„VICTOR BABEȘ” UNIVERSITY OF MEDICINE AND PHARMACY FROM TIMIȘOARA

FACULTY OF MEDICINE

DEPARTMENT XII – Obstetrics and Gynecology

MITRU ALINA - EMILIA

PhD THESIS

IMPLICATIONS OF PROTEIN-CALORIC MALNUTRITION IN ACUTE INFECTIONS IN MULTI-HOSPITALIZED PATIENTS

ABSTRACT

Scientific Coordinator

PROF. UNIV. DR. BOIA MĂRIOARA

T i m i ș o a r a
2023

Contents

INTRODUCTION

The relationship between infection and diet was not well understood in the 1950s. Until then, it was thought that severe protein deficiency, or kwashiorkor, rather than total calorie deficiency, or marasmus, was the main cause of nutritional issues in children and infants. This was because severe protein deficiency was directly linked to the development of the immune system and the production of antibodies. The emphasis subsequently turned to energy, with the idea that one might meet all of their nutritional demands provided they ingested enough kilocalories of energy [1]. Malnutrition is now acknowledged as a global health emergency, a major risk factor for a number of diseases, and a difficult issue to address. Any illness, whether acute or chronic, increases the risk of malnutrition in developing nations and has the potential to either cause or worsen malnutrition in certain situations. Because a number of variables contribute to the development of malnutrition, it is thought to be a complex problem [2].

Inadequate food intake causes the slowing down of growth and development among children and the weakening of immunity. A person who is malnourished may be more vulnerable to infection, and an infection can exacerbate malnutrition, creating a vicious cycle [3]. Because inadequate nutrition causes children to be susceptible to infections due to inflammation and compromised epithelial integrity, there is a strong correlation between infant mortality and this illness [4]. The impacts of certain pathogens on nutrition complicate the link between immune suppression, infection and malnutrition. Improves in mass vaccination programs, more real-time noninvasive sampling techniques, such as saliva or urine tests for analysis, gene sequencing, and proteomics to examine individual susceptibilities, and a better understanding of the dynamics and kinetics of particular immune responses are all anticipated in the twenty-first century [3].

Malnutrition induces to infection , which also makes infections more severe and fatal. Infection increases tissue deterioration, decreases nutritional intake, and obstructs substrate usage. It is crucial to approach the two issues jointly as a result. Infection and malnutrition interact viciously in a mutually destructive way. They both compound each other's effects in a cyclical way.

The first part of this thesis provides information from the recent literature about malnutrition, the causes, risk factors and consequences of this pathology. It also reports aspects about malnutrition in cancer, chronic diseases, but also the link between malnutrition and infections, especially among children. Infection and malnutrition have always been closely linked. Later, the link between malnutrition and COVID-19 - the pathology that marked the existence of humanity - was addressed, and more the link

between malnutrition and sepsis - the body's extreme response to infection - was exposed.

In the first phase, the personal contribution consisted in quantifying and analyzing the risk factors that influenced the severe effects of the COVID-19 disease among children suffering from malnutrition secondary to the disease. Moreover, a hospital-level protocol was developed for prompt intervention in severe cases of COVID-19 in malnourished children. Furthermore, knowing the detrimental effect of malnutrition on cellular immune competence, the sepsis response of blood cell counts in infants with disease-related malnutrition was characterized.

AIM AND OBJECTIVES

The aim of this thesis was to evaluate the impact of malnutrition caused by the disease among children and to characterize the influence of this disease in association with COVID-19 and sepsis.

Objectives:

- quantifying the factors that induced severe effects among malnourished children with COVID-19
- the identification of hematological indices for discriminating the presence and severity of sepsis in malnourished children

PERSONAL CONTRIBUTIONS

STUDY I. CLINICAL FACTORS ASSOCIATED WITH COVID-19 SEVERITY IN CHRONIC HOSPITALIZED INFANTS AND TODDLERS: DATA FROM A CENTER IN THE WEST PART OF ROMANIA

Results

A total of 33 children were already hospitalized in the Pediatric Clinic when the first case of COVID-19 was diagnosed. The mean age of all 33 children was 7.0 months (ranging from 2.0 to 24.0 months). The median age adjusted for gestational age was 4.9 months (1.0 to 23.6 months). Both median age and adjusted median age were higher in the COVID-19 positive group (8.0 months to 7.8 months) compared to the COVID-19 negative group (4.5 months to 3.9 months), but these differences did not reach statistical significance (age: $p = 0.23$; age corrected: $p = 0.09$). Furthermore, when analyzing birth weight according to gestational age, it was found that the majority of children were AGA ($n = 20$, 60.6%) and 13 (39.4%) were of extreme weight (10 SGA and three LGA). The

number of children classified as SGA or LGA was more than double in the COVID-19 positive group compared to the COVID-19 negative group (nine versus four). The most relevant clinical and personal history characteristics in all three groups are shown in Table 1.

Table 1. The clinical and personal history features distribution for the studied groups.

Characteristics	COVID-19 Positive	COVID-19 Negative	All	*p*-Value
	17	16	33	
Sex:				
Male	13 (76.5)	7 (43.7)	20 (60.6)	0.052
Female	4 (23.5)	9 (56.3)	13 (39.4)	(ref)
Age:				
0–3 months	3 (17.6)	5 (31.2)	8 (24.2)	0.36
4–12 months	7 (41.2)	8 (50.0)	15 (45.5)	0.61
>12 months	7 (41.2)	3 (18.8)	10 (30.3)	0.15
Comorbidities:				
Prematurity *	7 (41.2)	11(68.8)	18 (54.5)	0.10
Nutritional status:				
Appropriate weight	10 (58.8)	14 (87.5)	24 (72.2)	0.11
Stunning	9 (52.9)	5 (31.2)	14 (42.4)	0.20
Wasting	8 (47.0)	3 (18.8)	11 (33.3)	0.12
Underweight	6 (35.3)	2 (18.8)	8 (24.2)	0.08
Personal history of:				
Neurodevelopmental disorders	9 (52.9)	9 (56.2)	18 (54.5)	0.84
Cardiac or circulatory congenital anomalies	7 (41.2)	5 (31.2)	12 (36.4)	0.55
Gastrointestinal anomalies including surgical correction	3 (17.6)	5 (31.2)	8 (24.2)	0.36
Pulmonary diseases	1 (5.9)	0 (0.0)	1(3.0)	-
Genetic Syndromes	1 (5.9)	2 (12.5)	3 (9.1)	-
Perinatal exposure to maternal infectious diseases **	2 (11.8)	0 (0.0)	2 (6.1)	-
Others ***	3 (17.6)	7 (43.7)	10 (30.0)	0.100
Vaccination status:				
BCG	3 (17.6)	5 (31.2)	8 (24.2)	0.361
Anti VHB	7 (41.2)	6 (37.5)	13 (39.4)	0.892
Hexavalent + P13(1st dose)	10 (58.8)	10 (62.5)	20 (60.6)	0.892
Hexavalent + P13(2nd dose)	6 (35.3)	3 (18.7)	9 (27.3)	0.282

As shown in the table above, a large percentage of children (72.2%) were considered “weight appropriate” as defined by the weight-for-height z-score value. After analyzing individual growth charts, we noticed that 10 of the 24 "appropriate weight" children were, in fact, stunted. Half of the children in this category (n = 5) were also underweight.

Better nutritional status as defined by weight, height and weight-for-height z-scores was found in children negative for COVID-19 compared to positive, but the differences were not statistically significant ($p > 0.05$). The main anthropometric characteristics and differences between groups are presented in Table 2.

Table 2. Anthropometric measurements of the study group according to SARS-CoV-2 infection status.

Participants, n (%)				
Characteristics	**COVID-19 Positive**	**COVID-19 Negative**	**All**	***p*-Value**
	17	16	33	
Weight (kg)	7.00 (3.40–9.30)	5.65 (4.00–10.50)	6.20 (3.40–10.5)	0.12
Weight z-score	−1.92 (−4.52–+0.70)	−0.91 (−2.62–+1.92)	−1.23 (−4.52–+1.92)	0.06
Height (cm)	68 (52–89)	59.5 (50–90)	61 (50–90)	0.22
Height z-score	−2.02 (−5.89–+1.53)	−0.90 (−3.48–+1.72)	−1.22 (−5.89–+1.72)	0.15
Weight-for-height z-score	−1.29 (−4.11–+2.36)	−0.33 (−3.64–+1.60)	−0.44 (−4.11–+2.36)	0.36

All 17 children who tested positive for SARS-CoV 2 had respiratory or digestive symptoms. Only one child, already on anticonvulsant medication (levetiracetam and sodium valproate) for his chronic neurological problems, presented with generalized seizures as the first sign of infection. Another had very mild nasal symptoms and conjunctivitis. Over time, five of the 17 children (29.4%) developed a severe outcome of COVID-19 as defined above. Three of the five children developed dyspnea, tachypnea, and a positive pulmonary clinical examination. Positive pulmonary clinical examination was defined by the presence of wheezing as well as fine and coarse expiratory crackles on auscultation. Supplemental oxygen (mean FiO2 of 4 L/min) and systemic corticosteroid therapy with intravenous dexamethasone were added to initial treatment.

The other two patients with severe evolution developed digestive symptoms (vomiting, diarrhea) with moderate dehydration in the first 36 hours. Subsequently, they presented with expiratory dyspnea, wheezing, and coarse expiratory crackles on auscultation. In addition, they received systemic corticosteroid treatment, but no supplemental oxygen was required. None of the children developed acute respiratory distress syndrome (ARDS) or multisystem inflammatory syndrome (MISC-C) in the following months. The average duration, in days, until the first SARS-CoV-2-negative test

was 10.7 days (minimum 4 days, maximum 15 days). This period was slightly longer in those experiencing a severe form, where the average was 11.5 days (minimum 8 days and maximum 15 days). The clinical profiles of children who develop a severe form of COVID-19 compared to those with mild and moderate forms are shown in Table 3. After applying logistic regression for each individual risk factor, only a positive pulmonary clinical examination was found to be associated with risk of severe progression (OR 2.00; 95% CI, 0.33–5.66; p = 0.028), but the results did not reach statistical significance.

Table 3. Identification of risk factors for severe outcome in COVID-19 children (mild vs. severe outcome).

Participants (n=17)			
Characteristics	**Mild/Moderate** n (%) n = 12	**Severe** n (%) n = 5	**p-Value**
Sex Male	10 (58.8)	3 (17.6)	0.31
Female	2 (11.8)	2 (11.8)	(ref)
Age 0–3 months	2 (11.8)	1 (5.9)	0.87
>3 months	10	4	(ref)
Extreme birth weight (LGA/SGA)	5	4	0.17
Prematurity	5	2	0.94
Nutritional status			
Malnutrition	8 (47.1)	4 (23.5)	0.57
Stunning	4	4	0.13
Wasting	6	1	0.38
Underweight	5	2	0.70
Comorbidities			
Neurodevelopmental disorders	5	3	-
Cardiac or circulatory congenital anomalies	4	2	-
Gastrointestinal anomalies including surgical correction history	2	1	-
Anemia	1	2	-
Positive personal history *	8 (47.1)	5 (29.4)	0.82
Clinical signs			
Fever	7	2	0.70
Temperature	4	3	0.31
Cough	7	4	0.38
Positive pulmonary clinical exam	2 (11.8)	4 (23.5)	0.02
Digestive symptoms	1	2	0.13

STUDY II. THE NEUTROPHIL-TO-LYMPHOCYTE RATIO (NLR) CAN PREDICT SEPSIS'S PRESENCE AND SEVERITY IN MALNOURISHED INFANTS — A SINGLE CENTER EXPERIENCE

Results

A total of 167 infants with disease-related malnutrition were included in the study, nearly two-half of whom were septic. The majority of patients were under six months of age, with a mean age of 3 months for both groups. While male gender was more prevalent in both groups, the percentage was lower in the sepsis group. All infants presented with acute malnutrition, with more than half (58.6%) having multiple anthropometric deficits: 43.7% associated with heartburn and 34.7% underweight.

The sepsis group included cases with a more severe degree of malnutrition (mean z-score for weight of -2.48), unlike the group with infection (mean z-score for weight of 2.09), as depicted in Figure 1. Underweight was more prevalent in the sepsis group ($p = 0.008$).

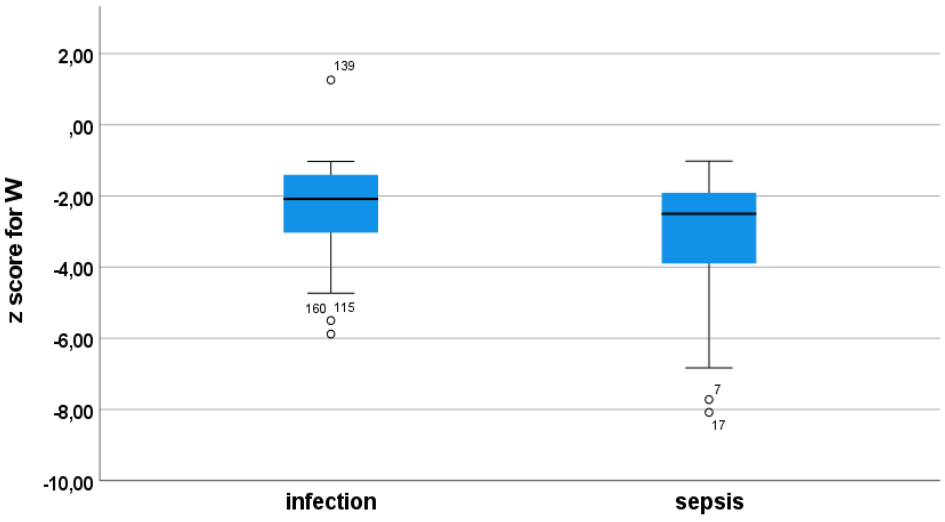

Figure 1. Box plot comparison between z score for weight in infants from the bacterial infection group and in infants from the sepsis group

Almost two-thirds (70.1%) of the entire study group had chronic underlying disease, with no statistically significant differences in associated comorbidities between infants with bacterial infection and those with sepsis. As expected, in terms of laboratory parameters, infants with sepsis showed higher levels of classical biomarkers of infection such as CRP and procalcitonin ($p < 0.001$). Moreover, significant statistical differences were observed between the two groups when analyzing indices derived from CBC.

Regarding the source of infection, as illustrated in Figure 2, pneumonia was the most common cause in both study groups, followed by digestive and urinary tract infections. The source of infection remained unidentified in 16.9% of sepsis cases (18 patients).

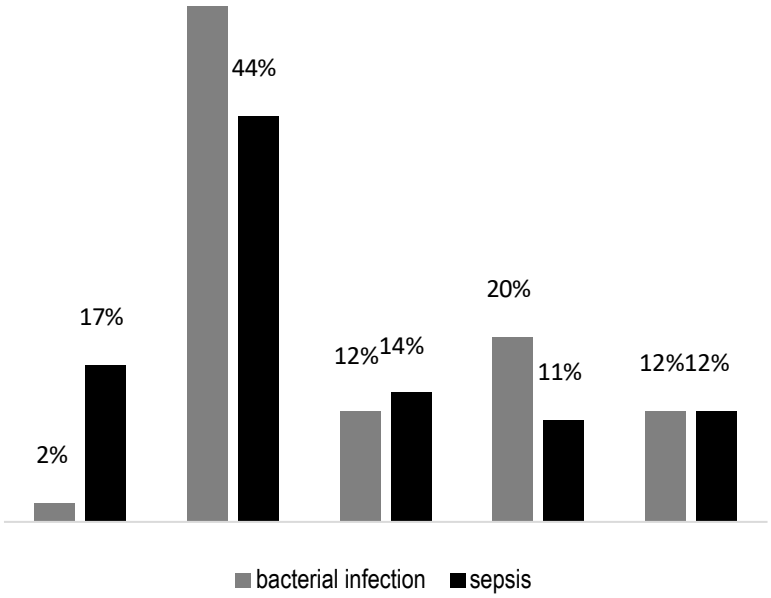

Figure 1. The prevalence of infection type among the entire sample

We also performed a subgroup analysis to characterize the sepsis group and assess the relationship between infection biomarkers and sepsis severity, as shown in Table 4.

Table 4. Subgroup analysis regarding clinical parameters of the sepsis lot.

Parameters	Sepsis (*n* = 47)	Severe Sepsis (*n* = 33)	Septic Shock/MOF (*n* = 26)	*p*-Value
Age (months)	3 (2, 5)	3 (2, 4)	3.5 (2, 5)	0.508
GA (weeks)	37 (31, 39)	38 (32, 40)	37.5 (33.5, 39)	0.633
Weight for age (z)	−2.23 (−2.77, −1.41)	−2.71 (−4.03, −1.98)	−3.45 (−4.70, −2.27)	0.002
Height for age (z)	−0.79 (−1.31, −0.20)	−0.73 (−1.59, −0.15)	−0.84 (−1.85, −0.37)	0.904
Weight for height (z)	−2.38 (−3.11, −1.40)	−2.83 (−3.90, −2.09)	−3.47 (−5.08, −2.25)	0.011
Mechanical ventilation % (n)	6.38 (3)	24.2 (8)	69.2 (18)	<0.001
Prolonged ICU stay % (n)	31.9 (15)	48.5 (16)	57.7 (15)	0.032
Irresuscitable arrest % (n)	0	0	57.7 (15)	<0.001
CRP (mg/L)	65.5 (20.1, 154)	47.1 (7.09, 88.5)	94.1 (35.5, 51.1)	0.293
PCT (ng/mL)	4.35 (1.83, 12.4)	13.1 (4.37, 21.5)	38.3 (6.73, 71.8)	<0.001
WBC ($\times 10^3$ µL)	18.9 (13.7, 24.2)	17.9 (13.9, 29.9)	19.3 (13.5, 28)	0.877
PLT ($\times 10^3$ µL)	336 (179, 488)	362 (204, 497)	280 (90.7, 451)	0.273

Regarding infection biomarkers, only procalcitonin and Neutrophil-to-lymphocyte ratio showed a gradual increase between the three groups ($p < 0.001$). Of the sepsis group, 43.3% required ICU hospitalization for more than 7 days. The overall case mortality in our sepsis group was 14.2%, with the majority (86.7%) having multiple anthropometric deficits. Furthermore, 27% required intubation and mechanical ventilation, mainly male infants.

Even more, we analyzed in greater detail the sepsis group in terms of sepsis severity. First, regarding malnutrition severity, as would be imagined, we noticed a progressive trend of decrease in z score for weight with the increase of sepsis severity. As such, infants from the most severe forms of sepsis, which displayed multiorgan failure and required inotrope perfusion in order to sustain their cardio-vascular function (those with septic shock) presented the lowest z score for weight values, as can be seen in Figure 3.

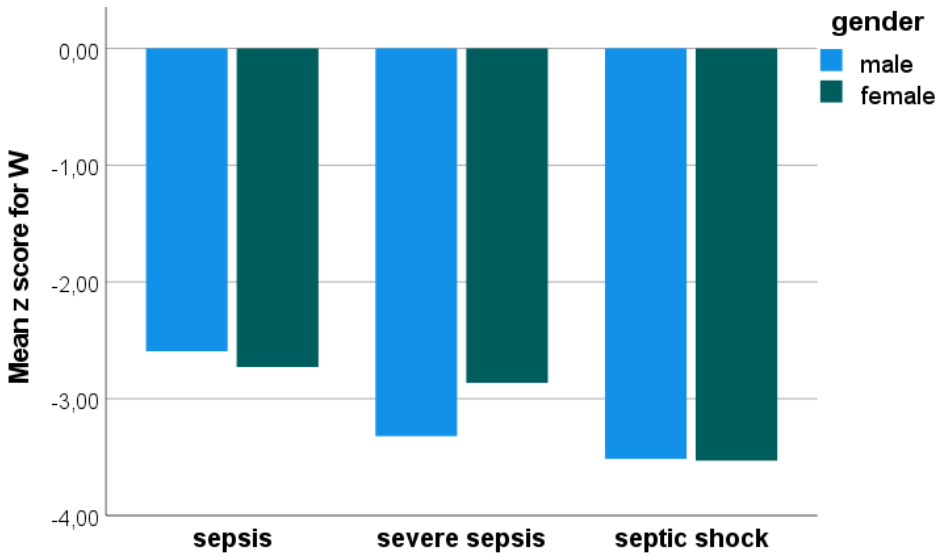

Figure 3. Relationship Between Sepsis Severity, Gender, and Mean Weight Z Score in Infants

To further evaluate the relationship between mean Neutrophil-to-lymphocyte ratio and the presence of sepsis, we performed in depth statistical analysis, mainly Spearman's correlation analysis. We analyzed the correlation between the laboratory measurements, both classic (procalcitonin and C-reactive protein) and CBC-derived index (Neutrophil-to-lymphocyte ratio), and specific potential outcomes: prolonged ICU stay (>7 days), acute organ dysfunction, nonresuscitable arrest and sepsis severity. As can be noted in Table 5, while both Neutrophil-to-lymphocyte ratio and procalcitonin correlate with sepsis severity, only NLR correlates positively with all outcome parameters investigated. Additionally, no significant correlations were found for CRP, except for prolonged ICU stay ($p = 0.032$).

Table 5. Correlation analysis of infection biomarkers with outcome in the sepsis group.

	NLR		CRP		PCT	
	r	*p*	*r*	*p*	*r*	*p*
Prolonged ICU stay (>7 days)	0.345	<0.001	−0.214	0.032	−0.032	0.769
Acute organ dysfunction	0.201	0.038	−0.109	0.280	−0.021	0.847
Mechanical ventilation	0.529	<0.001	−0.038	0.706	0.133	0.222
Nonresuscitable arrest	0.405	<0.001	0.001	0.992	0.109	0.319
Sepsis severity	0.470	<0.001	−0.015	0.879	0.429	<0.001

Receiver operating characteristic (ROC) curves were plotted to assess the accuracy of PCT, CRP, and NLR in diagnosing sepsis in the entire study cohort (Figure 4). The area under the ROC (curve) revealed similar excellent discriminatory power of NLR and PCT in recognizing septic cases, in contrast to CRP, with NLR, PCT and CRP having sensitivities of 0.85, 0.82 and 0.70 and specificities of 0.69, 0.76 and 0.65, respectively. The threshold values determined by the Youden index for NLR, PCT, and CRP were 1.43, 1.56 ng/mL, and 28.3 mg/L, respectively.

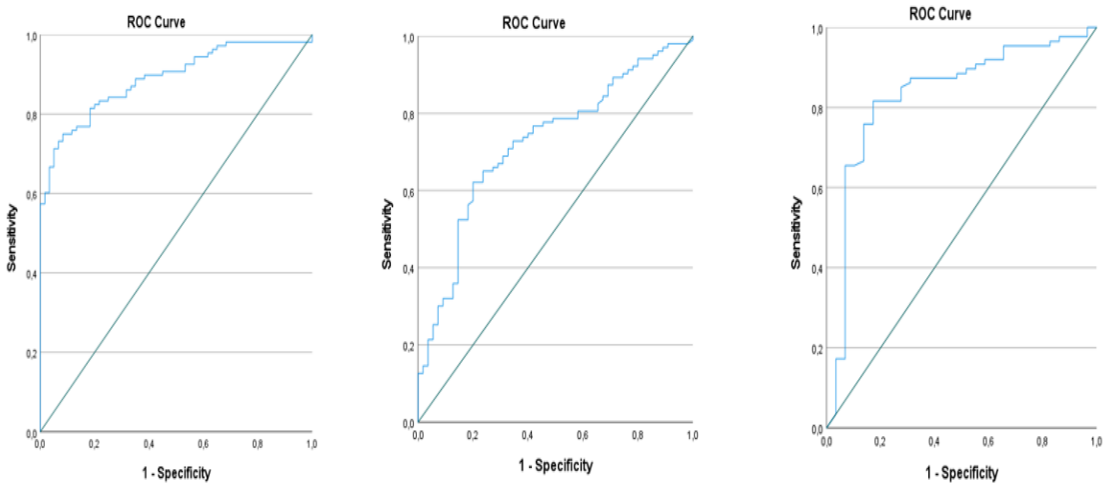

Figure 4. The area under the curve of neutrophil-to-lymphocyte ratio/ C-reactive protein/procalcitonin as sepsis marker in malnourished infants.

CONCLUSIONS

Based on what is currently knew, even in high-risk communities, COVID-19 disease in children frequently manifests as a minor illness. Understanding the risk factors is crucial for creating age-specific treatment guidelines, as well as for admission priority criteria, monitoring, and even vaccination, even though the data are still lacking.

Malnutrition appears to have a detrimental effect on the disease's clinical course, encompassing both undernutrition and obesity. The interplay among extreme birth weight, malnutrition, and COVID-19 disease severity underlines the importance of nutritional assessment and intervention across all patient populations, particularly those at risk for COVID-19. Furthermore, this pandemic may lead to the development of early nutritional intervention measures and the implementation of a nutritional screening program for younger children. In order to evaluate these patients, the traditional clinical pulmonary exam is still a valid screening tool. However, additional research is required to validate these findings with more costly but standardized techniques.

Moreover, in this work it was shown that, in addition to procalcitonin, the neutrophil/lymphocyte count can be utilized as an additional diagnostic marker, in discriminating the presence and severity of bacterial sepsis in malnourished newborns. In addition, when there is a high rate of infant malnutrition in low-income settings and other sepsis laboratory markers are not always available, the neutrophil count/lymphocyte count value might be employed.

We suggest that multicenter studies be conducted to validate these findings. Furthermore, long-term research assessing these indicators following nutritional recuperation may offer fresh perspectives on the part malnutrition plays in systemic infection.

In conclusion, it is critical to improve our understanding of the development causes and co-existence of malnutrition with other disorders in order to close the gaps in the global reporting and prioritization of malnutrition status data. In order to combat the widespread infectious diseases and other nutrition-related health issues, comprehensive, realistic, and long-lasting plans to reshape and redefine the future are also necessary in order to overcome malnutrition.

BIBLIOGRAPHY

1. Keusch G. The history of nutrition: malnutrition, infection and immunity, J Nutr 2003;133:336-40
2. Fan Y, Yao Q, Liu Y, Jia T, Zhang J and Jiang E. Underlying Causes and Co-existence of Malnutrition and Infections: An Exceedingly Common Death Risk in Cancer. Front Nutr 2002;9:814095.
3. Katona P, Katona-Apte J. The Interaction between Nutrition and Infection. Clinical Infectious Diseases 2008;46:1582–1588
4. Better nutrition could save millions of kids—study, Reuters;17