Research Article



Impact of malnutrition on pediatric risk of mortality score and outcome in Pediatric Intensive Care Unit

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Abstrac

Objectives: This study was done to determine the effect of malnutrition on mortality in Pediatric Intensive Care Unit (PICU) and on the pediatric risk of mortality (PRISM) scoring. **Subjects and Methods:** This was a prospective study done over I year. There were total 400 patients (I month I4 years), who were divided into cases with weight for age $<3^{rd}$ centile and controls with $\ge 3^{rd}$ centile of WHO charts. Cases were subdivided into mild/moderate (61–80% of expected weight for age) and severe malnutrition (<60%). **Results:** Out of total, 38.5% patients were underweight, and malnutrition was more in infancy, 61/104, i.e. 58.5% (P - 0.003). There was no significant difference in vitals at admission. Cases needed prolonged mechanical ventilation (P - 0.0063) and hospital stay (P - 0.0332) compared to controls. Mean and median PRISM scores were comparable in both the groups, but mortality was significantly higher in severely malnourished (P - 0.027). **Conclusion:** Severe malnutrition is independently associated with higher mortality even with similar PRISM score. There is need to give an additional score to children with weight for age <60% of expected.

Keywords: Anthropometric data, malnutrition, outcome in malnourished children, pediatric risk of mortality



Introduction

The World Health Organization (WHO) defines malnutrition as the cellular imbalance between the supply of nutrients and energy and the body's demand for them to ensure growth, maintenance, and specific functions. Undernutrition could be primary (not consuming adequate calories, e.g., poverty, etc.,) or secondary (abnormal nutrient loss, due to diarrhea or chronic illness or increased energy expenditure).^[1] The studies have documented that severely malnourished children are at a much higher risk of dying than are healthy children and also these children have more severe disease episodes, associated with more complications, and also spends more time ill for each episode.^[2,3] There is a high incidence of malnourished

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children in developing countries than in developed countries. Nutritional status can be assessed using clinical signs of malnutrition, biochemical indicators, and anthropometry. Anthropometric measurements, such as weight and height, and the interpretation of these, are an objective and quantitative element of nutritional assessment. Anthropometry has an important advantage over other nutritional indicators, whereas biochemical and clinical indicators are useful only at extremes of malnutrition, body measurements are sensitive over the full spectrum. Is noninvasive, inexpensive, and relatively easy to obtain.

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There is not enough data available to know if malnourished children admitted to Pediatric Intensive Care Unit (PICU), have a worse outcome as compared to other critically sick children with normal nutritional status. In a study done in Brazil showed that presence of malnourishment increases mortality of children admitted to PICU.^[7] The previous study from All India Institute of Medical Sciences, India, on the pediatric risk of mortality (PRISM) score concluded that there was a trend toward higher standardized mortality ratio for severely malnourished children using all the three scoring systems (PRISM, pediatric index of mortality [PIM], PIM II).^[8]

PRISM is the most widely used scoring system to predict mortality. Even in developing countries, including authors unit, it is now routinely been applied to PICUs to identify factors related to structure or process of intensive care that are associated with quality of care. [9,10] PRISM scoring has many parameters but does not take nutritional status into consideration. Since malnutrition is common in developing countries, this prospective study was done to assess the nutritional status by doing weight and height of children admitted to ICU, to correlate growth parameters with the outcome, and to assess mortality in malnourished children in relation to PRISM score.

Subjects and Methods

It was a prospective study conducted in ten bedded PICU at a tertiary care, teaching hospital, Ludhiana, over a period of 1 year. All patients admitted to PICU in the age group of 1 month 14 years were included in the study. Detailed history and examination were done in all the patients including the relevant investigations. The physiological data were collected at admission including the vitals.

Anthropometric parameters including weight for age, height (length) for age, weight for height were measured within 24 h of admission. Weight for age was taken as the gold standard for interpretation. For children more than 10 years, BMI as per WHO charts was taken to assess nutrition and growth. Weighing scale Goldtech Model Gtep, accuracy 20 g, range 400 g to 200 kg was used for weighing children and Essae DS 252 model BS250, accuracy 20 g, range 400 g to 15 kg was used for infants. Height/length was taken using the standard technique.

Patients who died within 24 h of admission or discharged against medical advice were excluded from the ultimate outcome (mortality). Patients who were small for gestational age (birth weight <2.5 kg),

diagnosed to have chromosomal syndromes, and neonates were also excluded from the study. At the end of the study period, patients were divided into two groups, children with normal weight (no malnutrition) i.e. $>3^{\rm rd}$ percentile as per WHO growth charts were taken as controls and weight for age $<3^{\rm rd}$ centile were taken as cases. Cases were further subdivided into various grades of malnutrition with <60% of expected as severe malnutrition and between 60% and 80% of $50^{\rm th}$ centile of weight for age as mild to moderate malnutrition. Chronic malnutrition or stunting was taken if height for age was <90% of expected, with weight for height ratio as normal.

PRISM scoring (14 components)^[12] was done in all the patients within 24 h of admission. The original version of PRISM software was used in the study as in this; mortality is predicted as per score of the individual patient. The study was approved by the Ethical Committee of the Institution, and consent was taken from all the parents. For socio-economic status of the families, Kuppuswamy's Socioeconomic Status Scale-Updating for 2007 was used.^[13]

Appropriate statistical methods (Student's *t*-test, Chi-square test, and Z-test) were used to know the significance of the impact of growth parameters on PRISM in determining the outcome.

Results

After exclusion of all neonates and patients who stayed in PICU for <24 h, 400 children were enrolled in the study. Anthropometry (weight for age, height for age, and weight for height) was done in all these patients at admission, and the data were interpreted according to the WHO charts (in percentiles) as the standard and then classified into underweight and grades of malnutrition. Weight was taken as the gold standard for interpretation of the observations.

Mean and median age of the patients was 57.9 and 39 months, respectively. There were 246 (61.5%) patients who had normal weight for age as per WHO charts and grouped as controls and the rest 154 (38.5%) had weight for age $<3^{\rm rd}$ centile and labeled as cases. Out of the underweight children, 107 (69.5%) patients had mild to moderate malnutrition, i.e., 60–80% of $50^{\rm th}$ centile of weight for age and 47 (30.5%) patients were severely malnourished <60% of the expected weight. In addition, 43 patients were stunted, out of these 49% had severe malnutrition.

These were not separately assessed because of less number.

Table 1 shows the age wise distribution and demography of cases and controls. Infants were significantly more

malnourished as compared to other age groups, and there was no difference in gender distribution or socioeconomic status of patients regarding nutritional status.

Primary system involvement in controls versus cases

It was noted that major systems were equally involved in cases and controls, but in cardiovascular system-related diseases, more number of patients had malnutrition, which was statistically significant (0.0320) and almost all these had underlying congenital heart diseases.

Vitals in controls versus cases

All the 14 components of PRISM score were used in this study, namely, systolic BP, diastolic BP, heart rate, respiratory rate, pupillary reaction, GCS score, PaO2/FiO2, PaCO2, PTI, bilirubin, calcium, potassium, glucose, bicarbonate were noted in cases and controls. A total of 91 patients had tachycardia at admission 14 had bradycardia, 89 had tachypnea, 66 patients were brought in respiratory arrest, but there was no statistically significant difference in vitals at admission between cases and controls.

Anemia was found in almost two-third of children in both groups. Thrombocytopenia and hypoglycemia were significantly higher in malnourished children (P < 0.01). There was not a significant difference in other investigations among cases and controls.

Morbidity and mortality among cases and controls are shown in Table 2. Mortality was 11.6% in controls and 13.3% in cases (not significant).

Outcome in relation to weight for age

Final outcome in children with normal weight for age and children with mild to moderate malnutrition was compared a shown in Table 3, and there was no significant difference.

When further mortality was compared in different grades of malnutrition, i.e., between mild to moderate (60-80% weight for age) and severe grades of malnutrion (grade III and IV, <60% of weight for age), mortality was significantly (P-0.014) higher in severely malnourished group compared to children with borderline malnutrition as shown in Table 4. Although mortality in children with borderline malnutrition was slightly less than the children with normal nutrition but this difference was not statistically significant as shown in Table 3 (P-0.2957).

Table 1: Distribution of patients, controls versus cases

Feature	Controls, n=246 (%)	Cases $<3^{rd}$ centile, n=154 (%)	P
Age range (months)			
<12	43 (17.5)	61 (39.6)	0.0003
12-60	95 (38.6)	36 (23.4)	0.0272
60-120	52 (21.1)	28 (18.1)	0.6145
>120	56 (22.7)	29 (18.8)	0.4632
Sex			
Female	65 (26.4)	40 (25.9)	1.000
Male	181 (73.5)	114 (74.0)	1.000
Class ^a			
Upper/upper middle	174 (70.7)	104 (67.5)	0.8087
Lower middle/ lower	72 (29.2)	50 (32.5)	0.6717

 $^{\rm a}$ Kuppuswamy's Socioeconomic Status Scale-Updating for 2007. In bold is P<0.01, and <0.05

Table 2: Morbidity and mortality in cases versus controls

Morbidity	Controls, n=246 (%)	Cases, n=154 (%)	P
Mechanical ventilation	76 (30.8)	51 (33.1)	0.7547
Inotropic support	65 (26.4)	50 (32.4)	0.3869
Duration of ventilation (days)			
<3	39 (51.3)	07 (13.7)	0.0265
3-5	20 (26.3)	14 (27.4)	1.0000
>5	17 (22.3)	30 (58.8)	0.0063
Duration of PICU stay (days)			
<7	157 (63.8)	92 (59.7)	0.7394
7-14	70 (28.4)	38 (24.6)	0.5768
>14	19 (7.7)	24 (15.6)	0.0332
PRISM score	` '	, ,	
<10	100 (40.6)	59 (38.3)	0.7731
>10	146 (59.3)	95 (61.6)	0.8020
Final outcome	,	,	
Survived ^a	190 (88.3)	110 (86.6)	0.9347
Died	25 (11.6)	17 (13.4)	0.7362
DAMA	31 (12.6)	27 (17.5)	0.2528

 a Survival was determined excluding patients who were DAMA, main reason being financial constraints. In bold is P<0.01, and <0.05. DAMA: Discharged against medical advice; PICU: Pediatric Intensive Care Unit; PRISM: Pediatric risk of mortality

Table 3: Outcome in normal weight for age compared to mild-moderate malnutrition

Outcome	>80% weight for age, n=246 (%)	60-80% weight for age, n=107 (%)	Р
Surviveda	190 (88.3)	80 (93.0)	0.8605
Died	25 (11.6)	06 (6.9)	0.2245
DAMA	31 (12.6)	21 (19.6)	0.1528

DAMA: Discharged against medical advice

Table 4: Outcome in relation to degree of malnutrition

Outcome	60-80% weight for age, n=107 (%)	<60% weight for age, n=47 (%)	P
Surviveda	80 (93.0)	30 (73.1)	0.4774
Died	06 (6.9)	11 (26.8)	0.0141
DAMA	21 (19.6)	06 (12.7)	0.4938

^aSurvival was determined excluding DAMA. DAMA: Discharged against medical advice

Mean and median PRISM score in children with normal weight for age was 12.89, 12, respectively. In

cases (weight for age <3rd centile) mean, and median PRISM score was 13.07, and 12, respectively. Further in malnourished children, mean score among mild to moderately nourished and severely malnourished was 12.7 and 13.9, respectively (*P* - 0.4890). There was no statistical significant difference in PRISM score among cases and controls and also in mild to moderately nourished to severely malnourished children in this study.

PRISM scoring was done, and actual mortality was plotted against predicted mortality as per score shown in Figure 1.

Although PRISM score was not significantly different between normal, mild to moderately malnourished, and severely nourished children, but the mortality was much higher in severely malnourished children, higher than predicted by PRISM score [Figure 2].

On correction for mortality as per the scoring, it was found that weight for age <60% corresponded to additional four points to PRISM score, if everything else remains the same.

Discussion

PICU is an important component of tertiary pediatric care service. These units are points of major technology transfer and constitute one of the main consumers of hospital budgets. There are relatively few efficiently equipped PICUs in developing countries.^[14] The main purpose of the PICU is to prevent mortality by intensively monitoring and treating critically ill children who are considered at high risk of mortality. The capability to estimate the patient risk of death is considered important because such estimate would be useful in achieving many different goals such as

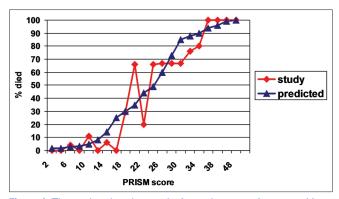


Figure 1: The graph with pediatric risk of mortality score of patients in X-axis and predicted mortality on Y-axis in broken lines and actual mortality in the study in continuous lines, and these were almost parallel to each other, with mortality increasing with increasing score

assessing patient's prognosis, ICU performance, ICU resource utilization and also evaluating therapies controlling, and matching the severity of illness in clinical methods. Intensive care scoring systems are devised to determine probable outcome of the patients being admitted to the ICU.^[15] ICU scoring systems are also important while conducting clinical trials to remove the bias by selecting patients with similar severity of illness. PRISM score is considered to be the most effective in predicting the risk of mortality, including developing countries also and in authors unit too.^[9,10,16,17]

However, patient's mortality is not only affected by ICU performance but also depends on many factors such as demographic and clinical characteristic of population, infrastructure and nonmedical factors, nutritional status, case mix, and admission practice. A better understanding of the role of malnutrition as a cause of death is of vital importance, in terms of the interpretation of anthropometric data, and subsequent prioritization of intervention and targeting strategies. Assessment of malnutrition is often used to determine the severity of morbidity and mortality.^[18]

It has already been established that we need to modify our scoring systems for accurate prediction of mortality. PRISM score has been modified to PRISM III for that matter which includes division of patients into age groups and accordingly giving them a score. However, nutritional status is not taken into consideration in this score. Therefore, there is need for field testing of these scoring system in setting different from the one in which they were originally developed and with that aim this study was done to know the effect of the growth of children on mortality. [19] Original PRISM score with 14 components was used in this study, which gives predicted mortality also. [12]

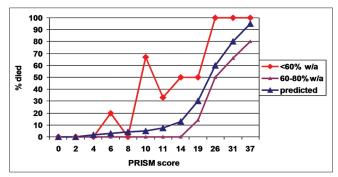


Figure 2: Pediatric risk of mortality score on X-axis and mortality on Y-axis. Large dash line shows the predicted mortality as per the score, small dash line shows the actual mortality in study group with mild to moderate malnutrition, and continuous line shows actual mortality in children with severe malnutrition, i.e., <60% of expected weight for age

In this study, malnutrition was most commonly seen in infants and children younger than 5 years compared to other age groups. Infancy is the common age for malnutrition, due to many factors, including delayed weaning and as many these infants had diseases which could lead to failure to thrive, like congenital heart disease. Punjab state is one of the state with highest per capital income and primary malnutrition due to insufficient diet is not that common, though secondary malnutrition due to diseases such undiagnosed congenital heart disease and celiac disease are more common. It was also observed that children with underlying CHDs were significant more underweight compared to other system involvement in this study. Children with CHD have significant nutritional defects, and these defects are more evident in the weight-for-age index. [20,21] Rests of the systems were equally involved in both the groups.

There was no difference in vitals at admission in both groups. Although 16% malnourished children had hypokalemia compared to 9% in healthy group, but it was not statistically significant. Hypokalemia, hypocalcemia, and hypoglycemia were more in malnourished children in the study as shown in other studies also. Anemia was the most common abnormality found in both groups. In India about 75% of toddlers are anemic. Malnourished group had significantly more thrombocytopenia in our study as has been reported previously.

When morbidity was compared in both groups, almost equal proportion of patients needed ventilatory support and inotropes. However, when the duration of ventilation was compared, it was observed that the children with normal nutrition needed ventilation for significantly less number of days, nearly half needing for <3 days and ventilation were significantly prolonged in malnourished group in spite of the almost similar disease profile needing ventilation. Nearly, 59% malnourished patients needed ventilation for more than 5 days compared to 22% in patients with normal group (P - 0.0063). This has been reported before also that children admitted to ICUs due to respiratory failure associated with malnutrition are more prone to respiratory fatigue or respiratory decompensation. In malnutrition, muscle function is affected, originating muscle fatigue and a reduction of up to 75% in work intensity. [27-30]

Mortality was almost the same in both the groups 12–13%. Malnourished group was further divided into groups, one with mild to moderate malnutrition (weight for age 60–80% of expected) and second who were

severely malnourished (weight for age <60% expected), it was noted that mortality was significantly higher in later group 27% compared to 7% in other group (P - 0.01). Although mortality was less in children with borderline malnutrition compared to children with normal weight for age (7% vs. 11%), but this difference was not statistically significant. Hence, in our study, mortality in mild to moderately malnourished children, who are critically sick, is not different from other critically ill children with normal weight for age. It had been seen that children with mild to moderate malnutrition have 2.2 times, whereas severely malnourished children (60% of the reference median weight-for-age) had 6.8 times the risk of dying during the follow-up period than better-nourished children (80% of the median reference weight-for-age).[31] However, this increase in mortality in malnourished children (both mild to moderate or severely malnourished) is mentioned in otherwise healthy children and not those admitted to PICU, whereas in our study, all children were critically sick. This is the first such study where outcome in critically ill children in relation to malnutrition is studied.

There was no statistically significant difference in PRISM scores in cases versus controls, mean being 12.9 versus 13.both the groups. PRISM score in mild to moderately nourished to severely nourished was 12.7, 13.9, respectively (*P* - 0.4890).

PRISM score was able to predict mortality in children with normal weight for age and children with mild to moderate malnutrition, but mortality in severely malnourished children was much higher than predicted by this score. It was noted in this study that borderline malnutrition per se in critically ill children does not increase mortality compared to other critically ill with normal weight for age, but severe malnutrition (IAP Grade III, IV, weight for age <60%) independently increases the risk of mortality and thus should be included as part of PRISM component. We may say from our study that weight for age <60% of expected is an independent risk factor for higher mortality. We tried to give score to this factor, and it was observed that if weight for age <60% predicted is given score of 4 then PRISM can predict mortality. This study suggests that weight for age would improve the discriminatory power of the PRISM score, and a larger prospective study is needed to confirm this. The number of patients with severe malnutrition was less; more studies involving larger number of patients in this group are needed to predict the exact score for this factor. It is desirable that scoring systems should be devised that work in both developed and developing nations. This may involve modifying or adapting existing scoring systems in a way that may not affect their current functioning in the developed world but may appropriately modify their use within the developing world.

Conclusion

Nutritional status or the growth parameters significantly affect the variables in the PRISM score as well as the mortality and morbidity of the patients. Weight for age <60% of expected needs to be included as an independent prognostic factor in the PRISM score.

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Conflicts of interest

There are no conflicts of interest.

References

- Grover Z, Ee LC. Protein energy malnutrition. Pediatr Clin North Am 2009;56:1055-68.
- Young H, Jaspars S. Review of Nutrition and Mortality Indicators for the Integrated Food Security Phase Classification (IPC) Reference Levels and Decision-Making by Helen; September, 2009A.
- Pelletier DL, Frongillo EA Jr., Schroeder DG, Habicht JP. A methodology for estimating the contribution of malnutrition to child mortality in developing countries. J Nutr 1994;124 10 Suppl: 21068-228
- Hartman C, Shamir R, Hecht C, Koletzko B. Malnutrition screening tools for hospitalized children. Curr Opin Clin Nutr Metab Care 2012;15:303-9.
- Alam N, Wojtyniak B, Rahaman MM. Anthropometric indicators and risk of death. Am J Clin Nutr 1989;49:884-8.
- Briend A, Bari A. Critical assessment of the use of growth monitoring for identifying high risk children in primary health care programmes. BMJ 1989;298:1607-11.
- El Halal MG, Barbieri E, Filho RM, Trotta Ede A, Carvalho PR. Admission source and mortality in a pediatric intensive care unit. Indian J Crit Care Med 2012;16:81-6.
- Thukral A, Lodha R, Irshad M, Arora NK. Performance of pediatric risk of mortality (PRISM), pediatric index of mortality (PIM), and PIM2 in a pediatric intensive care unit in a developing country. Pediatr Crit Care Med 2006;7:356-61.
- Singhal D, Kumar N, Puliyel JM, Singh SK, Srinivas V. Prediction of mortality by application of PRISM score in intensive care unit. Indian Pediatr 2001;38:714-9.
- Bellad R, Rao S, Patil VD, Mahantshetti NS. Outcome of intensive care unit patients using Pediatric risk of mortality (PRISM) score. Indian Pediatr 2009;46:1091-2.
- World Health Organization. WHO child growth standards and the identification of severe acute malnutrition in infants and children 2009.

- World Health Organization; 2009.
- Pollack MM, Ruttimann UE, Getson PR. Pediatric risk of mortality (PRISM) score. Crit Care Med 1988;16:1110-6.
- Kumar N, Shekhar C, Kumar P, Kundu AS. Kuppuswamy's socioeconomic status scale-updating for 2007. Indian J Pediatr 2007;74:1131-2.
- Gemke RJ, Bonsel GJ, Bught AJ. Outcome assessment and quality assurance in pediatric intensive care. In: Tibboel D, van der Voort E, editors. Intensive Care in Childhood. A Challenge to Future. 2nd ed. Berlin: Springer; 1996. p. 117-32.
- Pollack MM, Cuerdon TT, Patel KM, Ruttimann UE, Getson PR, Levetown M. Impact of quality-of-care factors on pediatric intensive care unit mortality. JAMA 1994;272:941-6.
- El-Nawawy A. Evaluation of the outcome of patients admitted to the pediatric intensive care unit in Alexandria using the pediatric risk of mortality (PRISM) score. J Trop Pediatr 2003;49:109-14.
- Castello FV, Cassano A, Gregory P, Hammond J. The pediatric risk of mortality (PRISM) score and injury severity score (ISS) for predicting resource utilization and outcome of intensive care in pediatric trauma. Crit Care Med 1999;27:985-8.
- Rodríguez L, Cervantes E, Ortiz R. Malnutrition and Gastrointestinal and Respiratory Infections in Children: A Public Health Problem. Int J Environ Res Public Health. 2011;8:1174-1205.
- Lindskog U, Lindskog P, Carstensen J, Larsson Y, Gebre-Medhin M. Childhood mortality in relation to nutritional status and water supply

 A prospective study from rural Malawi. Acta Paediatr Scand 1988;77:260-8.
- Staebel O. Malnutrition in Belgian children with congenital heart disease on admission to hospital. J Clin Nurs 2000;9:784-91.
- da Silva VM, de Oliveira Lopes MV, de Araujo TL. Growth and nutritional status of children with congenital heart disease. J Cardiovasc Nurs 2007;22:390-6.
- Singhi S, Marudkar A. Hypokalemia in a pediatric intensive care unit. Indian Pediatr 1996;33:9-14.
- Ashworth A. Treatment of severe malnutrition. J Pediatr Gastroenterol Nutr 2001;32:516-8.
- Mishra SK, Bastola SP, Jha B. Biochemical nutritional indicators in children with protein energy malnutrition attending Kanti Children Hospital, Kathmandu, Nepal. Kathmandu Univ Med J 2009;7:129-34.
- Pasricha SR, Black J, Muthayya S, Shet A, Bhat V, Nagaraj S, et al. Determinants of anemia among young children in rural India. Pediatrics 2010;126:e140-9.
- Tyagi A, Chandra J, Narayan S, Sharma D. Platelet function tests in protein energy malnutrition. Indian Pediatr 1992;29:228-31.
- Mota EM, Garcia PC, Piva JP, Fritscher CC. The influence of poor nutrition on the necessity of mechanical ventilation among children admitted to the Pediatric Intensive Care Unit. J Pediatr (Rio J) 2002;78:146-52.
- Arora NS, Rochester DF. Respiratory muscle strength and maximal voluntary ventilation in undernourished patients. Am Rev Respir Dis 1982;126:5-8.
- Keens TG, Bryan AC, Levison H, Ianuzzo CD. Developmental pattern of muscle fiber types in human ventilatory muscles. J Appl Physiol Respir Environ Exerc Physiol 1978;44:909-13.
- Rochester DF. Respiratory muscles and ventilatory failure: 1993 perspective. Am J Med Sci 1993;305:394-402.
- Schroeder DG, Brown KH. Nutritional status as a predictor of child survival: Summarizing the association and quantifying its global impact. Bull World Health Organ 1994;72:569-79.