status categories (Table 2) revealed a significant age difference between the groups ($P < .01$). The excess-weight category had the highest number of patients aged <24 months. CRP > 4 mg/dL was significantly more frequent in the excess-weight group vs the adequate/normal-weight group. For all other comparisons, a significant difference was observed only in the underweight group vs other categories regarding worse outcomes. The behavior of excess-weight and normal-weight groups was similar. Overall sample mortality was 3.8% (53 patients); expected mortality according to PIM2 was 4.4% (61.6 patients). Considering an SMR of 0.86 (95% CI, 0.65–1.12), the performance of PIM2 in the study population was adequate. When nutrition status categories were compared in terms of mortality, significance was detected

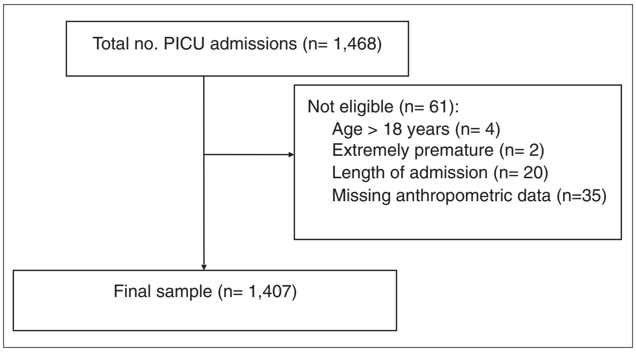

Figure 1. Flowchart of patient inclusion. no., number; PICU, pediatric intensive care unit.

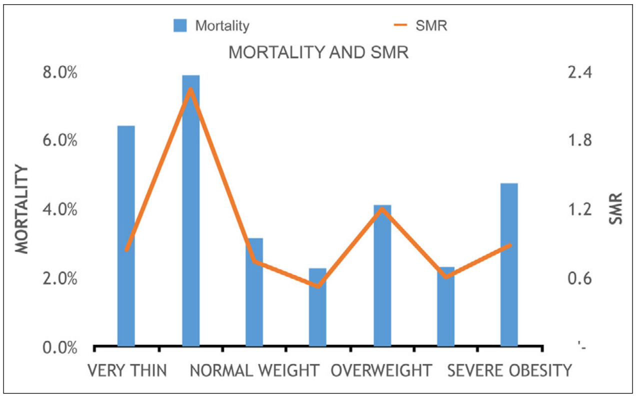

Figure 2. Distribution of mortality and SMR according to nutrition status (body mass index for age). SMR, standardized mortality ratio.

Table 1. Characteristics of the Sample (n = 1407).

Variable	Patients
Age in months, median (IQR)	17.6 (4.9–77.9)
Age ≤ 24 months, n (%)	771 (54.8)
Male sex, n (%)	761 (54.1)
Weight in kg, median (IQR)	10 (5.7–21)
Height in cm, median (IQR)	79 (61–115)
H/A *z*-score, median (IQR)	-0.6 (-0.2 to 0.5)
BMI/A *z*-score, median (IQR)	-0.13 (-1.36 to 1.04)
Type of admission, n (%)	
Medical	907 (64.5)
Surgical	500 (35.5)
With CCC, n (%)	697 (49.6)
Severity on admission (PIM2, %), median (IQR)	1.2 (0.4–3.4)
Nutrition status according to BMI/A, n (%)	
Adequate weight	956 (68)
Normal	824 (58.6)
Risk of overweight	132 (19.4)
Excess weight	228 (16.2)
Overweight	121 (8.6)
Obesity	86 (6.1)
Severe obesity	21 (1.5)
Underweight	223 (15.8)
Thin	114 (8.1)
Very thin	109 (7.7)
H/A categories, n (%)	
Normal	1054 (74.9)
Low height	165 (11.7)
Very low height	189 (13.4)

BMI/A, body mass index for age; CCC, complex chronic condition; H/A, height for age; IQR, interquartile range; PIM2, Pediatric Index of Mortality 2.

for the association with underweight (P = .01). Mortality was not associated with normal weight or excess weight.

Descriptive analysis of mortality and PIM2-adjusted mortality (SMR values) revealed a higher percentage of mortality in patients classified as thin (7.9%) and severely obese (4.8%). SMR values also indicated worse clinical outcome in these groups (Figure 3).

In Figure 3, the causal diagram represents our theoretical model, considering clinical status severity on admission (PIM2), CRP (>4 mg/dL) and lactate (>4 mmol/L) values, MODS, and CCC. These variables were used for adjustment in the multivariate model (Figure 1).

In the multivariate analysis (Table 3), low weight was associated with mortality in models 1 (gross), 2 (indicated by diagram), and 3 (all variables considered). However, in model 4, no independent variable an association was observed between mortality and any category of nutritional status.

Discussion

In the present 3-year cohort, unfavorable clinical outcomes were not observed in excess-weight patients as compared with those in other nutrition status categories. Considering the difficulty of establishing an association in the presence of a large number of confounding factors and differences in clinical characteristics on admission, a causal diagram including theoretical assumptions was used to adjust for confounding variables. This is a novel method of analysis in studies investigating the association between nutrition status and mortality. When an adjustment analysis was performed with the variable indicated by the diagram (CCC), we observed an association of the underweight category with the mortality outcome. As we included the other variables tested, there was no longer an association of any of the categories with the outcome.

The physiological risk linked to overweight cannot be ignored. Overweight may have a deleterious impact on several organs and systems, with metabolic complications and increased inflammatory response.[9,10,31] Nevertheless, there is little evidence of an association between mortality and overweight in critically ill patients, and the assessment of an independent relationship between these factors is difficult. Few studies have evaluated clinical outcomes of overweight patients during hospitalization considering treatments, nutrition support, and response to treatment, all of which are important aspects for discussion, especially in extremely obese patients. Martinez et al,[8] in a report of 2 adolescents with severe obesity admitted to a PICU in Boston, Massachusetts, had difficulties in estimating nutrition needs; also, prolonged admission and use of mechanical ventilation, infections, and need for cardiocirculatory and renal support were described.[32] A retrospective cohort study by the same research group, performed with PICU patients aged 2–21 years, showed worse outcomes in patients with a diagnosis of excess weight, as well as suboptimal nutrient delivery and poorly documented nutrition assessment.[33] In our cohort, which aimed to assess the relationship between nutrition status at admission and outcomes, we did not collect data regarding the nutrition support offered to patients.

The clinical profile on admission is a relevant aspect for discussion in the present study, in which excess-weight patients had a less severe status—lower prevalence of CCCs, higher age, and higher prevalence of elective surgical admissions. The comparison of groups with different physiological status may have impacted our findings. However, we believe that exclusion of the underweight group would have compromised scientific soundness. This is a point discussed by Davis et al,[14] who excluded underweight patients from their analysis. Underweight still affects a high number of hospitalized patients with complications that have been extensively described in the literature.[34-36] The present findings support our initial hypothesis that both nutrition extremes

Table 2. Demographic and Clinical Characteristics and Outcomes According to Nutrition Category. n, Sample Size.

Characteristic	Underweight (n = 223)	Excess weight (n = 228)	Normal weight (n = 956)	*P*
Age ≤ 24 months, n (%)	156 (69.9)[a]	61 (26.7)[b]	554 (57.9)[c]	<.01*
Male sex, n (%)	127 (56.9)	130 (57)	504 (52.7)	.32
Medical admission, n (%)	162 (72.6)[a]	127 (55.7)[b]	618 (64.6)[b]	<.01*
With CCC, n (%)	141 (63.5)[a]	126 (55.2)[b]	430 (44.9)[b]	<.01*
Associated CCC, n (%)	41 (18.4)[a]	28 (12.2)[b]	98 (10.2)[b]	<.01*
PIM2 > 3.4, n (%)	66 (29.6)	47 (20.6)	239 (25)	.08
Normal height (H/A), n (%)	136 (61)[a]	179 (78.5)[b]	739 (77.3)[b]	<.01*
CRP > 4 mg/dL, n (%)	62 (27.8)[a,b]	98 (43.0)[a]	255 (26.7)[b]	.01*
Lactate > 4 mmol/L, n (%)	15 (6.7)	25 (11)	49 (5.1)	.3
Outcome				
Death, n (%)	16 (7.2)[a]	8 (3.5)[a,b]	29 (3)[b]	.01*
Prolonged length of admission	75 (33.6)[a]	42 (18.4)[b]	245 (25.6)[b]	<.01*
MODS	74 (33.1)	46 (20.1)	277 (28.9)	.18
Mechanical ventilation	118 (52.9)[a]	85 (37.2)[b]	429 (44.8)[c]	<.01*

Bonferroni correction represented by superscript letters (a, b, c); different letters indicate difference between the variables.
BMI/A, body mass index for age; CCC, complex chronic condition; CRP, C-reactive protein; H/A, height for age; IQR, interquartile range; MODS, multiple organ dysfunction syndrome; PIM2, Pediatric Index of Mortality 2.
*Significance ($P < .05$). Pearson χ^2 or Kruskal-Wallis, depending on the distribution of variables.

will entail risk of unfavorable outcomes, each involving specific physiological and clinical features.

Regarding the methods used to assess and classify nutrition status, the present study also differs from some previous studies.[13,14,16] For assessment of nutrition status, we only used WHO curves, the current international standard of optimal growth and development. Categories were established on the basis of BMI *z*-scores, chosen for their applicability to the entire study age range. Age correction was performed for premature children up to 24 months of age, a methodological step that is essential in nutrition assessments. A systematic review covering hospitalized children (but not exclusively critically ill children)[15] indicates as a limitation the heterogeneity in the methods of nutrition status assessment and classification. Alipoor et al,[37] who performed a meta-analysis of studies performed strictly in PICUs, also highlight this limitation, underscoring the importance of additional prospective studies. Nevertheless, that meta-analysis does detect a relationship between nutrition risk in obese children and the outcomes of mortality and length of admission.[37]

It is clear that analyzing nutrition status based solely on BMI has limitations because body composition, which was not taken into consideration, is an important factor to identify body fat percentage, which entails higher risk associated with overweight. It should be noted that anthropometric assessment for determination of nutrition status in the PICU is complicated by patient handling and changes in body composition. However, in pragmatic terms, BMI/A assessment is indicated in this setting.[8]

Our descriptive analysis with PIM2 adjustment of mortality showed higher number of deaths and worse outcomes according to SMR in nutrition extremes. These results support the findings of a previous multicentric study performed in 50 PICUs in the United States, which found an independent association between overweight and mortality and a stronger relationship between observed and expected deaths according to SMR in the groups in the lowest and highest ends of the *z*-score range.[13]

Table 3. Multivariate Analysis of the Association Between Nutrition Status and Mortality in Patients in the Pediatric Intensive Care Unit.

Adjustment of variables	OR	95% CI	*P*
Model 1—Raw analysis			
Excess weight	2.365	1.285–4.355	.71
Underweight	2.274	1.242–4.164	<.01*
Model 2—Adjustment for CCC			
Excess weight	1.055	0.482–2.312	.89
Underweight	2.024	1.093–3.749	.02*
Model 3—Adjustment for age and CCC			
Excess weight	0.989	0.445–2.202	.97
Underweight	2.109	1.129–3.938	.01*
Model 4—Adjustment for age, CCC, PIM2, MODS, CRP, and lactate			
Excess weight	1.173	0.498–2.759	.71
Underweight	1.604	0.806–3.194	.17

CCC, complex chronic condition; CRP, C-reactive protein, MODS, multiple organ dysfunction syndrome; OR, odds ratio; PIM2, Pediatric Index of Mortality 2.*

Some limitations of the present study must be considered. First is the use of mechanical ventilation as a

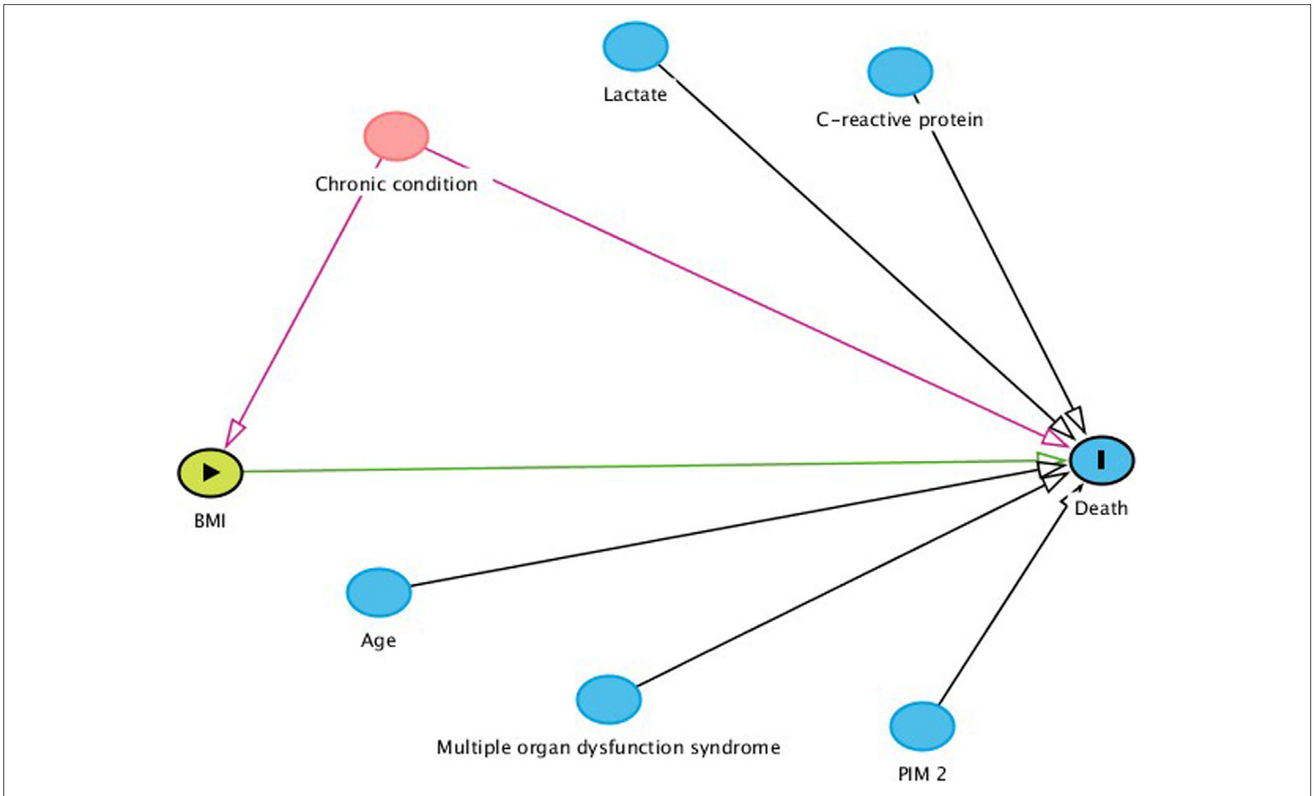

Figure 3. Causal diagram showing the association between nutrition status and mortality as outcome in critically ill children. The diagram represents the variables used in the multivariate analysis. The predictor variable (BMI for age) can be identified on the left and the outcome (mortality) in the center. The remaining variables were used for adjustment, with chronic condition being pointed out by the diagram as a potential confounding factor for BMI and mortality. BMI, body mass index; PIM2, Pediatric Index of Mortality 2.

categorical variable, since the best way to study this outcome would be based on ventilator-free days. However, we were unable to retrieve this information retrospectively from our database. In addition, inflammatory and biochemical markers used to evaluate clinical outcomes should ideally be measured throughout the hospitalization period, not only on admission, which was not possible because of the retrospective nature of the study. Anthropometric measurements may be compromised in PICU patients, a limitation, as previously noted, further enhanced by the retrospective nature of the study. We also acknowledge the inclusion of all age groups as a possible study bias, since the diagnosis of overweight and obesity in children younger than 2 years is still controversial, especially because of the short-term follow-up in this cohort. Finally, we analyzed a mixed medical/surgical PICU, including groups with different admission and severity profiles, complicating comparisons.

In conclusion, despite the absence of an independent association with mortality, overweight on admission should be considered as a potential risk factor for adverse outcomes in PICUs.

Statement of Authorship

C. A. D. Costa and P. C. R. Garcia contributed to the conception or design of the study and acquisition, analysis, or interpretation of the data; drafted the manuscript; critically revised the manuscript; gave final approval; and agree to be accountable for all aspects of work ensuring integrity and accuracy. R. Mattiello and G. C. Forte contributed to the acquisition, analysis, or interpretation of data; critically revised the article; gave final approval; and agree to be accountable for all aspects of work ensuring integrity and accuracy. G. R. H. Andrades, F. Crestani, I. P. Dalenogare, P. R. Einloft, and C. T. Tonial contributed to the conception or design of the study, 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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