

## **Persistent inflammation, immunosuppression and catabolism syndrome (PICS): a proposal for definition in critically ill children**

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**Background:** Persistent inflammation, immunosuppression and catabolism syndrome (PICS) has been described in critically ill adults and may contribute to unfavorable outcomes. However, PICS has not been evaluated in critically ill children. This study aimed to define and characterize PICS in critically ill children and to verify its association with clinical outcomes.

**Methods:** Prospective study conducted in a Pediatric Intensive Care Unit (PICU), with children aged between 1 month and 15 years admitted for at least 48 hours to medical and surgical PICU in the south of Brazil. Exclusion criteria were death within 72 hours of admission. Clinical, demographic, anthropometric, biochemical and nutritional therapy parameters were assessed. Duration of mechanical ventilation, PICU and hospital length of stay (LOS) and overall-mortality were recorded in the patient chart. Based on the model proposed by adults, we selected several variables to propose different models to identify patients with PICS. Logistic and Cox regression were applied, and the results were expressed, respectively, as odds ratio (OR) and hazard ratio (HR). P-value <0.05 was considered significant.

**Results:** There were included 201 children (median age 27 months, 63% male). The mortality rate was 13%. Among the 47 surgical patients, 5 (10.64%) were neurosurgery, 10 (21.28%) were cardiac surgery and 32 (68.09%) were general surgery. Among the 6 PICS models proposed, only the model 1 (PICU LOS >14 days; C-reactive protein (CRP) >10.0 mg/L; lymphocytes <25%; reduction of z-score mid-upper arm circumference) was associated with mortality (Table 1). Based on model 1, the prevalence of PICS was 3.5%. The pediatric index of mortality (PIM 2) (p=0.156), and diagnostic (p=0.208) were not different between patients with and without PICS, while the duration of vasoactive drugs and antibiotics, in days, were higher in patients with PICS (p<0.001). After adjustment for PIM 2, patients with PICS had lower chance of an earlier PICU discharge (HR 0.28; 95% CI 0.10; 0.76; p=0.012), hospital discharge (HR

0.28; 95% CI 0.10; 0.77;  $p=0.013$ ) and extubation (HR 0.28; 95% CI 0.10; 0.78;  $p=0.015$ ). Similar results were found for a subset of critically ill children that required mechanical ventilation for more than 48 hours (Table 2).

**Conclusions:** The definition of PICS proposed in this study was associated with clinical outcomes in critically ill children. More studies are needed to properly define and validate PICS for this population.

**Keywords:** Length of Stay. Pediatric Intensive Care Units. Inflammation. Immunosuppression. Muscle Proteins. Mortality.

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**Table 1** – Different models for Persistent inflammation, immunosuppression, and catabolism syndrome (PICS) and the association with overall-mortality.

Models	PICS n (%)	Crude		Adjusted <sup>a</sup>	
		OR (95% CI)	P-value	OR (95% CI)	P-value
<b>Model 1</b> PICU LOS >14 days CRP >10.0 mg/L lymphocytes <25% reduction of MUAC/A z-score after 14 days	7 (3.48)	5.58 (1.17; 26.51)	<b>0.031</b>	5.09 (1.06; 24.58)	<b>0.043</b>
<b>Model 2</b> PICU LOS >14 days CRP >10.0 mg/L nosocomial infection albumin <3.0 g/dL	7 (3.48)	2.83 (0.52; 15.43)	0.228	3.30 (0.60; 18.26)	0.172
<b>Model 3</b> PICU LOS >14 days CRP >10.0 mg/L lymphocytes <25% albumin <3.0 g/dL	5 (2.49)	4.78 (0.76; 30.07)	0.096	5.43 (0.85; 34.68)	0.073
<b>Model 4</b> PICU LOS >14 days CRP >10.0 mg/L nosocomial infection reduction of MUAC/A z-score after 14 days	5 (2.49)	1.71 (0.18; 15.92)	0.637	1.47 (0.15; 14.07)	0.737
<b>Model 5</b> PICU LOS >14 days CRP >10.0 mg/L nosocomial infection MUAC/A z-score <-2 at any time	3 (1.49)	3.46 (0.30; 39.57)	0.318	2.61 (0.22; 31.34)	0.450
<b>Model 6</b> PICU LOS >14 days CRP >10.0 mg/L nosocomial infection reduction of MUAC/A z-score at any time	8 (3.85)	4.43 (0.99; 19.80)	0.051	4.17 (0.92; 18.86)	0.064

<sup>a</sup> adjusted for Pediatric Index of Mortality (PIM) 2

OR: odds ratio; PICU: Pediatric Intensive Care Unit; LOS: length of stay; CRP: C-reactive protein; BMI/A: body mass index-for-age; MUAC/A: mid upper arm circumference-for-age.

**Table 2** - Cox Regression of clinical outcomes in critically ill children (n=201) and in a sample of critically ill children with mechanical ventilation (MV) >48 hours (n=146).

<b>PICS – model 1<sup>a</sup></b>				
<b>Variables</b>	<b>Crude</b>		<b>Adjusted<sup>b</sup></b>	
	<b>HR (95% CI)</b>	<b>p-value</b>	<b>HR (95% CI)</b>	<b>p-value</b>
<b>PICU LOS</b> (days) (n=201)	0.26 (0.10; 0.71)	<b>0.009</b>	0.28 (0.10; 0.76)	<b>0.012</b>
<b>Hospital LOS</b> (days) (n=196)	0.27 (0.10; 0.73)	<b>0.010</b>	0.28 (0.10; 0.77)	<b>0.013</b>
<b>Duration MV</b> (days) (n=179)	0.27 (0.10; 0.74)	<b>0.011</b>	0.28 (0.10; 0.78)	<b>0.015</b>
<b><i>MV &gt;48 hours</i> (n=146)</b>				
<b>PICU LOS</b> (days) (n=146)	0.31 (0.11; 0.84)	<b>0.022</b>	0.33 (0.12; 0.90)	<b>0.031</b>
<b>Hospital LOS</b> (days) (n=142)	0.31 (0.11; 0.86)	<b>0.024</b>	0.33 (0.12; 0.91)	<b>0.033</b>
<b>Duration MV</b> (days) (n=146)	0.28 (0.10; 0.78)	<b>0.015</b>	0.30 (0.10; 0.82)	<b>0.019</b>

HR: Hazard ratio; PICU: Pediatric Intensive Care Unit; LOS: length of stay; MV: mechanical ventilation; CI95%: confidence interval 95%; <sup>a</sup> PICU LOS >14 days and C-reactive protein (CRP) >6.0 mg/dL and lymphocytes <25% and reduction of mid upper arm circumference-for-age z-score after 14 days <sup>b</sup> Adjusted for Pediatric Index of Mortality 2