Persistent inflammation, immunosuppression and catabolism syndrome (PICS) in critically ill children is associated with clinical outcomes: a prospective longitudinal study


1Nutrition Department, Federal University of Santa Catarina, Florianópolis, Brazil
2Federal University of Santa Catarina, Florianópolis, Brazil
3Nutrition, Joana de Gusmão Children’s Hospital, Florianópolis, Brazil
4Pediatric Intensive Care Unit, Joana de Gusmão Children’s Hospital, Florianópolis, Brazil

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Abstract

Background: Persistent inflammation, immunosuppression and catabolism syndrome (PICS) has been described in critically ill adults and may contribute to unfavourable outcomes. The present study aimed to describe and characterise PICS in critically ill children (PICS-ped) and to verify its association with clinical outcomes.

Methods: A prospective longitudinal study was conducted in a paediatric intensive care unit (PICU) with children aged between 3 months and 15 years. PICS-ped, based on adult definition, was described. PICS-ped was defined as PICU length of stay >14 days; C-reactive protein >10.0 mg L⁻¹; lymphocytes <25%; and any reduction of mid-upper arm circumference Z-score. Clinical, demographic, nutritional status, nutrition therapy parameters and clinical outcomes were assessed. Statistical analysis comprised Mann–Whitney and Fisher’s chi-squared tests, as well as logistic and Cox regression. \( P < 0.05 \) was considered statistically significant.

Results: In total, 153 children were included, with a median age of 51.7 months (interquartile range 15.6–123.4 months), and 60.8% male. The mortality rate was 10.5%. The prevalence of PICS-ped was 4.6%. Days using vasoactive drugs and days using antibiotics were associated with PICS-ped. PICS-ped was associated with mortality in crude (odds ratio = 6.67; \( P = 0.013 \)) and adjusted analysis (odds ratio = 7.14; \( P = 0.017 \)). PICS-ped was also associated with PICU and hospital length of stay, as well as duration of mechanical ventilation. Similar results were found in a subset of critically ill children who required mechanical ventilation for more than 48 h.

Conclusions: Children with PICS-ped required antibiotics or vasoactive drugs for a longer period. PICS-ped was associated with poor clinical outcomes in critically ill children. More studies are needed to properly define PICS-ped for this population.
characterised by prolonged stay in an intensive care unit (ICU) (>14 days), low-grade organ dysfunction and multiple phenotypes, including chronic long-term inflammation, immunosuppression and catabolism (1).

Therefore, patients who survive the acute phase and develop CCI show a phenotype called persistent inflammation, immunosuppression, and catabolism syndrome (PICS), which recently has been described in critically ill adults. The most common biomarkers that describe this syndrome in adults are: inflammation: C-reactive protein (CRP) >50 μg dL⁻¹ (0.5 mg L⁻¹), retinol-binding protein <1 mg dL⁻¹; immunosuppression – total lymphocyte count <0.80 × 10⁹; and protein catabolism – serum albumin <3.0 g dL⁻¹, creatinine height index <80%, weight loss (Fig. 1) (2). These biomarkers are not direct measurements of inflammation, immunosuppression or protein catabolism, although they are considered as surrogates available in most services (3).

As a result of protein catabolism, adult patients with PICS have increased susceptibility to nosocomial infections, which leads to more inflammation and resumption of the vicious cycle (2). Critically ill children are at high risk of loss of lean mass and poor clinical outcomes (4). In response to stress, inflammatory mediators increase, whereas nutritional status deteriorates (5). During the critical illness, there is an activation of the immune system, characterised by an exacerbation of pro-inflammatory response, which is associated with loss of lean body tissue and proteolysis (6). Also, critically ill children with sepsis have early innate and adaptive immune suppression, which is associated with longer periods of organ dysfunction (7).

We hypothesise that PICS in paediatrics (PICS-ped) exists in critically ill and children with PICS-ped have different characteristics compared to critically ill children without PICS-ped. In addition, PICS-ped is associated with longer hospital length of stay (LOS) and with a longer duration of mechanical ventilation (MV). Therefore, considering that PICS-ped has not been evaluated and properly defined in critically ill children, the present study aimed to describe and characterise PICS-ped for critically ill children based on the published adult definition, as well as to verify its association with hospital LOS and duration of MV in an exploratory study.

Materials and methods

Study design and participants

A prospective single-centre cohort study was conducted between July 2013 and January 2016. Critically ill children, aged 3 months to 15 years old, admitted for at least 48 h to medical and surgical PICU in a state in Southern Brazil, were included. Exclusion criteria were death within 72 h of admission and oral nutrition therapy. A non-probability sampling process by time saturation was applied. The study was approved by the local Institutional Review Board (Human Research Ethics Committee) (402.469). Informed consent was obtained from the parents or guardians of all the patients enrolled in the study.

Persistent inflammation, immunosuppression and catabolism syndrome in the paediatric population

To our knowledge, PICS for children has not been defined yet. Therefore, based on the definition proposed for adults, (3) variables that are more frequently used in the clinical practice were selected to identify patients with
PICS-ped. To define the cut-off of PICU LOS for CCI, a receiver operating characteristic curve was constructed, using as an outcome the overall mortality. Similarly to the adult definition, it was determined the cut-off ≥14 days (area under the curve = 0.70; 95% CI = 0.59–0.82; sensitivity 50% and specificity 85%).

For persistent inflammation, hs-CRP (\(\text{mg L}^{-1}\) >10.0 mg L\(^{-1}\)) at day 14 was used, based on a reference value for acute-phase inflammatory responses \((8)\). Lymphocytes <25% on day 14 were used as biomarkers for immunosuppression \((9)\). Protein catabolism was defined as any decrease in the mid-upper arm circumference-for-age \(Z\)-score (MUAC\(Z\)) after 14 days. Weight and body mass index (BMI) were not used as a result of limitations of weight measurement in this population, nor albumin because of inflammation bias \((10)\). CRP, lymphocytes and MUAC were also measured at PICU admission. To minimise the inter-variability in the anthropometric measures, MUAC was recorded by a trained researcher or a dietitian and the same researcher assessed the measure on day 1 and day 14. The PICS-ped is described in Table 1. To be classified with PICS-ped, the child should meet all four criteria.

### Demographic and clinical characteristics

At admission, the Pediatric Index of Mortality 2 (PIM2) was calculated and expressed as the probability of death \((11)\). The reason for admission was classified as medical or surgical. Complex Chronic Condition (CCC) was assessed \((12)\). The duration (in days) of vasoactive drugs and antibiotics was assessed. The dose and the duration of vasoactive drugs and antibiotics were defined by the local staff based on the daily clinical condition of the patient. Fluid overload (in the first 3 days) was calculated and expressed as a percentage. Nosocomial infections, duration of MV, PICU and hospital LOS, and overall mortality were recorded in the patient chart. Nosocomial infection was considered as any acquired infection: bloodstream, urinary tract or pneumonia after 48 h of PICU admission \((13)\). Overall mortality was defined as PICU and hospital mortality combined.

### Nutritional status

Weight, height, and MUAC were measured within 72 h of admission and repeated weekly until the patient’s discharge, in accordance with World Health Organization (WHO) methodology \((14)\). Weight was measured on a paediatric scale (BP Baby; Filizola, São Paulo, Brazil), with a precision of 1 g. Length/height was measured by an anthropometer with a precision of 0.1 cm and, when height was not feasible, for children ≥6 years old, it was predicted based on knee height \((15)\). The Z-scores for body mass index-for-age (BMI\(Z\)) and height-for-age (HA\(Z\)) were calculated using ANTHRO or ANTHROPLUS (WHO, Geneva, Switzerland). MUAC was measured by a previously trained professional with a flexible inelastic tape (cm), with a precision of 0.1 cm, at the midpoint between the acromion and the olecranon. The Z-score for MUAC\(Z\) was calculated in accordance with WHO values in children <5 years old, and according to Frisancho \((16)\) for children ≥5 years old. Nutritional status was classified as moderate undernutrition (≤−2 Z-score), mild undernutrition (≤−1 Z-score) and eutrophic (>−1 Z-score) \((17)\).

### Biochemical parameters

Biochemical parameters were measured within 72 h of admission and repeated weekly until patient discharge. Serum albumin was assessed using the bromocresol green method, with Kit Quimiab – Albumin (EBRAM Ltda, São Paulo, Brazil) using the automated equipment QUI-MISAT 450 (EBRAM Ltda). Serum high-sensitive CRP (hs-CRP) \((\text{mg L}^{-1})\) was determined using the latex immunoturbidimetric method with a commercial kit (Turb – PCR; EBRAM Ltda). The hs-CRP/albumin ratio, obtained as the ratio between the hs-CRP concentration and the albumin concentration, was expressed as \(\text{mg L}^{-1} : \text{g d L}^{-1}\). The hemogram was analysed by the semi-automated method using Heco 5 Plus equipment (Radim Company, Pomezia, Italy) and the values of leucocyte, neutrophil and lymphocytes were expressed in cells mm\(^{-3} \times 10^3\).

### Nutrition therapy

Nutrition therapy variables included time to initiate nutrition therapy, route of delivery, and actual energy

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**Table 1** Criteria for persistent inflammation, immunosuppression and catabolism syndrome in pediatric patients (PICS-ped)

<table>
<thead>
<tr>
<th>PICS-ped criteria</th>
<th>Variable</th>
<th>Cut-off</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic critical illness</td>
<td>PICU length of stay (days)</td>
<td>&gt;14 days*</td>
</tr>
<tr>
<td>Persistent inflammation</td>
<td>C-reactive protein (mg L(^{-1}))</td>
<td>&gt;10 mg L(^{-1}) after 14 days</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>Lymphocytes (% of total leucocytes)</td>
<td>&lt;25% after 14 days</td>
</tr>
<tr>
<td>Catabolism</td>
<td>Mid-upper arm circumference (Z-score)</td>
<td>Any reduction in ≤14 days</td>
</tr>
</tbody>
</table>

PICU, pediatric intensive care unit.

*Area under the curve = 0.70; confidence interval 95% 0.59; 0.82; sensibility 50%; specificity 85%.
and protein intake during the PICU stay. Early nutrition therapy (enteral and/or parenteral nutrition) was defined as initiation within 24 h after PICU admission.

Outcomes

The main outcomes were hospital LOS and duration of MV.

Statistical analysis

Statistical data analysis was performed using STATA, version 11.0 (Stata Corp., College Station, TX, USA). Categorical variables were described in absolute values and frequency. Quantitative variables were reported as the median and interquartile range (IQR).

Crude and adjusted for PIM2 logistic regression analyses were performed to explore the effect of PICS-ped on the overall mortality. The results were expressed as odds ratio (OR) and 95% confidence intervals (95% CI). To explore variables associated with PICS-ped, Fisher’s chi-square and Mann–Whitney tests were applied. To assess the influence of PICS-ped on the duration of MV, PICU and hospital LOS, crude and adjusted Cox regressions were used, and the results were expressed as hazard ratio (HR) and 95% CI. The association with clinical outcomes was also tested in a subset of critically ill children who required MV for more than 48 h, excluding children with potentially milder disease. \( P < 0.05 \) was considered statistically significant.

Results

Patient characteristics

Between July 2013 and January 2016, 715 critically ill children were admitted to the PICU. Of these, 591 were eligible and 153 were included in the study. A flowchart of the recruitment of the participants is provided in the Supporting information (Fig. S1). The median age was 51.7 months (IQR = 15.6–123.4), 60.8% were male and the median PIM2 was 4.7% (IQR = 1.3–16.0). Patients were mainly admitted for medical diagnostics (73.9%). Mortality was observed in 10.5% of the cohort. Clinical and nutrition characteristics are shown in Table 2. The median MUAC\_z reduction after 14 days was a \( Z \)-score of \(-1.02 \) (IQR = \(-1.56 \) to \(-0.75 \)).

Variables associated with persistent inflammation, immunosuppression and catabolism syndrome in critically ill children

The prevalence of PICS-ped was 4.6% (\( n = 7 \)). The prevalence of CCC in patients without PICS-ped was 27.7%, whereas no patient with PICS-ped had CCC. However, a higher prevalence of CCC was observed in surgical patients (42.5%) compared to clinical patients (22.1%) (\( P = 0.013 \); data not shown). Table 3 shows the comparison of variables between patients with and without PICS-ped. Days using vasoactive drugs and days using antibiotics were associated with PICS-ped. There were no significant differences between patients with and without PICS-ped regarding nutrition therapy within the first 7 days (Table 3).

Association between persistent inflammation, immunosuppression and catabolism syndrome in critically ill children and clinical outcomes

PICS-ped was associated with mortality in crude (OR = 6.67; \( P = 0.013 \)) and adjusted analysis (OR = 7.14;
Table 3  Characterisation of critically ill children in a pediatric intensive care unit stratified by PICS-ped (n = 153)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Median [IQR]/n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>without PICS-ped (n = 146)</td>
</tr>
<tr>
<td>Sex (female) n (%)</td>
<td>56 (38.36)</td>
</tr>
<tr>
<td>Age (months)</td>
<td>52.6 [15.5–123.4]</td>
</tr>
<tr>
<td>Reason for admission n (%)</td>
<td></td>
</tr>
<tr>
<td>Medical</td>
<td>109 (74.7)</td>
</tr>
<tr>
<td>Surgical</td>
<td>37 (25.3)</td>
</tr>
<tr>
<td>Respiratory insufficiency n (%)</td>
<td>46 (31.5)</td>
</tr>
<tr>
<td>Fluid overload* (n)</td>
<td>66.3 [35.1–114.0]</td>
</tr>
<tr>
<td>Nutritional status at PICU admission</td>
<td></td>
</tr>
<tr>
<td>Albumin (g dL⁻¹) (n = 147)</td>
<td>3.00 [2.50–3.45]</td>
</tr>
<tr>
<td>C-reactive protein (mg L⁻¹) (n = 143)</td>
<td>29.45 [8.35–66.25]</td>
</tr>
<tr>
<td>C-reactive protein/albumin (g L⁻¹: mg dL⁻¹) (n = 139)</td>
<td>10.63 [2.61–25.81]</td>
</tr>
<tr>
<td>Lymphocytes (%) (n = 144)</td>
<td>14.6 [7.8–25.1]</td>
</tr>
<tr>
<td>Nutritional therapy</td>
<td></td>
</tr>
<tr>
<td>Early NT n (%)</td>
<td>91 (63.2)</td>
</tr>
<tr>
<td>Route of NT (n = 139) n (%)</td>
<td></td>
</tr>
<tr>
<td>Enteral only</td>
<td>108 (81.8)</td>
</tr>
<tr>
<td>Parenteral + enteral or Parenteral</td>
<td>24 (18.2)</td>
</tr>
<tr>
<td>Energy intake</td>
<td></td>
</tr>
<tr>
<td>Goal (kcal kg⁻¹ day⁻¹)†</td>
<td>48.2 (36.4–56.9)</td>
</tr>
<tr>
<td>Prescribed within 7 days (kcal kg⁻¹ day⁻¹)</td>
<td>33.1 (19.5–47.3)</td>
</tr>
<tr>
<td>Actual energy intake within 7 days (kcal kg⁻¹ day⁻¹)</td>
<td>29.0 (14.9–41.7)</td>
</tr>
<tr>
<td>Prescribed within 8–14 days (kcal kg⁻¹ day⁻¹)</td>
<td>47.2 (35.7–65.3)</td>
</tr>
<tr>
<td>Actual energy intake 8–14 days (kcal kg⁻¹ day⁻¹)</td>
<td>42.5 (29.7–51.2)</td>
</tr>
<tr>
<td>Protein intake§</td>
<td></td>
</tr>
<tr>
<td>Prescribed within 7 days (g kg⁻¹ day⁻¹)</td>
<td>1.00 (0.67–1.48)</td>
</tr>
<tr>
<td>Actual protein intake within 7 days (g kg⁻¹ day⁻¹)</td>
<td>0.86 (0.47–1.21)</td>
</tr>
<tr>
<td>Prescribed within 8–14 days (g kg⁻¹ day⁻¹)</td>
<td>1.76 (1.17–1.95)</td>
</tr>
<tr>
<td>Actual protein intake 8–14 days (g kg⁻¹ day⁻¹)</td>
<td>0.96 (0.51–1.53)</td>
</tr>
</tbody>
</table>

Clinical outcomes

| Nosocomial infection n (%) | 33 (23.2) | 3 (42.9) | 0.360† |
| Duration of MV n = 125 (days) | 4 (3–8) | 26 (20–40) | <0.001‡ |
| PICU LOS (days) | 6 (4–11) | 29 (21–40) | <0.001‡ |
| Hospital LOS (days) | 20 (13–31) | 59 (45–142) | <0.001‡ |

BMz, body mass index-for-age; LOS, length of stay; MV, mechanical ventilation; MUACz, mid-upper arm circumference-for-age; NT, nutrition therapy; PICU, pediatric intensive care unit; PIM2, Pediatric Index of Mortality 2.

Early NT: enteral and/or parenteral nutrition initiated within 24 h after PICU admission.

*on the first 3 days.
†Fisher’s chi-squared.
‡Mann–Whitney test.
§Based on the Schofield equation.
‡Protein goal was defined as 1.5 g kg⁻¹ day⁻¹.

P = 0.017). After adjustment for PIM2, patients with PICS-ped had lower chance of an earlier hospital discharge (HR = 0.22; 95% CI = 0.08; 0.61; P = 0.003) and extubation (HR = 0.21; 95% CI = 0.07; 0.57; P = 0.003). Similar results were found in a subset of critically ill children who required MV for more than 48 h (Fig. 2).
Discussion

PICS-ped (defined as PICU LOS >14 days; CRP> 10.0 mg L\(^{-1}\) after 14 days; lymphocytes <25% after 14 days; reduction of MUACz after 14 days) was observed in 4.58% of the critically ill children. These children required antibiotics or vasoactive drugs for a longer period. PICS-ped was associated with poor clinical outcomes. Our results complement existing knowledge regarding PICS and highlight the importance of the early identification of children that are at risk of PICS-ped. By identifying factors that may contribute to PICS condition and characterise this subset of critically ill children, it is possible to recognise conditions that increase the risk for PICS-ped. Therefore, it could improve both early detection and strategies that focus on the treatment of these potential risk factors.

The term PICS is a proposed definition for the persistent inflammation, immunosuppression and catabolism framework that occurs in CCI patients (3). The prolonged PICU LOS may increase the risk for mortality in critically ill children by up to five-fold (18). There is no consensus of the CCI definition for PICU and, consequently, few studies have used it as an outcome for this population (19). Studies have reported that the definition of CCI in the paediatric population ranges from ≥12 days to 30 days. More recently, studies have suggested a definition for CCI in PICU that includes ≥14 consecutive days; or who have a history of prolonged PICU stay and ≥2 acute care/PICU admissions within 12 months (18). In an observational study with 1629 critically ill children, the prevalence of prolonged PICU LOS (>14 days) was 19.6% and the mortality rate was 14.7% versus 11.1% in patients with no prolonged PICU LOS (20).

Patients who progress to CCI usually show signs of a persistent inflammatory response and immunosuppression. In adults, based on genomic analysis, the current evidence suggests that critically ill patients with complicated clinical outcomes exhibit a persistent genomic expression change with defects in the adaptive immune response and increased inflammation (21). Critically ill children with septic shock exhibit early adaptive immunosuppression, which is associated with poor outcomes (22). In a study with 113 critically ill children, prolonged lymphopenia (lymphocyte count of <1000 cells mm\(^{-3}\) for longer than 1 week) was associated with the development of nosocomial infection (OR = 5.5; 95% CI = 1.7–17; \(P < 0.05\)) and mortality (OR = 6.8; 95% CI = 1.3–34; \(P < 0.05\)) (23). Acute-phase proteins, such as CRP, increase after an injury, whereas other proteins decrease, such as serum albumin (5). Therefore, although the role of CRP is not entirely clear, it is considered as an established biomarker of infection and inflammation, especially in paediatrics (24).

The continued activation of inflammation may lead to prolonged catabolism (1). It has been established that critically ill children are exposed to a catabolic state, characterised by increased protein turnover and muscle protein breakdown, resulting in a negative protein balance (25). Lower lean mass and undernutrition, in critically ill children, have been associated with infectious and non-infectious complications, a longer duration of MV, and mortality (26,27). To promote positive nitrogen balance and lower risk of nutrition deterioration, adequate energy and protein intake should be prioritised. Several nutritional status markers are available for use in critically ill children, such as weight and height and MUAC (4). However, the adequate measurement of weight and height is a barrier. Immobility, the need for MV, oedema, and haemodynamic instability are the main reasons why weight accuracy is limited in this population (28). Also, MUAC appears to be less affected by hydration status than weight (29). Therefore, considering the limitations for weight measurement in a PICU population, our
PICS-ped definition uses MUAC, in addition to albumin, as a surrogate for catabolism.

In the present study, days using vasoactive drugs and antibiotics were associated with PICS-ped. Critically ill children who require antibiotics or vasoactive drugs for a longer period are usually the most severe patients and, consequently, show a higher risk for infection, inflammation, and catabolism. In the first 7 days, energy and protein intake were not associated with PICS-ped. However, it has been shown that cumulative energy deficit, in the first week of PICU admission, is associated with worse clinical outcomes and nutritional status deterioration (4).

Energy and protein delivery are associated with the reduction of infections and mortality rates and with lower PICU LOS (30–32). Underfeeding during critical illness aggravates the catabolism and may lead to lean body mass reduction in the already undernourished patient (33). Nonetheless, the excess of energy intake may inhibit autophagy and increase the risk of cell death, organ dysfunction and, consequently, it might be associated with prolonged hospitalisation and mortality (34).

Regardless of the lack of a unified definition, PICS has been associated with poor outcomes in adults. Other than in neonates, (35) no studies were found in the paediatric population. In the present study, patients with PICS-ped had a longer hospital LOS, a longer duration of MV and a higher risk of mortality. PICS in neonates has been associated with metabolic dysregulation, growth impairment and a longer LOS (35). In a study with 123 adults with enterocutaneous fistula, the incidence of PICS was 43.1%. Moreover, the PICS group experienced longer ICU LOS and a higher rate of mortality (28.3% versus 7.1%) (36). In the present study, an overall mortality of 10.5% (16/153) was observed. Mortality in patients with PICS-ped was 42.8% (3/7), whereas, in patients without PICS-ped, it was 8.9% (13/146). In a retrospective cohort study conducted with 214 adult patients with severe acute pancreatitis and prolonged intensive care (>14 days), 149 (69.6%) met the criteria of PICS. Patients with PICS showed longer ICU LOS and higher post-ICU mortality (HR = 4.5; 95% CI = 1.2–16.3; P = 0.024) (37). Patients who develop PICS may experience recurrent infectious and inflammatory complications with consequences as readmissions and surgical procedures. Therefore, despite its low incidence, PICS leads to a substantial burden on the patient and on hospitals (38).

In a previous study, at ICU discharge, PICS patients showed significantly worse nutritional status (37). Furthermore, a substantial loss of lean body mass occurs mainly as a result of the persistent inflammation that leads to catabolism and blocks anabolism, and the decrease in muscle mass appears to happen despite the traditional nutrition support. Also, in the present study, no difference regarding energy and protein prescriptions and goals were found between PICS and no PICS patients. These data may suggest that, in PICS-ped, energy and protein intake were unable to overcome catabolism, and therefore it is important to investigate new nutritional strategies for this subset of critically ill children. In a study conducted with 56 adult patients with CCI, despite receiving nutrition support according to the adult guidelines, sepsis survivors progressed into a chronic malnourished state. The recommendation of nutrition support for patients with CCI and PICS is limited, even for the adult population (39). Therefore, future studies should investigate anabolic nutrition strategies so that patients progress more quickly to the recovery phase and also provide evidence for the development of protocols to optimise nutrition therapies (1).

The present study has some limitations. Despite being a single-centre study, it was conducted in a reference centre in Southern Brazil. The cut-offs and the parameters proposed for PICS in adults may not be appropriate for the paediatric population and the selected parameters may also be used to describe other diseases’ status. However, there is no consensus for the criteria to diagnose PICS, especially in critically ill children. In addition, because MUACz is available for children aged >3 months, we excluded younger children. However, MUAC is considered to be a more feasible measure nutritional status marker than BMI and it appears to be less affected by hydration status than weight, (29) reflecting the nutritional status deterioration more accurately. Also, the median reduction of MUACz was more than 0.67 Z-scores, corresponding to nutritional status deterioration (40). Some of the non-significant differences and unexpected results observed between patients with and without PICS-ped may be a result of the inadequate power and the small sample size. Even though the sample size was small and only 4.58% developed PICS-ped, to our knowledge, this is the first study describing PICS in a pediatric population. Considering the sample size, and the wide 95% CI, we suggest that future studies validate and confirm the definition of PICS-ped in critically ill children.

Conclusions

In an exploratory study of PICU patients, PICS-ped exists in critically ill children. Although it was observed in only 4.6% of the patients, PICS-ped should be investigated in futures studies. The PICS-ped for critically ill children defined in the present study was associated with duration of MV, hospital LOS and mortality, even in a subset of critically ill children mechanically ventilated for more than 48 h. Efforts to determine the factors associated with PICS-ped are important for improving outcomes in this population.
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Conflict of interests, source of funding and authorship

The authors declare that they have no conflicts of interest.

DBH, LDAO and JCV received a scholarship provided by the Coordination for the Improvement of Higher Education Personnel (CAPES).

DBH, LDAO and JCV conceived and designed the study, designed the data collection instruments, collected data, carried out the analyses, contributed to the interpretation of the data, and drafted the initial manuscript. MSF, EB and NLB contributed to the design of the research and the interpretation of the data, and drafted the initial manuscript. YMFM conceived and designed the study, designed the data collection instruments, coordinated and supervised data collection, carried out the analyses, contributed to the interpretation of the data, and drafted the initial manuscript. All authors have critically reviewed its content, approved the final manuscript submitted for publication and agree to be accountable for all aspects of the work.

Transparency declaration

The lead author affirms that this manuscript is an honest, accurate and transparent account of the study being reported. The reporting of this work is compliant with STROBE. The lead author affirms that no important aspects of the study have been omitted and that any discrepancies from the study as planned have been explained.

References


Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Recruitment flowchart.