



# Undernutrition in critically ill children

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**Abstract:** Malnutrition remains a serious issue in the pediatric intensive care unit (PICU) and it is associated with poor clinical outcomes. However, it is commonly unrecognized. There is still no consensus on the best definition of pediatric malnutrition. The scope of this review is to describe and critically discuss the undernutrition identification at admission and during PICU stay and the prevalence of undernutrition in critically ill children reported in the literature. We provide some discussion regarding the implications of undernutrition on the short- and long-term outcomes in critically ill children. In critical illness, negative protein balance with muscle protein loss is higher in comparison to other diseases. This review identified that previous studies have used diverse nutritional indicators and cut-offs to recognize undernutrition in critically ill children, as well as anthropometric measurements and laboratory markers. Besides the undernutrition at admission, critically ill children are also at risk of worsening nutritional status (NS) during PICU stay. Nevertheless, few studies have evaluated the NS deterioration during PICU stay. The prevalence of acute undernutrition in critically ill children may range from 7.2% to 64.9%, according to age, severity of illness, and the nutritional parameter used. NS changes and loss of muscle mass leads to worse prognosis at short and long term, with impairment of function and quality of life. Future data to properly define undernutrition and NS deterioration during PICU stay are needed.

**Keywords:** Malnutrition; critical illness; children; nutritional status (NS)

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## Introduction

Globally, in 2018, 49 million (7.3%) children under 5 years presented acute malnutrition (wasting), and 149 million (21.9%) children under 5 years suffered from stunting (1). Malnutrition remains a leading cause of childhood mortality. According to the Global Burden of Disease Study 2013, the number of deaths for protein-energy malnutrition, age-standardized, was 9.8/1,000,000 in children and adolescents aged 0 to 19 years in the 50 most populous countries. Considering the level of development, malnutrition-related death was 11/100,000 in developing and 0.1/100,000 in

developed countries (2).

Malnutrition is common, but underreported, among hospitalized children. Poor nutritional status (NS) at admission or worsening of NS during hospitalization is recognized to adversely affect clinical outcomes and increase healthcare costs. Thus, there is a need for better identification, documentation, and coding of pediatric malnutrition (3-5).

Mehta and colleagues suggest a new paradigm for defining pediatric malnutrition that includes the chronicity, etiology, mechanisms, severity, and the impact on the outcomes. In addition, obesity and excess energy intake can

be also classified as malnutrition (6). For the purpose of this study, we will consider malnutrition only as pediatric undernutrition.

Despite efforts to properly define and report pediatric malnutrition (6,7), there is still no consensus on the best definition. The disparity of the reported prevalence of undernutrition in hospitalized children, ranging from 2.4% to 39.7%, depends on the population studied, clinical settings, parameters, and classification methods (3).

In critically ill children, the reported prevalence of undernutrition at pediatric intensive care unit (PICU) admission range from 8.1% (8) to 71.7% (9), but the differences in nutritional indices, presence of chronic illness, age and severity of critical illness should be considered when evaluating these numbers. Critically ill children are also at risk of nutritional deterioration due to the illness itself and inadequacy of nutrient delivery (10,11).

Early identification of pediatric undernutrition and the recognition of NS deterioration can lead to prompt and adequate nutritional interventions, which may improve clinical outcomes. This review aimed to report and discuss the undernutrition identification at PICU admission and during PICU stay, and also, to discuss the implications of undernutrition on outcomes in critically ill children.

## **Undernutrition in pediatric critical illness: definition and evaluation**

### *Metabolic response to stress*

In critical illness, the metabolic response to acute conditions, like trauma, infection, or surgery, leads to neuroendocrine, metabolic, and immunologic modifications. The main characteristics are the protein turnover amplified with an increase in hepatic protein synthesis and negative protein balance, insulin resistance, and consequently hyperglycemia and increased lipolysis (12,13). Pediatric critical illness can be characterized in three phases: acute, stable, and recovery phase (12,14). The acute phase, which can last for hours to days after an event, is represented by severe catabolism (12,15). It is considered an adaptive response to protein breakdown to provide free amino acids and energy supply to vital tissues triggering an intense catabolic state (14,16,17).

Therefore, due to the negative protein balance, protein loss is frequently observed, which can result in loss of lean body mass (17). Multiple intracellular signaling pathways are responsible for the expression of atrogenes, which triggers proteolysis by the ubiquitin-proteasome complex

(UPS) and autophagy. The most predominant proteolytic pathway that leads to muscle atrophy is forkhead box protein O (FOXO) and UPS. It provides negative feedback to the phosphoinositol-3 kinase/protein kinase B (PI3K/AKT) pathway, leading to inhibition of protein synthesis and, together with the accelerated proteolysis, leads to muscular atrophy (18,19). In face of infections and severe inflammation, levels of inflammatory cytokines increase and may amplify the process enhancing the protein breakdown (14). Although studies in pediatrics are scarce, it has been shown in a study conducted with critically ill adults that muscle wasting occurred early and fast during the first week of critical illness (20) (*Figure 1*).

The following phase is characterized by stabilization, but some features of the metabolic response remain unsolved. Finally, in the recovery phase, when there is no need of vital organ support, it is observed the resolution of the stress response and the anabolism state with protein synthesis (12). Therefore, patients can progress to death, recovery, or as described more recently, to chronic critical illness (CCI). Patients that develop this new condition may show multiple phenotypes, including persistent inflammation and immunosuppression. The sustained activation of inflammation may lead to prolonged catabolism with loss of muscle mass (21). The loss of lean body mass that leads to deterioration in muscle function is associated with the protein catabolism, immobilization, and nutritional deficits (22).

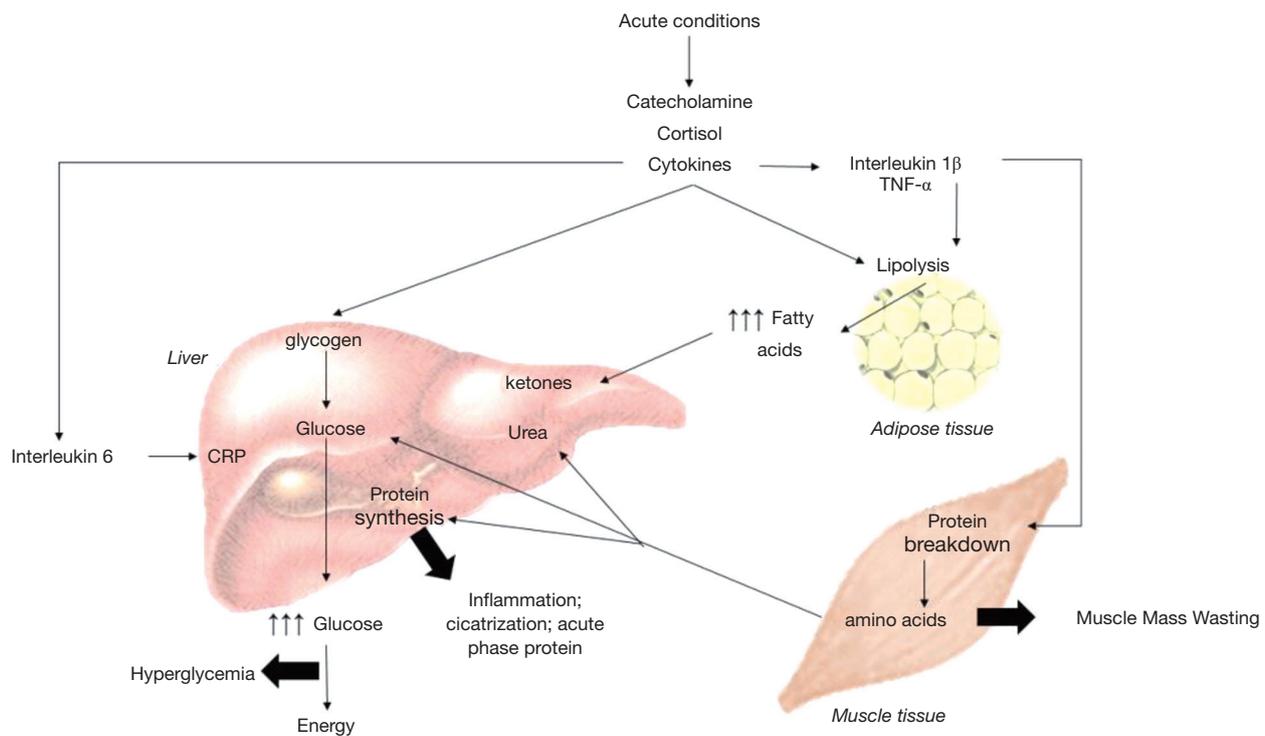
### *NS assessment*

The ideal nutritional approach in PICU should include NS assessment of all critically ill children within 48 hours of admission, to identify undernutrition before hospitalization or during PICU stay (11,23).

The NS assessment can be performed by different indicators, such as anthropometric measurements, physical examination, assessment of serum proteins, and/or inflammatory markers (11,24). Although there is no consensus about the best method to evaluate the NS of critically ill children (25), it should combine static nutritional indices and dynamic nutritional assessment before and during PICU stay, to integrate malnutrition etiology and consequences in its interpretation (6,26).

### **Nutritional risk screening**

Nutritional screening tools (NSTs) have been developed to assist in the early detection of children at risk of



**Figure 1** Metabolic response to stress in critically ill children. CRP, C-reactive portein; TNE, tumor necrosis factor. Adapted from Mehta; Duggan (2009) (12).

malnutrition during hospitalization (6,27). Children identified with a high nutritional risk by NSTs are more likely to benefit from an early nutrition intervention and need close monitoring of NS (11,27).

Previous studies applied NSTs in critically ill children, such as the Screening Tool for Risk of Impaired Nutritional Status and Growth tool (STRONGkids) (28) and the Pediatric Yorkhill Malnutrition Score (PYMS) (29,30), and found divergent results regarding the ability of these NSTs to detect malnutrition risk in these population (31-33). Nutritional risk assessed by STRONGkids presented an area under the curve (AUC) of 0.822, 92.1% sensitivity and 61.1% specificity when compared with WAz (32), and was associated with NS assessed by WAz, HAz and BMIz (31,33). In addition, PYMS presented an AUC of 0.759, 76.2% sensitivity and 63.9% specificity when compared with WAz. However, no significance was found in the effectiveness of both NSTs in screening for malnutrition in these population (32). Furthermore, it should be noted that these NSTs were developed for general hospitalized children and excluded PICU patients in their development. To date, no validated NST for

critically ill children has been identified or developed, and none of the NSTs developed for hospitalized children are validated for PICU patients (11,25).

### Anthropometric parameters

According to the guidelines, it is recommended that weight and height/length (11,34), mid-upper arm circumference (MUAC), and head circumference, in young children <36 months (34), should be measured. The evaluation should include the calculation of the z-scores for body mass index (BMI)-for-age (BMIz) or, weight-for-length (WLz) in children <2 years, or weight-for-age (WAz), if accurate length/height is not available (11,34).

To diagnose undernutrition by anthropometric measurements, reference curves must be used, considering the cut-off points for z-scores established by the World Health Organization (WHO) and/or the Centers for Disease Control and Prevention (CDC) (6). The degrees of undernutrition based on z-scores include “mild or at risk of undernutrition” when z-scores < -1; “moderate undernutrition” when z-scores between -2 and -3; and, “severe undernutrition” when z-scores < -3. The chronicity

of undernutrition can be classified as “*acute undernutrition*” when the duration is lower than 3 months, usually evaluated by WAZ, weight-for-height (WHZ), or BMIz; or “*chronic undernutrition*”, lasting for at least 3 months and evaluated by HAZ (6,7).

There are many challenges in obtaining anthropometric measurements in critically ill children. In an international survey to characterize the barriers to anthropometric measurement, 84% of the health care providers agreed that anthropometric measurements were important, but only 3% indicated that such measurements were always obtained upon PICU admission. The presence of medical devices, need for extracorporeal life support, and unstable hemodynamic status were the most reported perceived patient-specific barriers (35). Besides these barriers, it is important to highlight that weight measurements should be interpreted in the context of fluid shifts, such as the presence of fluid overload and edema (36).

### Growth status

Faltering growth (also called failure to thrive) is considered a dynamic approach that allows to assess growth status and detect impaired growth before reaching undernutrition, according to WHO cut-off points. It is used to describe when children are not growing or gaining weight as expected, and it is defined as a non-voluntary deceleration on WAZ, HAZ, or BMIz decline greater than 1 z-score (6,26,37).

A history of underlying chronic disease has been shown to correlate with the risk of being malnourished and/or presenting with faltering growth at PICU admission. However, faltering growth assessment is rarely performed, due to the necessity of the children’s previous growth data (26,38).

### Laboratory parameters

In addition to anthropometry, laboratory markers can be used as complementary measures in the NS of critically ill children. The role played by serum biomarkers in diagnosing or monitoring undernutrition is still controversial, due to their relatively low specificity and by the fact that they reflect the presence of inflammatory, hypermetabolic, and/or hypercatabolic conditions (6,39,40).

The most commonly used biomarkers in clinical practice include C-reactive protein (CRP), serum albumin, prealbumin, and retinol-binding protein (25,41). While these markers were associated with clinical outcomes such as mortality, length of stay (LOS), and mechanical

ventilation independently from the inflammatory response (42-45), studies showing their predictive value on NS are lacking (41).

Although there is no recommendation for the best laboratory parameters, it is clear that the complex role of inflammation and disease etiology must be accounted in the assessment of pediatric undernutrition (11), and novel biomarkers to track NS during critical illness and in response to interventions should be identified (34).

### Micronutrient status

Micronutrients such as zinc (Zn), selenium (Se), manganese (Mn), and copper (Cu) play an important role in biological functions including antioxidant defense, immune function, DNA repair, glucose control, and healing (46). However, critical illness and inflammation affect serum/plasma micronutrient status, limiting its assessment in intensive care (46,47). In infants and children, due to the immature organ function, specific age-dependent metabolic demands, and susceptibility to environmental influences, it is more complicated to determine their micronutrient status (46).

Recently, a scoping review of micronutrient status during pediatric critical illness summarized some important gaps in knowledge that must be considered for future studies. To date, there are not enough data to establish micronutrient requirements in pediatric critical illness (47,48). Although there is evidence of micronutrient role in the immune and metabolic responses, the causality of the association between micronutrient levels and clinical outcomes remains unclear, as well as the impact of micronutrient supplementation during PICU admission on those outcomes (46,47).

### NS deterioration

NS deterioration is defined as a weight loss or a decline of NS indicators during PICU stay (6,49). Variables such as the severity of illness and PICU LOS may account for NS deterioration, and they may be related to inflammation, oxidative stress (48) and underfeeding in critically ill children. Also, acquired undernutrition during PICU stay and muscle loss may lead to ventilation weaning failure and PICU-acquired weakness (37).

Few studies have evaluated the NS deterioration during PICU stay and there is a lack of standardization of the cut-off points. A prospective study with 579 critically ill children has defined NS deterioration as a weight loss >5% or a decline in BMIz >0.5 SD (37), whereas a case-control study with 80 critically ill children after surgery for congenital heart disease has defined NS deterioration as a decline

in WAZ  $>0.67$  z-score (50). Other studies with critically ill children evaluated NS deterioration based on the reduction of continuous values of different NS indicators, such as MUAC (cm) (51), triceps skinfold thickness (TSF) (mm) (51), arm muscle area (cm<sup>2</sup>) (51), WAZ (38,51-53), HAZ (38), BMIz (51), MUAC for-age z-score (MUACz) (38,51), TSF-for-age (38), biceps skinfold thickness-for-age z-score (38), and calf circumference-for-age z-score (38). Considering that different nutritional indicators and cut-off points are evaluated, it is difficult to compare results between studies.

### Muscle mass wasting

In critical illness, negative protein balance with consequent muscle protein loss is higher in comparison to other diseases, and it is even more intense in the most severely ill patients (54). Also, muscle atrophy in mechanically ventilated critically ill children is common and rapid. It can occur within 5–7 days and, age and traumatic brain injury are risk factors associated with greater muscle loss (55).

The proper definition of muscle mass loss and the use of validated and reproducible tools to assess muscle mass in PICU allows the early identification of muscle wasting in the clinical setting (22,56). However, a comprehensive evaluation of muscle loss in critically ill children can be challenging in clinical practice (55,57).

The current methods available to estimate body composition and muscle mass may show some limitations in PICU. Skinfold thickness, MUAC, and bioelectrical impedance analysis (BIA) may not be reliable for muscle changes, since they are affected by hydration states (57). Also, computerized tomography (CT) or magnetic resonance imaging (MRI) are impractical to perform at bedside (22,57,58). In this context, ultrasound, as a noninvasive technique and available at the bedside, may be a promising method to measure skeletal muscle (22,56). Although there are not sufficient studies investigating ultrasound as a surrogate for muscle mass in critically ill children, the quadriceps femoris (QF) muscle is one of the most commonly measured. In a longitudinal study conducted with critically ill children, QF muscle assessed by ultrasound showed an early and clinically important decrease. However, ultrasound may be compromised by the hydration status (56,57).

For muscle wasting detection, assessing skeletal muscle turnover with more complex methods are being studied in critically ill children. In a study with 19 critically ill children after thoracic surgery, a <sup>15</sup>N glycine urinary end-product enrichment technique was used to investigate whole-body

protein turnover. The method was considered feasible and noninvasive. It was observed an increased protein breakdown resulting in increased protein turnover and net negative protein balance (59).

Therefore, early identification of muscle wasting allows the provision of adequate nutrition therapy and other potential interventions to minimize muscle wasting, and the poor outcomes associated. It is relevant to consider methods for continued measurement of lean mass at the bedside, such as ultrasound or BIA (17,57).

## Prevalence of undernutrition in pediatric critical illness

### Prevalence of undernutrition at PICU admission

Table 1 describes the definition and prevalence of undernutrition in critically ill children at PICU admission. NS at PICU admission is mainly evaluated by anthropometry. Most of the studies defined undernutrition based on WAZ, WHz, or BMIz (z-scores  $< -2$ ), which evaluate acute undernutrition. The prevalence of acute undernutrition ranged from 7.2% to 64.9% as described in Table 1 and Mehta *et al.*'s study (104). Some studies also assessed the presence of chronic undernutrition, evaluated by HAZ, ranging from 16% to 42.8% (38,44,51,60,70,76,79, 89,90,92). Moreover, few studies considered the presence of chronic diseases to evaluate undernutrition (87,88,92). Several studies reported different approaches, z-scores cut-offs, percentiles or weight and height ratios based on Waterlow's recommendations (9,97-103). The dynamic approach was observed only in three studies, conducted in French PICUs, that reported the prevalence of faltering growth, based on WAZ, of 13.7% (26) and 4.8% (67) and 10.2% based on BMIz (37).

The differences in the prevalence of undernutrition can be attributed to the large variability in ages, severity of the disease, presence of complex chronic conditions, and PICU settings and countries. The main risk factors associated with undernutrition at admission were younger age and underlying chronic condition (37,98,100).

### NS deterioration during PICU stay

Table 2 describes the NS deterioration during PICU LOS. Few studies have described the NS changes during PICU stay, and there is a lack of standardization of the cut-off points. Therefore, it is not possible to estimate the real

**Table 1** Reported undernutrition at pediatric intensive care unit (PICU) admission: definitions and prevalence

| Definition                    | Country/region                          | Population   | Undernutrition (%)  | Reference |
|-------------------------------|---|--|---|-----------|
| < -2 z-scores                 |   |  |   |           |
| WAZ, HAZ, BMIz, WHz, MUACz    | China, Single-center                    | Pediatric oncology, 58 months [IQR 1–205], severe critical illness: 26.25%; (N=160)  | WAZ: 11.3%, HAZ: 16.3%, BMIz: 21.3%, WHz: 14.4%, MUACz: 34.4% | (60)      |
| WHz                           | Korea, Single-center                    | MV children, 17.38 months [IQR 0.5–205], PRISM3 17.4 (SD 7.37); (N=70)   | 45.7%   | (61)      |
| <2 years: WHz; >2 years: BMIz | Brazil, Single-center                   | Children with respiratory insufficiency, 6 months [IQR 2–13], PIM2 ≤4%: 75% (N=71)   | 26%   | (62)      |
| WHz                           | Singapore, Single-center                | Children with severe bronchiolitis, 4.9 months [IQR 2–10.4], 62.2% with multiorgan dysfunction; (N=74)                     | 20.3%   | (63)      |
| BMIz                          | 3 Countries, 31 PICUs                   | Children with inotropic support and/or MV and developed hyperglycemia, <2 years: 30.4%; (N=608)                            | 7.2%  | (64)      |
| BMIz                          | Brazil, Single-center                   | Children, 23.1 months [IQR 3.9–89.1], PIM2 4.2 [IQR 1.3–15.7]; (N=199)   | 18%   | (65)      |
| BMIz                          | France, Single-center                   | Children, 13.6 months [IQR 1.9–96.1], PIM2 4.5 [1.5–8.5]; (N=579)  | 15%   | (37)      |
| WAZ                           | United States, 12 PICUs                 | Children, 6.61 years [IQR 1.64–12.92], PIM2 1.34% [IQR 0.79–4.41] (N=2069)   | 21.4%   | (66)      |
| BMIz                          | France, 27 PICUs                        | Children, 2.9 years [IQR 0.5–10.6], PIM2 2.1 [IQR 0.8–8.7]; (N=432)  | 18.5%   | (67)      |
| WHz                           | India, Single center                    | Children with acute gastroenteritis with severe dehydration, 9.5 months [IQR 5–18], sepsis 61%; (N=62)                     | 64.9%   | (68)      |
| WAZ                           | United Kingdom and Netherlands, 2 PICUs | Children aged 0–12 months, with a PICU stay ≥7 days, 2.6 months [0.3–6.0] (PICU1) and 2.6 months [0.4–3.6] (PICU2); (N=53) | 26.41%; (PICU1): 40%; (PICU2): 14%                            | (69)      |
| WAZ, HAZ, WHz                 | United Kingdom, Single-center           | MV children, 2 years [IQR 0.6–4.9], PIM2 score 3.2 [IQR 0.9–6.2]; (N=87)   | WAZ: 15%, HAZ: 17%, WHz: 8%                                   | (70)      |
| BMIz                          | Brazil, Single-center                   | Children, 4.8 years, PIM 2.7; (N=247)  | 15%   | (71)      |

Table 1 (continued)

Table 1 (continued)

| Definition                                 | Country/region   | Population   | Undernutrition (%)   | Reference |
|--|--|--|--|-----------|
| WAZ  | Turkey, Single-center                                  | Children, 16.17 months (range 1.43–92.1), PRISM3 10 (range 0–30) (N=81)                                      | 28.3%  | (40)      |
| BMIZ                                       | France, Single-center                                  | Children, 18.8 months [IQR 2.7–103.8], PIM2 2 [IQR 1–6]; (N=683)   | 13%  | (26)      |
| <2 years: WHz; >2 years: BMIZ              | United States, Single-center                           | MV children, 9.5 months, PRISM3 $\geq 10$ : 26.4%; (N=106)   | 7.5%   | (72)      |
| BMIZ                                       | 26 countries, 129 PICUs                                | Children with severe sepsis, <12 months: 37%; (N=417)  | 18%  | (73)      |
| BMIZ                                       | 15 countries, 57 PICUs                                 | MV surgical children, 2 years [IQR 0.5–8]; (N=519)   | 19%  | (74)      |
| WAZ  | Taiwan, Single-center                                  | Children, 4.4 years (range 0.1–18); (N=282)  | 8.2%   | (75)      |
| WAZ, HAZ, BMIZ                             | Brazil, Single-center                                  | MV children, 21.1 months [IQR 4.4–82.2], PIM2 8.0 [IQR 1.6–21.1]; (N=72)                                     | WAZ: 33.9%;<br>HAZ: 41.2%<br>BMIZ: 22.1%;                                      | (76)      |
| WAZ  | Rwanda, Single-center                                  | Children, newborn – 15 years, <1 year: 60%; (N=210)  | 59%; Severe: 30%   | (77)      |
| BMIZ                                       | 16 countries, 90 PICUs                                 | MV children, 4.5 years (SD 5.1), severe severity of illness: 29%; (N=1622)                                   | 18%  | (78)      |
| <2 years: WAZ, HAZ, WHz;<br>>2 years: BMIZ | Brazil, Single-center                                  | Children, 34 months [9–85], PIM2 3.12 [1.17–8.57]; (N=271)   | 42.4%  | (44)      |
| WAZ, HAZ, MUACz                            | Brazil, Single-center                                  | Children with sepsis, 24 months; (N=14)  | WAZ: 33.3%; HAZ:<br>42.8%; MUACz:<br>66.6%                                     | (79)      |
| BMIZ                                       | India, Single-center                                   | Children, PIM2>15: 23%; (N=332)  | 57.2%  | (80)      |
| WAZ  | Netherlands, Single-center                             | Children receiving enteral nutrition (newborns 138, infants 99 and children 88), PRISM 8 [IQR 0–31]; (N=325) | 19%  | (81)      |
| WAZ  | 15 countries, 59 PICUs                                 | MV children, 1.7 years [IQR 0.4–7.0], severe severity of illness: 22%; (N=1245)                              | 25%  | (82)      |
| WAZ  | United Kingdom, Single center Two cohorts (2009, 2010) | Children fed exclusively with EN, 0.3 to 49 years, PIM2 0.5–2.3; (N=130)                                     | <i>CHD surgical</i> : 31%; <i>Medical</i> : 15%; <i>General surgical</i> : 18% | (83)      |
| WAZ  | United States and Canada, 12 PICUs                     | Children, 2.4 years [IQR 0.5–9.8]; (N=5105)  | 28.16%   | (84)      |
| Non reported                               | Brazil, Single-center                                  | MV children, 28 months (range 1–201) (N=96)  | 50%  | (85)      |

Table 1 (continued)

Table 1 (continued)

| Definition   | Country/region               | Population  | Undernutrition (%)   | Reference |
|--|------------------------------|---|--|-----------|
| WAZ  | Malaysia, Single-center      | Children on enteral nutritional support, 10.2 months [IQR 5.1–50.5]; (N=53)   | 43.2   | (86)      |
| <2 years: WAZ; >2 years: BMIZ; chronic diseases: HAZ           | Brazil, Single center        | Critically, 2.3 years [0.6–13.5], PIM2 2.9 [1.2–6.5]; (N=281)   | 47.1%  | (87)      |
| WAZ, BMIZ; chronic diseases: HAZ                               | Brazil, Single center        | Children using EN or PN, 11.2 months [2.6–58.3], PIM2 3.5 [1.2–7.9]; (N=207)  | 54.1%  | (88)      |
| acute: WAZ; chronic: HAZ                                       | United States, Single-center | Children, 1.4 [IQR 0.3–9.4] years, no-AKI: 61%, AKI†: 12%, PRISM3 no-AKI: 3 [IQR 1–7] and AKI†: 7 [IQR 5–10.3]; (N=167) | acute: 20% (AKI: 33%); chronic: 17.6% (AKI: 23.8%)                               | (89)      |
| acute: WAZ; chronic: HAZ                                       | United States, Single-center | Children, PRIM3 III 5.0 (range 0–29); (N=240)   | chronic: 23.3%   | (90)      |
| BMIZ   | 8 countries, 31 PICUs        | MV children, 4.5 years (SD 5.1), severe severity of illness: 28.2%; (N=500)   | 17.1%; mild: 14.4%   | (91)      |
| <2 years: WAZ, HAZ, WHz; >2 years: BMIZ; chronic diseases: HAZ | Brazil, Single-center        | Children, 18.3 months [IQR 3.9–63.3], PIM2 2.0 [IQR 1–5.9] (N=385)  | 45.5%  | (92)      |
| <2 years: WAZ; >2 years: BMIZ                                  | Brazil, Single center        | Children receiving EN, 11 months [IQR 3–65], PIM2 11 [IQR 3–65]; (N=291)  | 41.2%  | (93)      |
| WAZ, HAZ, WHz, BMIZ, MUACz                                     | Brazil, Single-center        | Children with PICU LOS > 7 days, <2 years: 41%; (N=90)  | WAZ: 27.7%, HAZ: 50%, WHz: 8%, BMIZ: 13.3%, MUACz: 47.8%                         | (51)      |
| WAZ  | Canada, Single-center        | MV children, 0.65 years [IQR 0.17–6.2], PIM2 6.8 [4.9–10.5]; (N=49)   | 20%  | (94)      |
| <2 years: WAZ; >2 years: BMIZ                                  | Brazil, Single-center        | Children, 1.8 years [IQR 0.43–7.17], PIM2 1.45 [IQR 0.85–4.95]. N=82  | 39.1%  | (95)      |
| WAZ  | Brazil, Single-center        | Children, undernourished 25.6 months / well-nourished 10.7 months; (N=1077)   | 53%  | (96)      |
| acute: WAZ, MUACz; chronic: HAZ, TSFz                          | Netherlands, Single-center   | Children, >30 days: 32%, 1.4 years (range 31 days–17 years), PRISM 11 (range 0–38); (N=293)                             | In children > 30 days; acute: WAZ: 24%; MUACz: 15%; chronic: HAZ: 22%; TSFz: 10% | (38)      |

Table 1 (continued)

Table 1 (continued)

| Definition   | Country/region               | Population  | Undernutrition (%)          | Reference |
|--|------------------------------|---|-----------------------------|-----------|
| Others Cut offs                                    |                              |   |                             |           |
| BMI < P5   | United States, 53 PICUs      | Children with sepsis and septic shock; (N=7038)   | 11.6%                       | (97)      |
| <2 years: WHz < P5; >2 years: BMIz < -1.89 or < P3 | United States, Single-center | Children, <1 year: 24.8%; (N=1447)  | 15%                         | (98)      |
| <2 years: WA percentile; > 2 years: BMI percentile | Egypt, Single-center         | Children, 14.3 months (SD 13.9); (N=50)   | 24%                         | (99)      |
| BMI-z < -1.89                                      | 43 PICUs, (5 studies)        | Children older than 2 years with PARDS, 9.6 years (SD 5.1), PRISM3 11 [IQR 6–16]; (N=331).  | 12%                         | (100)     |
| <2 years: WH <P5; >2 years: BMI <P5                | Canada, Single-center        | Children, 17 months [IQR 5–51], PRISM3 4 [IQR 1.8–9] (N=100)  | 21%                         | (101)     |
| WA <P3; acute: W/P50 WA<0.85                       | Spain, Single-center         | Children with AKI receiving continuous renal replacement therapy, 18.5 months [IQR 4.0–81.8], PRISM score 13 [IQR 10–20]; (N=174) | 35%; acute: 56%             | (102)     |
| acute: W/P50 WH <80%; chronic: H/P50 HA <90%       | United States, Single-center | Children, 80 months, PRISM 8.89 (SE 0.76); (N=37)   | acute: 8.1%; chronic: 22.1% | (8)       |
| WA< P10; severe: WA< P3                            | Spain, Single-center         | MV children, 7.5 months [IQR 3.8–25.8], PIM2 3.7 [IQR 2.2–9.5]; (N=46)  | 71.7%; severe: 58.7%        | (9)       |
| acute: W/P50 WH <80%; chronic: H/P50 HA <90%       | Greece, Single-center        | MV children, 71.8 (SEM 6.8) months, PRISM 12.8 (SEM 0.84); (N=71)   | acute: 5.6%; chronic: 4.2%  | (103)     |

N, number of participants; BMI, body mass index; W, weight; H, height; HA, height-for-age; WA, weight-for-age; MUAC, mid-upper arm circumference; TSF, triceps skinfold; W / P50 WH, actual weight/ weight-for-height in 50th percentile ratio; SEM, standard error of mean; IQR, interquartile range; SD, standard deviation. WHz, weight-for-length z score; P, percentile; PIM2, pediatric index of mortality 2; PRISM, pediatric risk of mortality; CHD, congenital heart disease; AKI, acute kidney injury; PICU, pediatric intensive care unit; LOS, length of stay; MV, mechanical ventilation; PARDS, pediatric acute respiratory distress syndrome; EN, enteral nutrition. †, AKI: injury + failure.

prevalence of NS deterioration during critical illness in children. A French single-center prospective study found that in children who stayed longer than 5 days, PICU-acquired faltering growth was observed to be an early, significant, and relatively frequent phenomenon (37).

## Consequences of undernutrition during critical illness

### Short-term outcomes

Table 3 describes the association of undernutrition during critical illness and outcomes in children. Undernutrition at PICU admission, based on a single anthropometric

measurement, is associated to adverse clinical outcomes, such as increased mortality (65,78,102), increased duration of mechanical ventilation (60,76,78,92), increased PICU LOS (60,65,98), and hospital LOS (78,98). Although undernutrition based on a single anthropometric measurement is associated to adverse clinical outcomes, it is important to highlight that single anthropometric measurement does not evaluate important aspects of NS, such as growth velocity, chronicity, and functional status (6,25).

Additionally, NS deterioration may have an impact on PICU outcomes. However, there are limited data available on the NS change during PICU stay, and the intensity, frequency, and impact of NS deterioration on adverse

**Table 2** Nutritional status deterioration of critically ill children during PICU length of stay

| Parameters                             | Setting                    | Population   | NS Changes  | Reference |
|--|----------------------------|--|---|-----------|
| PICU-acquired faltering growth, BMIz   | France, Single-center      | Children, 13.6 months [IQR 1.9-96.1], PIM2 4.5 [1.5-8.5]; (N=579)  | Faltering growth: 10.2%; ↓ BMIz >0.5 SD: 27.8%  | (37)      |
| Weight                                 | Canada, Single-center      | Children, 17 months [IQR 5-51], PRISM3 4 [IQR 1.8-9] (N=100)   | <6 months: ↑ 3.0% of admission weight; 7–36 months: ↔ admission weight.; >37 months: ↓ 1.6% admission weight. | (101)     |
| WAZ, HAZ, WHz, BMIz, MUACz or TSF (mm) | Brazil, Single-center      | Children with PICU LOS > 7 days, <2 years: 41%. (N=90)   | In 7 days: ↓ MUACz and ↓ TSF (mm)   | (51)      |
| NS deterioration                       | Netherlands, Single-center | Children, 1.4 years (range 31 days-17years) in children older than 30 days, PRISM 11 (range 0–38); (N=293) | In children > 30 days: 4% with NS deterioration   | (38)      |

N, number of participants; BMI, body mass index; HA, height-for-age; WA, weight-for-age; MUAC, mid-upper arm circumference; TSF, triceps skinfold; IQR, interquartile range; SD, standard deviation. WHz, weight-for-length z score; pediatric index of mortality 2; PRISM, pediatric risk of mortality; PICU, pediatric intensive care unit. PICU-acquired faltering growth, decline of 1 standard deviation in BMIz. NS deterioration, decline of 1 standard deviation in weight-for-age z-score.

outcomes are still uncertain (37).

### Long term outcomes

Besides the effects during PICU stay, undernutrition in critical illness and the PICU experience itself, may also adversely affect overall long-term pediatric outcomes, such as the development and growth, in addition to other relevant outcomes (82). The increase in the number of survivors observed in the last few decades leads to a higher number of patients using and needing post-intensive care health services (82,85).

It is important to highlight that evaluating morbidity only at discharge may underestimate the consequences associated with a critical illness. Conditions present before the admission or acquired during PICU stay may progress after discharge, increasing morbidity and mortality of children previously admitted to a PICU (105). It is known from adult studies that the impact of the negative protein balance on muscle function and quality of life can continue for months or years (106). Although some studies showed a recovery on NS after 3 months (26) to 6 months (38) of PICU discharge, the influence of undernutrition, NS

deterioration, or muscle wasting during the critical illness on long-term outcomes is still unknown.

### Conclusions

The identification of undernutrition in critically ill children is important since they are most vulnerable and therefore potentially may benefit from timely nutrition intervention (11). In critically ill children, moderate to severe undernutrition is prevalent at PICU admission worldwide, and it is associated with worsened clinical outcomes. However, the prevalence of children at nutritional risk is unknown. Also, there are not NSTs validated for critically ill children. Considering that in a limited resource setting, timely and detailed nutrition assessment of every child in the PICU may not be feasible (11), efforts should be driven to the development of NSTs feasible to apply in PICU.

Moreover, there are limited data regarding NS deterioration during PICU LOS. The definition of NS deterioration and studies to evaluate the association of NS deterioration during pediatric critical illness and their impact on short-term and long-term outcomes are needed.

**Table 3** Association of undernutrition during critical illness and outcomes in children

| Undernutrition                                    | Setting                      | Population   | Main Results  | Reference |
|---|------------------------------|--|---|-----------|
| WAZ, HAZ, BMIz, WHz or MUACz: < -2 z score        | China, Single-center         | Pediatric oncology, 58 months [IQR 1–205], severe critical illness: 26.25%. (N=160)                    | <ul style="list-style-type: none"> <li>• WAZ, HAZ, WHz and MUACz: ↑ duration of MV</li> <li>• WAZ: ↑ PICU LOS</li> </ul> <i>(adjusted by sex, age, and pediatric critical illness score)</i>    | (60)      |
| WHz: < -2 z score                                 | Singapore Single-center      | Children with severe bronchiolitis, 4.9 months [IQR 2–10.4], 62.2% with multiorgan dysfunction. (N=74) | <ul style="list-style-type: none"> <li>• ↑ duration of MV</li> </ul> <i>(multivariate analysis SpO<sub>2</sub> to FiO<sub>2</sub> ratio, multiorgan dysfunction and baseline comorbidities)</i> | (63)      |
| BMIz, MUACz or TSFz: < -2 z score                 | Brazil, Single-center        | Children, 23.1 months [IQR 3.9–89.1], PIM2 4.2 [IQR 1.3–15.7]. (N=199)                                 | <ul style="list-style-type: none"> <li>• BMIz, MUACz or TSFz: ↑ 60-day mortality</li> <li>• MUACz: ↑ PICU LOS</li> </ul> <i>(adjusted by sex, age, PIM2, and complex chronic condition)</i>     | (65)      |
| <2 years: WH <P5 >2 years: BMI <P5                | United States 53 PICUs       | Children with sepsis and septic shock (N=7038)   | No association with mortality   | (97)      |
| <2 years: WHz < P5 >2 years: BMIz < -1.89 or < P3 | United States, Single-center | Children, <1 year: 24.8%. (N=1447)   | <ul style="list-style-type: none"> <li>• ↑PICU LOS (in comparison to normal or obese)</li> <li>• ↑ Hospital LOS</li> </ul> <i>(adjusted)</i>  | (98)      |
| <2 years: WHz >2 years: BMIz                      | United States, Single-center | MV children, 9.5 months, PRISM3 ≥10: 26.4%. (N=106)  | No association with any worse clinical outcome measure (duration MV, PICU LOS and hospital LOS)   | (72)      |
| BMIz < -2 z score                                 | 26 countries, 129 PICUs      | Children with severe sepsis, <12 months: 37%. (N=417)  | <ul style="list-style-type: none"> <li>• BMIz &lt; -3: ↑ all-cause ICU mortality</li> </ul> <i>(adjusted)</i>   | (73)      |
| Faltering growth                                  | France, Single-center        | Children, 18.8 months [IQR 2.7–103.8], PIM2 2 [IQR 1–6]. (N=683)                                       | <ul style="list-style-type: none"> <li>• ↑ PICU LOS</li> </ul> <i>(adjusted by age, sex, chronic underlying disease, acquired infection, and PIM2 score)</i>                                    | (26)      |
| WAZ < -2 z score                                  | Taiwan, Single-center        | Children, 4.4 years (range 0.1–18). (N=282)  | <ul style="list-style-type: none"> <li>• WAZ ≤ -2 and PIM2: ↑ morbidity (overall poor outcomes)</li> </ul> <i>(adjusted by age, PIM2, hypotension, noninfectious diseases, creatinine sex)</i>  | (75)      |

**Table 3** (continued)

Table 3 (continued)

| Undernutrition  | Setting                | Population  | Main Results  | Reference |
|---|------------------------|---|---|-----------|
| WAZ, HAZ, BMIz, UAMAz < -2 z score  | Brazil, Single-center  | MV children, 21.1 months [IQR 4.4–82.2], PIM2 8.0 [IQR 1.6–21.1]. (N=72)                            | • WAZ, HAZ or UAMAz: ↑ duration of MV<br>(adjusted by sex, age, PIM2)   | (76)      |
| BMIz < -2 z score   | 16 countries, 90 PICUs | MV children, 4.5 years (SD 5.1), severe severity of illness: 29%. (N=1622)                          | • BMIz: ↑ 60-day mortality†, ↑ acquired infections‡, ↓ VFD, hospital LOS‡<br>(adjusted by: †location, age, sex, study year, admission category, diagnosis category, PICU size, infections, LOS, and illness severity, ‡age, sex, study year, admission category, diagnosis category, illness severity, and PICU size) | (78)      |
| BMI-z < -1.89   | International 43 PICUs | Children older than 2 years with PARDS, 9.6 years (SD 5.1), PRISM-III score 11 [IQR 6–16]. (N=331). | No association with mortality   | (100)     |
| <2 years: WAZ/HAz/WHz < -2 z score >2 years: BMIz < -2 z score chronic diseases: HAZ < -2 z score | Brazil, Single-center  | Children, 18.3 months [IQR 3.9–63.3], PIM2 2.0 [IQR 1–5.9] (N=385)                                  | • ↔ hospital LOS<br>• ↑ duration MV<br>(adjusted by septic shock, PELOD>11, medical diagnose)   | (92)      |

N, number of participants; BMIz, body mass index-for-age z score; HAZ, height-for-age z score; WAZ, weight-for-age z score; WHz, weight-for-length z score; MUACz, mid-upper arm circumference-for-age z score; UAMAz, upper arm muscle area-for-age z-score; TSF, triceps skinfold; IQR, interquartile range; P, percentile; PIM2, pediatric index of mortality 2; PRISM, pediatric risk of mortality; PELOD, pediatric logistic organ dysfunction; PICU, pediatric intensive care unit; LOS: length of stay; MV, mechanical ventilation; VFD, ventilator free days. Faltering growth: decline of 1 standard deviation in WAZ.

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