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Nutritional Markers as Prognostic Factors in the Very Preterm Infants-Prospective Study

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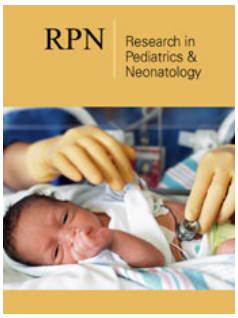

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Abstract

The development of premature newborns (PTN) depends on adequate nutritional support. About 15-30% of newborns in Neonatal Intensive Care Units (NICUs) have lower caloric intake than required. The neurodevelopment of PTN is very sensitive to nutrition in the first few weeks of life, and these effects may be long lasting. We pretend to evaluate the relationship between nutritional markers and clinical evolution and understand which markers are useful as poor prognostic factors.

Methods: Prospective study carried out at the NICU of a level II hospital from January 2020 to December 2021. Newborns with gestational age ≤32 weeks and/or birth weight ≤1500g were included. We measured total proteins (TotP), prealbumin, albumin (Alb), ferritin, vitamin D, alkaline phosphatase, phosphate, calcium (Ca) and hemoglobin (Hgb) in the first 24 hours, between the 7th-10th day and at 30 days and compared the results between the good and the poor prognosis group. As poor outcome group we had bronchopulmonary dysplasia, necrotizing enterocolitis, late sepsis, osteopenia, retinopathy, aminergic/trans fusional support and death.

Results: A total of 59 PTN were enrolled. Considering $p<0.05$ as indicating statistical significance, we found a difference between groups in TotP, Alb, Ca and Hgb, all significantly lower in the poor prognosis group. Differences in the incidence of late sepsis were also studied. There were statistically significant differences in in TotP, Alb and Ca. Alb and Hgb at 7-10 days and at 30 days were independent predictors for bad outcome in these PTN. For late sepsis Ca at 24 hours, Al and Hgb at 30 days were also independent predictors. Lower values of TotP and Alb at birth were related to the need for invasive ventilation. In the poor outcome group the parenteral diet tended to last longer, the total enteric diet was achieved later and supplementation-eoprotin, iron and vitamin D -were introduced later.

Conclusion: This study highlights the importance of nutritional markers as prognostic value in PTN outcomes. Anthropometric parameters are easily measured, but objective markers should be used to make decisions in nutritional support, yielding the best neonatal and neurodevelopmental outcomes.

Keywords: Nutritional markers; Preterm infant; Intensive care; Nutrition; Preterm newborns

Introduction

Advances in recent decades in neonatal medicine have led to a greater survival of preterm infants with progressively smaller birth weight and gestational age. Despite the intensive care offered, these children have increased risk of mortality and future morbidities [1-5]. Preterm births are the leading cause of newborn deaths [2,3,6]. The persisting suboptimal nutrition in survivors remains an issue and is associated with adverse outcomes, such as reduced weight gain, delayed wound healing, longer hospital stays, chronic lung disease (CLD), necrotizing enterocolitis (NEC), late sepsis (LS), metabolic morbidity and the most worrying, neurodevelopmental impairment, especially in the cognitive domains, which is increasing in prevalence [2,5,6]. These adverse developmental outcomes can be secondary to abnormal brain development, postnatal brain injury and suboptimal nutrition during hospital stay. Therefore, preterm birth can be considered a nutritional emergency [2]. Appropriate nutritional status

of the fetus can significantly influence the morbidity and mortality of the newborn [2-5,7-10]. Also, these newborns have higher rates of adverse health outcomes in early adulthood compared with their term counterparts [2,3,6].

The nutritional goal in the management of very low weight newborn is to achieve a postnatal growth that approximates the in-utero growth of a normal fetus at the same postconceptional age, without nutritional deficiencies, undesirable metabolic effects or toxicity, resulting from an exaggerated nutritional supply. Optimum nutrition leads to improved long-term neurodevelopmental outcomes in both preterm and term infants admitted to the neonatal intensive care (NICU) [1-5,7-10].

Despite improvements in the neonatal intensive care which have resulted in improved survival, half of low-birth-weight babies are still being discharged from the NICU with poor postnatal growth and a quarter with severe growth failure [5]. Monitoring nutritional status is required to detect nutritional deficits early and guide nutrition support in preterm infants under intensive care. Thus, nutritional assessment should be an essential skill of neonatal staff caring for preterm infants [1,11]. However, premature infants have immature gastrointestinal tracts, providing enteral nutrition alone through the immature gut cannot satisfy the nutritional demands of premature infants; thus, the inclusion of parenteral nutritional support is essential [9,12]. In preterm infants, anthropometry is useful for several purposes, including growth monitoring, diagnosis of fetal malnutrition, risk assessment of early metabolic complications, and early recognition of undernutrition or overnutrition [4,13]. However, a comprehensive approach for the evaluation of nutritional status also includes biochemical markers, clinical parameters, and dietary assessment [8]. While clinical signs of early malnutrition are largely imperceptible, certain clinical biochemical markers can provide a useful insight into nutritional status, helping to detect nutritional deficiencies before the appearance of clinical signs [1,11,14]. These markers should be interpreted with caution and used to complement other nutritional data [1,14,15]. Among the biochemical tests, the most sensitive are those that use the measurement of the organism's protein pool. The serum's short-term proteins such as prealbumin reflect the recent protein status and the balance between synthesis and degradation [4].

Objectives

With this study we sought to understand how these biochemical markers influence the clinical evolution and prognostic of the preterm newborns (PTNN) of gestational age (GA)≤32 weeks and /or birth weight (BW)≤1500g, and also understand how the evolution of these markers can be used as a prognostic factor in these PTN. We also pretended to identify PTNN at higher risk of nutritional deficits and optimize the nutrition strategy of our intensive care unit, minimizing the risk of malnutrition. Lastly, we had the purpose of identifying the most useful markers as a prognostic indicator on the short and long term (growth and psychological evaluation at 24 months of age) [16,17].

Methods

A prospective, observational, and descriptive study was conducted. We enrolled a cohort of very preterm infants with BW≤1500g and/or GA≤32 weeks, after approval by the Commission of Research and Ethics. PTNN that died within the first hours of life, in whom it was not possible to collect blood were excluded from the study. Anthropometric parameters were obtained at birth, throughout the stay at the NICU and at discharge: weight(g), length and cephalic perimeter(cm). The classification of the newborns in percentiles was based on Fenton reference curves for gestational age. Data about the mother, pregnancy and delivery was collected. The infant type of feeding, supplements, clinical evolution, and complications was registered. For this study we considered as a poor outcome: death, late sepsis(LS), necrotizing enterocolitis(NEC), need for aminergic support, need for transfusion, bronchopulmonary dysplasia(BPD), bone metabolic disease(BMD), prematurity retinopathy(ROP).

The data collected were as follows:

A. Data about the mother, complications during pregnancy, infant basic clinical data, including gender, GA, BW, mode of delivery, length of hospital stay, type of feeding, supplementation, and complications.

B. For every PTN we collected blood samples in three different timings: Within the first 24 hours(1), on the 7th to 10th day of age(2) and at 30 days of age(3). The biochemical markers evaluated were total proteins(TotP), albumin(Alb), prealbumin(PreAlb), ferritin(Fe), calcium(Ca), phosphate (Ph), alkaline phosphatase(AlkP) and vitamin D(Vit D). A hemogram was also performed, and reactive C protein(RCP) was evaluated whenever justified. There was never a clinically unjustified blood draw.

C. Clinical information and outcome (good versus poor outcome). For the statistical analysis we used the SPSS 25.0 software package (SPSS Inc, Chicago, IL, USA). Normal measures that conformed to a normal distribution were expressed as mean± standard deviation and comparisons between two independent sample groups were made using the paired t-test. Non-normally distributed measures were expressed as median and interquartile spacing [P50 (P25, P75)], plus group comparisons between two independent samples were performed using the Mann-Whitney U-test. Count data were expressed as the number of cases and percentages(%). The relationships between the anthropometric and biochemical parameters were calculated through the coefficient of Pearson. Univariate and multivariate binary logistic regression analyses were conducted to determine potential predictors of a poor outcome. The ROC curve was plotted and the area under the curve was calculated to determine the critical value. For all the analyses significant differences were considered when $p<0.05$. The flow chart of the study is shown in Figure 1.

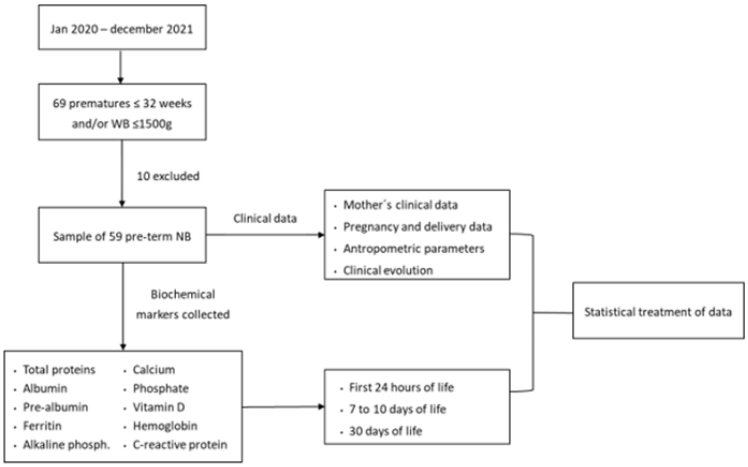

Figure 1: Flowchart of this study.

Results

During the period of the study, we collected data on 69 neonates. Of these, 10 were excluded due to death in the first hours of life and impossibility of collecting blood samples. Regarding pregnancy, there were 50 pregnancies, that originated 59 PTNN. Twenty-two (37.3%) were born of multiple gestation. The complication rate was 96.0% (n=48), the most common being intrauterine growth restriction (IUGR) 32% (n=16), followed by placental blood flow problems 22% (n=11) gestational diabetes 16% (n=8), oligoamines 14% (n=7) and pre-eclampsia 12% (n=6). Forty-two PTNN (71.2%) were male and seventeen (28.8%) were female. The median gestational age was 30.0 weeks (IQI 28-31), ranging from 23 to 34 weeks. The age of the mother varied from 19 to 45 years, with a mean of 30.03 (SD 5.57). The total number of mother's pregnancies ranged from 1 to 6, with a median of 2.14 (IQI 1-3). The median birth weight was 1260g (IQI 2010-1510), ranging from 500g to 1260g, and the median weight at discharge was 2200g (IQI 2010-2510), ranging from 1860g to 4605g (Table 1). The timing for regaining birth weight had a median of 10.0 days (IQI 8-14). The median stay in the Neonatal Unit was 47 days (IQI 34-57). Regarding the complications, 55.9% (n=33) of the newborns had severe complications or died. Table 2 depicts the complications that occurred, and their prevalence. The most common complication was late sepsis (45.8%). The PTN were categorized in two major groups: the poor prognosis group (n=33; 55.9%), constituted by PTN who died or had severe complications (LS, NEC, need for aminergic support, need for transfusion, BPD, BMD and ROP) and the good prognosis group, formed by PTN with mild or no complications (n=26; 44.1%). Table 3 summarizes the participant characteristics in different prognostic groups. Invasive ventilation was needed in 37.3% (n=22) of all PTN. There was a significant difference between the good and poor outcome group (p=0.01). In the good prognosis group 23.1% of the PTN needed invasive ventilation, in opposition to 51.5% in the poor outcome group (Figure 2).

Table 1: Biochemical markers of nutritional status in preterm infants [1, 11, 13-17].

Total proteins	Not good as individual indicator of protein status –>acute phase proteins, independent of nutritional status.
Albumin	Half-life of 17-20 days. Prolonged nutritional status.
Prealbumin (prelab)	Transporter protein. Short half-life (approximately 2 days): low levels may reflect current protein deficit. Levels may decrease in the presence of inflammation or infection. In children receiving steroid it may be falsely increased.
Serum calcium (Ca) Phosphate (Ph) Alkaline phosphatase (AlkP)	Commonly used to assess bone mineralization. Calcium: not good as an isolated biomarker BMD, not early marker Phosphate: <5.6mg/dL good correlation with BMD (specificity of 96% and sensitivity of 50%) AlkP: >900 U/L has a good correlation with BMD Combination AlkP >900 U/L and phosphate <5.6 mg/d: excellent as a marker of BMD (specificity of 70% and sensitivity of 100%)

Vitamin D (VitD)	Vit-D deficiency can lead to bone disease, such as rickets of prematurity, osteopenia of prematurity, or metabolic bone disease (MBD). It is also related with RDS and IUGR.
Ferritin	Low levels are associated with developmental retardation. Acute phase reactant-not good as an isolated marker. Useful to adjust dose of iron supplementation

Table 2: Prevalence of complications.

Complications (total of NB)		
Late sepsis	N=27	45.80%
Transfusion	N=15	24.40%
Aminergic supp.	N=7	11.90%
Death	N=5	8.50%
NEC	N=5	8,5%
ROP	N=4	6,8%
BPD	N=4	6,8%
OFP	N=3	5.10%

Table 3: Comparison of clinical data of neonates in different prognostic groups.

Variables	Good Outcome Group	Bad Outcome Group	1 Bad Outcome Factor	≥2Bad Outcome Factors
Gestational age(week)	Min 29-max 34	Min 29-max 34	Min 27-max 34	Min 23-max 34
	Median 31,0 (30,0-32.9)	Median 31,0 (30,0-32.9)	Median 30,0 (28,50-32.0)	Median 28 (25-30)
Maternal age(years)	Min 19-max 45	Min 21-max 42	Min 21-max 39	Min 24-max 42
	Median 35.5 (30.75-38.25)	Median 31.0 (28.0- 36.5)	Median 31.0 (28.0-36.5)	Median 33.0 (27.0-37)
Nº of pregnancies	Min 1-max 6	Min 1-max 5	Min 1-max 5	Min 1-max 5
	Mean 2.5(+/- 1.393)	Mean 1.85(+/- 1.149)	Mean 1.65(+/- 1.115)	Mean 2.05(+/- 1.079)
Birth weight(g)	Min 855-max 2600g	Min 500-max 2015g	Min 800 max 2015g	Min 500 max 1500g
	Med 1442.5 (1283.75-1496)	Med 1110.0 (839.0-1277.5)	Med 1230.0 (1087.5-1385)	Med 925.0 (615.0 -1260.0)
Weight at discharge(g)	Min 1910-max 3060	Min 1860-max 4605	Min 1860.0-max 2690.0	Min 1910-max 4605
	Med 2192 (1987.5–2437.5)	Med 2230 (2033.75-2513.75)	Med 2060 (2060.00-2457.5)	Med 2280 (2093.7-2611.25)
Length of stay(days)	Min 19-max 59	Min 5-max 70	Min 25-max 78	Min 5-max 170
	Med 39.5 (32.25-50.0)	Med 50.0 (38.0-67.0)	Med 47.0 (39.0-53.0)	Med 60.0 (24.0 -74.0)
PTN duration(days)	Min 0-max 17	Min 5-max 51	Min 6-max 30	Min 5-max 51
	Mean 9.31 (+/- 3.234)	Med 16.00 (10.0 -24.00)	Med 15.00 (9.0-19.00)	Med 17.00 (11.0-32.00)
Total proteins[1] (g/dl)	Med 4.4 (4.05-4.8)	Med 4.1 (3.6-4.5)	Med 4.2 (3.8-4.7)	Med 4.1 (3.5-4.4)
Albumin[1](g/dl)	Med 3.3 (3-3.5)	Med 3.0 (2.7-3.3)	Med 3.2 (2.9-3.8)	Med 2.85 (2.6-3.3)
Pre-albumin[1] (mg/dl)	Med 7.0 (6.0-8.0)	Med 8.0 (6.25-9.0)	Med 9.0 (2.9-11.5)	Med 7.0 (6.0-8.0)
Ferritin[1](mg/dl)	Med 214.0 (95.7-342.75)	Med 210.0 (101.35-325.0)	Med 242.0 (120.35-404.0)	Med 190.0 (74.6-267.0)
Vitamin D[1](nmol/L)	Med 53.0 (34.0-73.0)	Med 56.0 (40.0-72.5)	Med 58.0 (47.50-79.5)	Med 50.0 (37.0-72.0)
Phosphate[1](mg/dl)	Med 5.6 (4.5-6.35)	Med 6.4 (5.0-7.1)	Med 6.4 (5.2-7.0)	Med 5.9 (4.6-7.2)
Calcium[1](mg/dL)	Med 9.85 (9.25-10.48)	Med 8.85 (8.35-9.9)	Med 8.9 (8.27-9.95)	Med 9.10 (8.5-10.2)
Alkaline ph[-1](U/L)	Med 197.0 (147.5-239.0)	Med 178.0 (130.0-220.5)	Med 174.5 (128.0-215.25)	Med 178.0 (138.5-238.0)
CRP[1](mg/dl)	Med 0.13 (DP 0.403-0.28)	Med 0,030 (DP0 0.03-0.225)	Med 0.03 (0.03-1250)	Med 0.03 (DP0 0.03-0.55)
Hemoglobin[1](g/dl)	Med 17.1 (15.9-19.05)	Med 16.2 (13.08-18.05)	Med 16.55 (14.575-19.075)	Med 16.2 (12.8-18.50)
Total proteins[2] (g/dl)	Med 4.85 (4.6-5.175)	Med 4.7 (4.2-4.9)	Med 4.9 (4.35-5.1)	Med 4.5 (4.2-4.7)
Albumin (g/dl)	Med 3.6 (3.3-3.875)	Med 3.2 (3.0-3.6)	Med 3.3 (3.1-3.8)	Med 3.2 (3.0-3.45)
Pre-albumin[2] (mg/dl)	Med 9.0 (7.0-2.0)	Med 8.0 (5.0-11.0)	Med 9.0 (5.0-12-5)	Med 7.0 (6.0-10.0)
Ferritin[2](mg/dl)	Med 193.0 (104.75-298.75)	Med 309.0 (182.5-568.0)	Med 340.0 (183.0-620.0)	Med 259.5 (189.5-315.75)

Vitamin D[2](nmol/L)	Med 50.0 (41.0-73.0)	Med 58.5 (46.5-76.5)	Med 58.0 (48.0-78.0)	Med 53.0 (37.0-72.0)
Phosphate[2](mg/dl)	Med 6.2 (3.95-6.45)	Med 4.7 (4.0-6.2)	Med 5.2 (4.2-6.2)	Med 4.1 (3.6-5.3)
Calcium[2](mg/dL)	Med 10.15 (9.5-10.5)	Med 9.95 (9.35-10.68)	Med 10.3 (9.8-10.9)	Med 9.90 (9.225-10.675)
Alkaline ph[2](U/L)	Med 346.5 (247.25-420.75)	Med 310.0 (275.0-413.5)	Med 307.0 (285.0-371.5)	Med 329.5 (263.75-467.0)
CRP[2](mg/dl)	Mean 0.183 (+/-0.315)	Mean1.28 (+/-1.76)	Mean 1.102 (+/-1,25)	Mean 1.358 (+/- 2.15)
Hemoglobin[2](g/dl)	Med 14.0 (13.5-16.1)	Med 12.6 (11.4-15.5)	Med 13.150 (12.0-16.4)	Med 12.550 (10.725-14.85)
Total proteins[3] (g/dl)	Med 4.5 (4.35-4.65)	Med 4.1 (3.9-4.6)	Med 4.350 (4.0-4-750)	Med 4.0 (3.8-4.55)
Albumin[3](g/dl)	Med 3.5 (3.3-3.7)	Med 3.1 (2.8-3.5)	Med 3.3 (2.9-3.6)	Med 3.0 (2.8-3.7)
Pre-albumin[3] (mg/dl)	Med 9.0 (7.0-11.0)	Med 8.0 (6.0-10.0)	Med 7.5 (6.0-10.5)	Med 8.5 (6.75-10.25)
Ferritin[3](mg/dl)	Med 67.65 (28.83 -136.75)	Med 164.00 (64.6-275.0)	Med 165.0 (67.65-283.500)	Med 162.00 (92.1-283.250)
Vitamin D[3] (nmol/L)	Med 81.0 (59.0-88.0)	Med 80.0 (64.0-89.0)	Med 75.0 (64.0-82.0)	Med 80.0 (60.0-97.0)
Phosphate[3] (mg/dl)	Med 5.9 (4.8-7.3)	Med 5.3 (4.8-6.2)	Med 5.7 (5.05-6.150)	Med 4.95 (3.7-6.4)
Calcium[3] (mg/dL)	Med 9.9 (9.625-10.1)	Med 9.6 (9.1-10.2)	Med 9.8 (9.6-10.5)	Med 9.4 (8.85-9.75)
Alkaline ph.[3] (U/L)	Med 477.0 (378.0 -613.0)	Med 436.0 (371.75-605.25)	Med 436.0 (305.5-592.0)	Med 508.0 (387.0-607.00)
CRP[3](mg/dl)	Med 0.034 (0.009)	Med 0.247 (0.395)	Med 0.03 (0.03-0.04)	Med 0.399 (0.47)
Hemoglobin[3](g/dl)	Med 12.7 (9.0-13.0)	Med 10.1 (9.3-11.15)	Med 9.8 (8.650-12.40)	Med 10.7 (9.7-13.025)
Total enteric diet	Med 10.5 (9-13)	Med 19.0 (10.0-27.0)	Med 19.0 (10.5-22.5)	Med 20 (8.5-35.50)
Exoprotein introduction	Med 12.0 (9.0-14.0)	Med 20.00 (13.0-28.00)	Med 21.0 (14.0-22.0)	Med 16.0 (10.0-32.00)
Iron introduction	Med 12.0 (11.0-18.0)	Med 19.0 (13.5-26.0)	Med 10.00 (17.5 -25.50)	Med 18.50 (12.5-25.0)
Vitamin D intro.	Mean 10.73 (+/- 3.7)	Mean 21.23 (+/- 18.3)	Med 17.0 (11.0-20.0)	Mean 21.81 (+/-14.96)

Notes: All values are presented as the mean ±SD or as the median (med) (interquartile range).

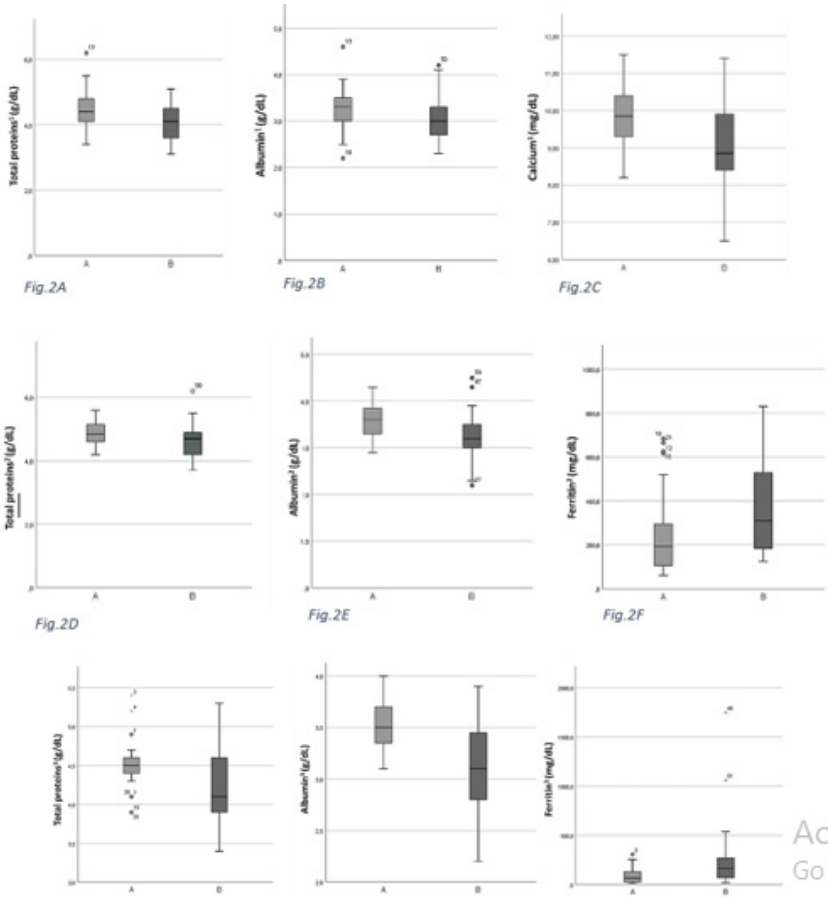

Figure 2: The levels of TotP[1], Alb[1], Ca[1], TotP[2], Alb[2], Ferritin[2], TotP[3], Alb[3], Ferritin[3], in poor outcome or good outcome group. (A) Good outcome group; (B) Poor outcome group.

Regarding the biochemical markers studied in the three blood samples we found a statistically significant difference between the good and poor prognosis group in TotP[1], Alb[1], Ca[1] Hb[1]; TotP[2], Alb[2], Hb[2]; TotP[3], Alb[3] and Hb[3], that were all significantly lower in the poor prognosis group. There was also a significant difference in Fe2 and Fe3, that had a higher value on the poor outcome group (Table 4). We also searched for differences between PTN that had only one complication, versus two or more complications. We found that there were statistically significant differences in TotP[1], Alb[1], TotP[2], TotP[3], Alb[3], Ca[3] (Table 5). Differences in the incidence of late sepsis were also studied. There were statistically significant differences in TotP[1], Alb[1], Ca[1], TotP[2], TotP[3], Alb[3] and Ca[3] (Table 6). For the need of ventilation there was a significant association with TotP[1] and Alb[1] values with lower concentrations linked to the need for invasive ventilation (Figure 3). Regarding the anthropometric results there was a positive correlation between TotP[1] and birth weight (r=0.275; p=0.044), birth length (r=0.287; p=0.043) and cephalic perimeter at birth (r=0.365; p=0.007) (Figure 4). There was also a positive correlation between Alb1 and CP at birth (r=0.365; p=0.007), Ca1 and weight at 15 days (r=0.353; p=0.03), Alb3 and weight at 15 days (r=0.463; p=0.001) (Figure 5). Weight at 30 days had a positively correlated with TotP[3] (r=0.379; p=0.011) and Ph[3] (r=0.539; p=0.011) (Figure 6-10). The evolution in weight percentiles during the stay in the NICU is shown in Figure 11. There were significant differences between the good and poor prognosis group regarding the weight, length and head perimeter at birth, weight at 15 days and at 30 days: All were lower in the poor prognosis group Table 7, Figure 7.

Table 4: Difference in clinical markers in good versus bad outcome group.

Good outcome Versus Bad Outcome Group					
TotP.[1]	p=0,009	TotP.[2]	p=0,036	TotP.[3]	p=0,021
Alb[1]	p=0,032	Alb[2]	p=0,003	Alb[3]	p=0,001
Prealb.[1]	p=0,120	Prealb.[2]	p=0,149	Prealb.[3]	p=0,096
Fe[1]	p=0,749	Fe[2]	p=0,037	Fe[3]	p=0,015
Vit. D[1]	p=0,496	Vit.D[2]	p=0,259	Vit.D[3]	p=0,695
Ph[1]	p=0,106	Ph[2]	p=0,276	Ph[3]	p=0,158
Ca[1]	p=0,009	Ca[2]	p=0,832	Ca[3]	p=0,317
Alk. ph.[1]	p=0,313	Alk. Ph.[2]	p=0,761	Alk. ph.[2]	p=0,590
RCP[1]	p=0,052	RCP[2]	p=0,052	RCP[3]	p=0,138
Hgb[1]	p=0,045	Hgb[2]	p=0,044	Hgb[3]	p<0,001

Table 5: Difference in clinical markers in one complication versus ≥2.

1 Outcome Factor Vs 2 or More					
TotP.[1]	p=0,019	TotP.[2]	p=0,029	TotP.[3]	p=0,012
Alb[1]	p=0,006	Alb[2]	p=0,188	Alb[3]	p=0,037
Prealb.[1]	p=0,069	Prealb.[2]	p=0,624	Prealb.[3]	p=0,978
Fe[1]	p=0,115	Fe[2]	p=0,244	Fe[3]	p=0,844
Vit. D[1]	p=0,683	Vit.D[2]	p=1,000	Vit.D[3]	p=0,172
Ph[1]	p=0,930	Ph[2]	p=0,074	Ph[3]	p=0,348
Ca[1]	p=0,717	Ca[2]	p=0,084	Ca[3]	p=0,011
Alk. ph.[1]	p=0,662	Alk. Ph.[2]	p=0,726	Alk. ph.[2]	p=0,642
RCP[1]	p=0,608	RCP[2]	p=0,972	RCP[3]	p=0,076
Hgb[1]	p=0,161	Hgb[2]	p=0,140	Hgb[3]	p=0,722

Table 6: Difference in clinical markers in incidence of late sepsis

Late Sepsis Vs No Ls					
TotP.[1]	p=0,092	TotP.[2]	p=0,023	TotP.[3]	p=0,008
Alb[1]	p=0.381	Alb[2]	p=0,002	Alb[3]	p<0,001
Prealb.[1]	p=0.140	Prealb.[2]	p=0.106	Prealb.[3]	p=0.153
Fe[1]	p=0.838	Fe[2]	p=0.132	Fe[3]	p=0,042
Vit. D[1]	p=0.851	Vit.D[2]	p=0.549	Vit.D[3]	p=1,000
Ph[1]	p=0.121	Ph[2]	p=0.309	Ph[3]	p=0.068
Ca[1]	p=0,021	Ca[2]	p=0.434	Ca[3]	p=0.239
Alk. ph.[1]	p=0.781	Alk. Ph.[2]	p=0.504	Alk. ph.[2]	p=0.843
RCP[1]	p=0,028	RCP[2]	p=0.056	RCP[3]	p=0,210
Hgb[1]	p=0.167	Hgb[2]	p=0.089	Hgb[3]	p=0,002

Table 7: Difference in anthropometry: good versus bad outcome group.

Good Outcome Versus Bad Outcome Group	
Birth Weight	p<0,001
Birth lenght	p<0,001
Birth CP	p=0,007
Weight at 15 days	p<0,001
Weight at 30 days	p<0,001
Discharge weight	p=0,472
Discharge lenght	p=0,883
Discharge CP	p=0,131

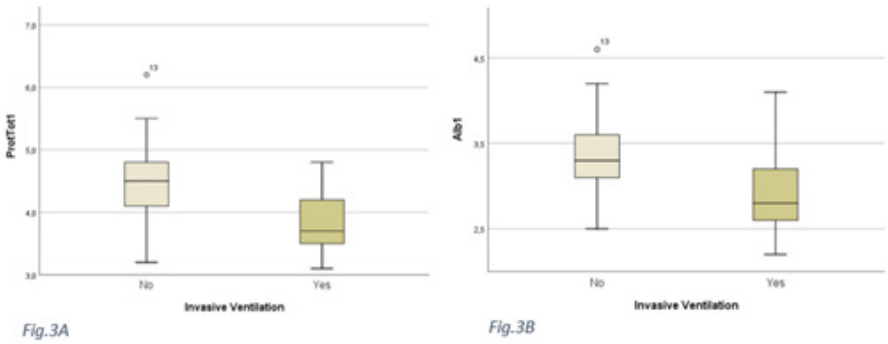

Fig.3A Fig.3B

Figure 3: Difference in ProtTot1 and Alb in PTN with no need versus need for invasive ventilation.

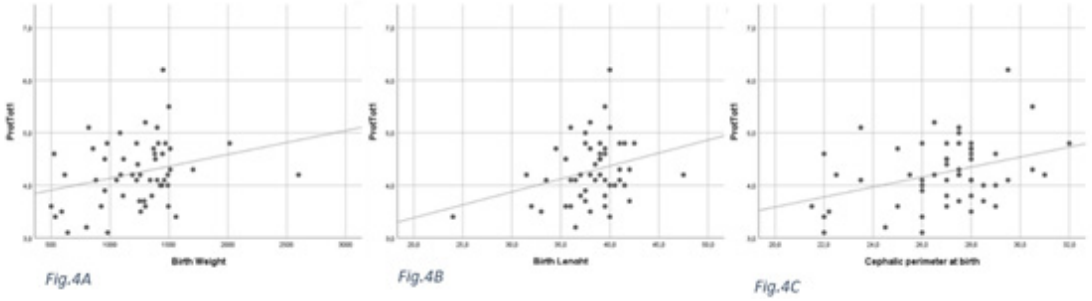

Figure 4: Correlation between TotP1 and anthropometric parameters at birth (BW, Length birth, CP at birth).

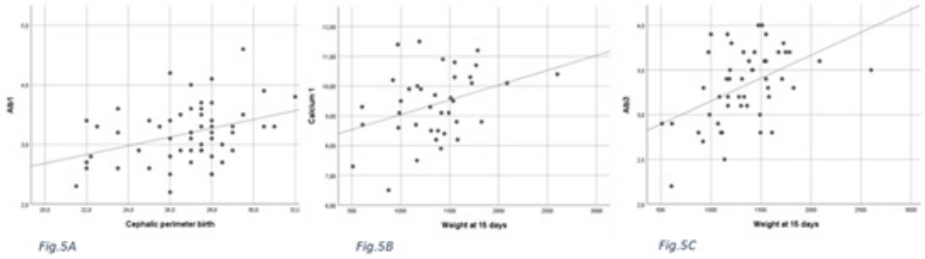

Figure 5: Correlation between Alb1 and CP at birth, Ca1 and weight at 15 days and Alb3 and weight at 15 days.

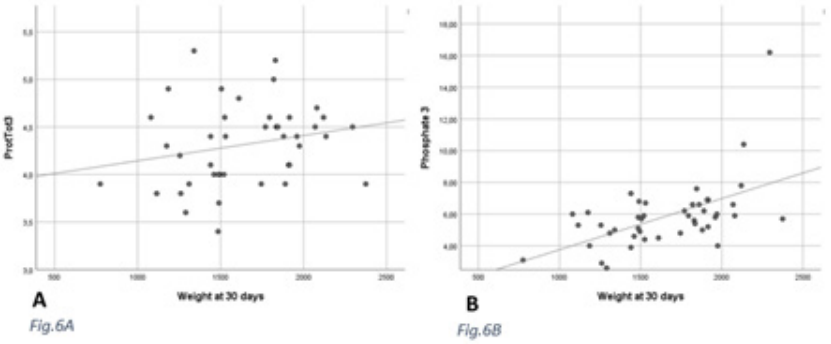

Figure 6: Correlation between weight at 30 days and ProtTot[3] and Ph[3].

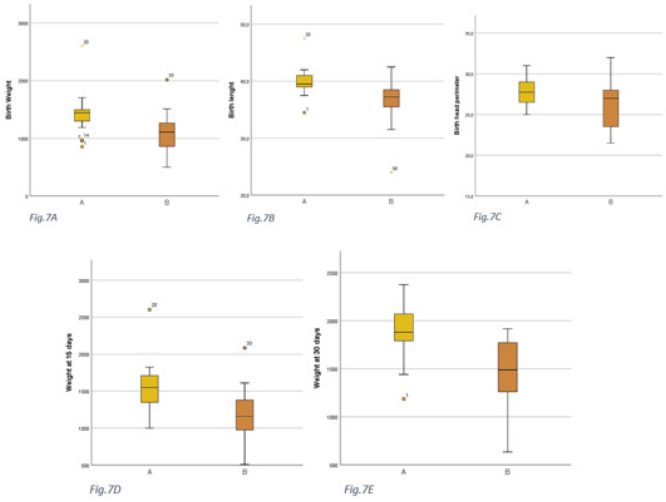

Figure 7: Difference in anthropometric values in good versus poor outcome. (A) Good outcome group; (B) Poor outcome group.

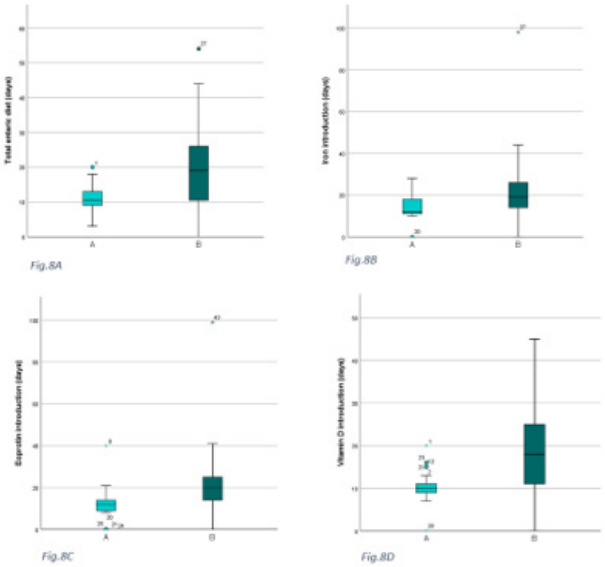

Figure 8: Difference in nutrition and supplementation in poor outcome or good outcome group. (A) Good outcome group; (B) Poor outcome group.

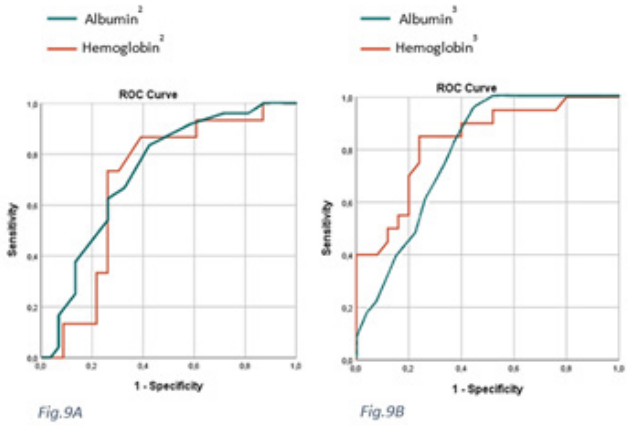

Figure 9: ROC curve for albumin[2], hemoglobin[2], albumin[3] and hemoglobin[3] in predicting poor prognosis PTN.

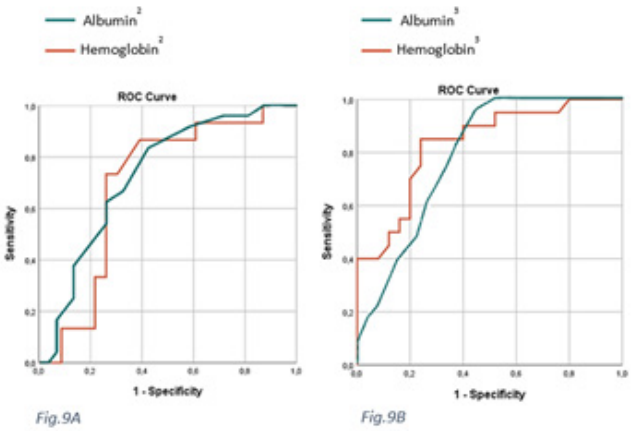

Figure 10: ROC curve for calcium[1], albumin[3] and hemoglobin[3] in predicting late sepsis.

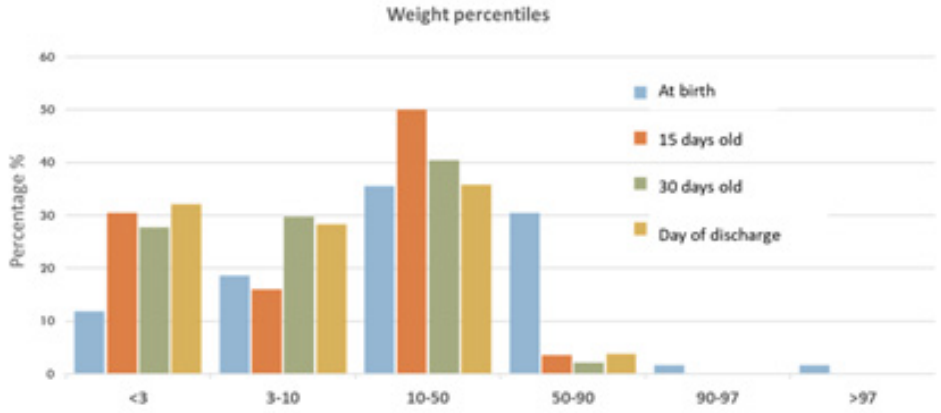

Figure 11: REvolution of weight percentiles of PTN during the stay in the NICU.

Table 8: Differences in diet and supplementation: good versus bad outcome.

Good Outcome Versus Bad Outcome Group	
Parenteric diet duration	p<0,001
Enteric total diet	p=0,001
Eoprotin introduction	p=0,001
Iron introduction	p=0,012
Vitamin D introduction	p<0,001

Table 9: Differences in nutritional markers in the first 24h and z-scores of anthropometric values (<2 Z score vs ≥ 2). (W: weight; L: length; CP:cephalic perimeter).

	Birth weight	Birth length	Birth CP
TotP.[1]	p=0,225	p=0,482	p=0,460
Alb[1]	p=0,172	p=0,446	p=0,897
PreAlb.[1]	p=0,009	p=0,097	p=0,107
Ferritin[1]	p=0,295	p=0,021	p=0,069
D vit.[1]	p=0,685	p=0,309	p=0,044
Ph[1]	p=0,004	p=0,009	p=0,036
Ca1	p=0,184	p=0,343	p=0,644
AlkPh.[1]	p=0,052	p=0,084	p=0,133
Hgb[1]	p=0,019	p=0,077	p=0,281

Regarding the diet and supplement introduction there were also differences in the two groups. In the bad prognosis group the parenteral diet tended to last longer, the total enteric diet was achieved later and supplementation-exoprotein, iron and vitamin D-were introduced later, when compared to the good prognosis group (Table 8, Figure 8). For the Z-scores of anthropometric results, there were also significative differences in the studied markers (Table 9-11). Table 12 shows the median values of those different markers. The biochemical markers collected on the 7th-10th day were the most associated with differences in z-scores of anthropometric measures. At discharge 42.4% (n=25) of the PTN were exclusively breastfed, 30.5% (n=18) had combined feeding and 13.6% (n=8) were fed exclusively with formula. Variables with P values<0.05 in the univariate analysis for bad vs poor outcome (Table 4), were selected for multivariable binary logistic regression analysis (Table 13). Albumin[2], hemoglobin[2], albumin[3] and hemoglobin[3] were independent predictors for bad outcome factors in these PTN. The same analysis was performed for the occurrence of late sepsis (Table 6). Calcium[1], albumin[3] and hemoglobin[3] were independent predictors for the occurrence of late sepsis (Table 14).

Table 10: Differences in nutritional markers in the 7th-10th days of life and z-scores of weight at 15 and 30 day of life (<2 Z score vs ≥2).

	W. 15 Days	W. 30 Days	W. Disch	L. Disch
Total prot.[2]	p=0,852	p=0,439	p=0,716	p=0,485
Albumin[2]	p=0,009	p=0,004	p=0,036	p=0,010
Pré-alb.[2]	p<0.001	p<0.001	p<0.001	p<0.001
Ferritin[2]	p=0,052	p=0,197	p=0,115	p=0,050
D vit.[2]	p=0,005	p=0,014	p=0,012	p=0,052
Phosphate[2]	p=0,007	p=0,009	p=0,024	p=0,072
Calcium[2]	p=0,642	p=0,791	p=0,862	p=0,896
Alkaline ph.[2]	p=0,359	p=0,827	p=0,779	p=0,365
Hgb[2]	p=0,123	p=0,300	p=0,255	p=0,348

Table 11: Differences in nutritional markers in the 30th day of life and z-scores of anthropometric values (<2 Z score vs ≥2).

	W. 30 days
Total prot.[2]	p=0,988
Albumin[2]	p=0,497
Pré-alb.[2]	p<0.035
Ferritin[2]	p=0,607
D vit.[2]	p=0,178
Phosphate[2]	p=0,547
Calcium[2]	p=0,989
Alkaline ph.[2]	p=0,362
Hgb[2]	p=0,923

Table 12: Comparative medians of the markers associated with anthropometric Z-scores.

Birth Weight (Median)		
	<2 Z-score	≥2 Z-score
PreAlb.[1](g/dL)	6.0(IQ 4.05-6.5)	7.0(IQ 7.0-8.0)
Ph[1](mg/dL)	4.1(IQ 2.85-5.25)	6.2(IQ 5.7-6.5)
Hgb[1](g/dL)	19.0(IQ 17.2-20.75)	16.5(15.7-17.3)
Birth Lenght (Median)		
	<2 Z-score	≥2 Z-score
Fe[1](mg/dL)	118.3(IQ 34.0-181.0)	242.0(164.0-307.0)
Ph[1](mg/dL)	4.4(IQ 3.4-5.3)	6.1(IQ 5.4-6.5)
Birth CP (Median)		
	<2 Z-score	≥2 Z-score
VitD.[1](mg/dL)	26.5(IQ 20.0-33.0)	56.0(IQ 50.0-64.0)
Ph[1](mg/dL)	4.45(IQ 3.6-5.3)	6.1(IQ 5.6-6.5)

	Weight at 15 Days (Median)		Weight at 30 Days (Median)	
	<2 Z-score	≥2 Z-score	<2 Z-score	≥2 Z-score
Alb[2](g/dL)	3.1(IQ 2.7-3.3)	3.6(IQ 3.3-3.8)	3.15(IQ 3.0-3.3)	3.4(IQ 3.2-3.7)
PreAlb[2](mg/dL)	7.0(IQ 5.0-7)	10.0(IQ 9.0-12.0)	7.0(IQ 5.0-7.0)	9.0(IQ 8.0-10.0)
VitD[2](mg/dL)	45.0(IQ 41.0-57.5)	60.0(IQ 50.5-76.49)	47.0(IQ 40.5-59.0)	56.0(IQ 50.0-67.0)
Ph[2](mg/dL)	4.1 (IQ 3.8-4.55)	6.2 (IQ 5.4-6.3)	4.0 (IQ 3.2-4.55)	5.4(IQ 4.8-6.3)
PreAlb[3](mg/dL)	_____	_____	7.0(IQ 6.0-9.0)	9.0(IQ 8.0-10.5)
	Weight at Discharge (Median)		**Lenght at Discharge (Median)**	
	<2 Z-score	≥2 Z-score	<2 Z-score	≥2 Z-score
Alb[2](g/dL)	3.1(IQ 2.65-3.3)	3.6(IQ 3.3-3.7)	3.2(IQ 2.8-3.35)	3.6(IQ 3.3-3.7)
PreAlb[2](mg/dL)	7.0(IQ 4.5-7)	10.0(IQ 9.0-12.0)	7.0(IQ 5.0-7.0)	10.0(IQ 9.0-12.0)
VitD[2](mg/dL)	46.0(IQ 42.0-59.0)	59.0(IQ 51.0-80.0)	_____	_____
Ph[2](mg/dL)	4.3(IQ 3.8-5.2)	6.2(IQ 5.3-6.3)	_____	_____

Table 13: Logistic Analysis Results of Predictors for Poor Outcome.

Variables	P Value	Odds Ratio
Total proteins[1]	0.279	0.305(0.035-2,617)
Albumin[1]	0.91	0.875(0.086–8.859)
Calcium[1]	0.104	0.537(0.254-1.136)
Hemoglobin[1]	0.735	0.953(0.722-1.259)
Total proteins[2]	0.139	10.024(0.474-212.178)
Albumin[2]	0.017	0.006(0.000-0.399)
Ferritin[2]	0.882	1.000(0.995-1.006)
Hemoglobin[2]	0.032	0.571(0.342-0.953)
Total proteins[3]	0.074	63.108(0.674-5912.262)
Albumin[3]	0.02	0.001(0.000-0.329)
Ferritin[3]	0.756	0.999(0.991-1.006)
Hemoglobin[3]	0.013	0.408(0.201-0.825)

Table 14: Logistic Analysis Results of Predictors for Late Sepsis.

Variables	P Value	Odds Ratio
Calcium[1]	0.023	0.441(0.218-0.892)
Total proteins[3]	0.868	0.857(0.139-5.303)
Albumin[2]	0.088	0.163(0.020-1.310)
Total proteins[3]	0.245	8.449(0.231-309.455)
Albumin[3]	0.029	0.005(0.000-0.575)
Ferritin[3]	0.298	0.997(0.992-1.002)
Hemoglobin[3]	0.022	0.557(0.337-0.920)

ROC curve analysis was then used to assess the predictive value of these markers. For the poor outcome group (Figure 9) the area under the ROC curve showed that albumin[3] (AUC 0.786; 95% CI, 0.660-0.912; P=0.001) and hemoglobin[3] (AUC 0.831; 95% CI, 0.711 -0.951; P= <0.001) had a rather good predictive value for on predicting a good versus poor outcome, being superior to albumin[2] (AUC 0.735; 95% CI, 0.602-0.868; P=0.003) and hemoglobin[2]

(AUC 0.696; 95% CI, 0.521-0.870; P=0.044). For the occurrence of late sepsis (Figure 10) the area under the ROC curve showed that albumin3 (AUC 0.796; 95% CI, 0.666-0.926; P<0.001) had the best predictive value on predicting the event of late sepsis. Calcium[3] (AUC 0.716; 95% CI, 0.554-0.879; P=0.021) and hemoglobin[3] (AUC 0.766; 95% CI, 0.625-0.907; p=0.002) also had a good predictive value. Table 15 depicts the optimal diagnostic threshold of these markers for predicting poor outcome, and Table 16 for predicting late sepsis. There was no predictive value for any marker for the occurrence of ≥2 complications. For any isolated complication there was also no predictive marker.

Table 15: Cut-off off values albumin[2], hemoglobin[2], albumin[3] and hemoglobin[3] in predicting poor prognosis PTN.

	Cut-Off	Sensitivity	Specificity	Auc
Albumin[2]	3.25g/dL	83.30%	58.10%	0.735
Hemoglobin[2]	13.8g/dL	73.30%	74.00%	0.696
Albumin[3]	3.25g/dL	82.60%	63%	0.786
Hemoglobin[3]	10.9g/dL	85.00%	76%	0.831

Table 16: Cut-off off values calcium1, albumin3 and hemoglobin3 in predicting the occurrence of late sepsis

	Cut-Off	Sensitivity	Specificity	AUC
Calcium[1]	9.2mg/dL	69.60%	64.70%	0.716
Albumin[3]	3.35g/dL	76.00%	72.00%	0.796
Hemoglobin[3]	10.9g/dL	77.30%	73.90%	0.766

Discussion

Inadequate energy intake results in poorer outcome: reduced weight gain, delayed wound healing, longer hospital stays, severe complications, and poorer long-term neurodevelopmental outcomes [3,5,18-21]. On the other hand, better nutrition in the early postnatal phases results in higher verbal intelligence quotient (IQ) scores and improved cognitive function in the long term [3,22-26]. Even though many biochemical markers have been used to assess nutritional status, there has been an effort trying to find nutritional prognosis indicators, and it remains uncertain what nutrient intake ensures normalized postnatal growth trajectories and neurodevelopment for very low birth weight (VLBW) infants [27]. In NICUs, nutritional assessment is necessary to devise therapeutic plans [19,23,28] and although anthropometric parameters can be easily and inexpensively measured, objective laboratory markers should be used to make proper decisions in terms of nutritional support [23]. This study demonstrates the importance of initial nutritional management in the care of PTN infants, as it demonstrates how some nutritional markers are related with poor outcome and malnutrition. In our study lower values of TotP1, Alb1, Ca1 Hb1; TotP2, Alb2, Hb2; TotP3, Alb3 and Hb3 were associated with a poor outcome. Several studies have shown the bond between proteins, albumin and pre-albumin in the prognosis of PTN. Recent works have shown that low plasma protein levels are associated with poor prognosis and high mortality among infants [29,30]. Low plasma proteins in the first day of life can be used as a prognostic factor for severe adverse outcomes [29-31]. Total proteins have also been shown to be an independent predictor for poor prognosis [32]. Although total proteins were not a predictor of a poor prognosis or the occurrence of sepsis in our study, total proteins were significantly lower in the poor outcome and sepsis group.

This highlights the importance of higher protein and energy intake during the NICU stay in these infants. Protein deficit is also associated with lower mental development index scores and higher risk of growth retardation at 18 months after birth [3,33]. Albumin has been studied as a biochemical marker in the assessment of nutritional status and PTN prognosis. Lower albumin levels can result from inflammation and inadequate protein intake [34]. Several works demonstrate a connection in albumin levels and sepsis, need for respiratory support and death [29,34]. We found that albumin collected in all three samples was lower in the poor prognosis group. In the first and third collect it was also lower in the sepsis group and in the ≥2 complications group. Albumin2 was also associated with weight at day 15 and 30. Early and higher protein and energy intake have also been correlated with faster head growth and an increase in head circumference in preterm infants [3,35,36], plus increase in head circumference has been positively correlated with improved cognitive outcomes [37]. Though albumin levels reflect the nutritional status, its half-life is long (17 to 20 days), and the liver synthesizes albumin continuously in the early stage of malnutrition; thus, serum albumin levels remain relatively constant and may not present early nutritional deficiency [35,38,39]. There was a predictive value for alb2 and alb3 for a bad outcome, with best cut-off values of alb2 3.25g/dL (83.3% sensitivity; 58.1% specificity) and alb3 3.25g/dL (82.6% sensitivity; 63% specificity). For the occurrence of LS alb3 had also a predictive value, with a cut-off of 3.35g/dL (76.0% sensitivity; 72% specificity).

Total protein and albumin levels at birth are associated with the need for invasive ventilation [39,40], and that association was also shown in our study. Compared to albumin, prealbumin is more sensitive to protein intake and is a good indicator of early nutritional status [1-4,29,41,42]. Even though prealbumin was not associated with a bad outcome in our study, there was a significant correlation with the length, weight, and head circumference z-scores for each moment. An increase in prealbumin levels has been demonstrated in neonates exposed to exogenous steroid administration or increased endogenous corticosteroid secretion [4,16] but such a correlation was not shown in our study. As already described [23]. Prealbumin can be considered as an indicator of sufficient growth in early preterm infants and growth is a marker of nutritional status being independently associated with long-term neurodevelopment, thus the importance of this marker in assessment of neurocognitive outcome [23,41].

Regarding ferritin, higher Fe2 and Fe3 were associated with a poor outcome. This is of no surprise, since ferritin is an acute phase reactant, and not a reliable indicator of iron storages on its own [1,43]. High ferritin has been shown to be linked to late sepsis and moderate or severe states of bronchopulmonary dysplasia

[43]. The prevalence of 2 or more complications was associated with lower values of TotP1, Alb1, TotP2, TotP3, Alb3, Ca3. We also demonstrated a relation in the incidence of LS with lower values of TotP1, Alb1, Ca1, TotP2, TotP3, Alb3 and Ca3. Vitamin D is an important factor in early lung development and maturation. Vitamin D levels during pregnancy have a significant effect on placental development and weight, and play an important role in embryogenesis, fetal lung maturation and development [34,42,44]. Our study found a difference in levels of vit-D and the Z-score of anthropometric values, with lower vit-D associated with lower z-scores of weight at 15 and 30 days, as well as CP at birth. The delay in the introduction of vitamin D supplementation was also linked to a poor outcome in this study.

All PTN that needed parenteral nutrition (PN) began in the first 24 hours, as it is recommended in the literature [1,3,5,9,36,45]. The median day to start an enteral diet was 3 days. In recent literature the recommended timing to start an enteral diet is the first day of life [3,5,46-49]. Although many centers use standardized PN in our unit we use individual parenteral solutions, made each day for each individual. As preterm infants do not constitute a homogeneous population, their requirements must be individualized, based on their clinical condition and developmental stage [2,50]. Even though individualized PN has been associated with more delays in initiation, in our Unit all PTN started PN in the first hours of life. Monitoring of biochemical and anthropometric parameters is essential to ensure that PN is tolerated, and to discard adverse effects, such as catheter-related complications, infections and sepsis, among others [1,3,51]. The postponement of enteral feeding may prolong the time to achieve full enteral feeding Furthermore, early versus late (72h after birth) initiation of enteral feeding has been found to be associated with a significantly lesser time to gain birth weight, and with shorter duration of parenteral nutrition and hospital stay, without any increase in the complication rate. A reduced incidence of osteopenia of prematurity and jaundice has also been noted with early versus late enteral feeding in very LBW infants [3,49,52]. These findings are in line with our study -delayed total enteral nutrition was associated with a poor outcome, as well as the more prolonged parenteral diet duration. Precocious introduction of enteral diet and lesser duration of PTN lead to a better outcome, along with a better neurodevelopment [27,47,53].

Ideally, enteric diet should be started with breast milk, as immediate breast milk feeding results in elevated insulin-like growth factor 1 (IGF-1), an essential intrauterine hormonal mediator of growth [2,52]. Early administration of parenteral and enteral nutrients helps to prevent neurodevelopmental impairment caused by extrauterine growth restriction, NEC, sepsis, BPD, and ROP [54]. Early trophic feeding with breast milk within 48 hours after birth in clinically stable PTN did not lead to higher mortality or an increased incidence of NEC [2,18,48]. Even though the optimal nutrition is enteric, we cannot forget the clinical evolution of these PTN, which do not always allow the ideal diet adjustments. The parenteral nutrition lasted at least 13 days for the majority of the PTN (>60%) and the enteral nutrition was achieved at day 15 for ~60% of PTN. At discharge 42.4% (n=25) of the PTN were exclusively breastfed, 30.5% (n=18) had combined feeding and 13.6% (n=8) were fed exclusively with formula. Neonatal anemia is a common complication of PTN. It may compromise oxygen transport to the brain and is associated with impaired neurological functioning [20,55-57]. Left untreated, severe anemia may adversely affect organ function due to inadequate oxygen supply to meet oxygen requirements, resulting in hypoxic tissue injury, including cerebral tissue [57]. Lower hemoglobin concentration in all blood samples was linked to a poor outcome. There was a predictive value of Hb2 and Hb3 for a bad outcome, with best cut-off values of Hb2 13.8g/dL (73.3% sensitivity; 74.0% specificity) and Hb3 10.9g/dL (85.0% sensitivity; 76% specificity). For the occurrence of LS Hb3 had also predictive value, with a cut-off of 10.9g/dL (77.3% sensitivity; 73.9% specificity). Most extremely low-birth-weight infants receive one or more RBC transfusions during their NICU stay [58,59]. Red blood cells transfusions are associated with increased risk for ischemia-reperfusion damage or oxidative injury [21], potentially resulting in transfusion-associated NEC, BPD and ROP [59,60]. Several studies comparing thresholds for RBC transfusion have been published [59,61,62], but controversies about when to transfuse anemic preterm infants still remain [57,63-65]. Individualized care regarding RBC transfusions during NICU admission, with attention to cerebral tissue oxygen saturation needs further investigation to improve both short-term effects and long-term neurodevelopment [57,63-65].

Concerning calcium, Ca1 values were lower in the poor outcome group, as well as in the LS group. Ca3 was also lower in the LS group and in the group with ≥2 complications. The Ca1 concentration had also a predictive value for the occurrence of late sepsis, with a cut-off value of 9.2mg/dL (sensitivity 69.6%; specificity 64.7%). Calcium is essential for tissue structure and function [1,66] and has been shown its association with late sepsis prognosis. Neonatal sepsis is an important cause of neonatal death, especially in PTN and BPD, cerebral injury, ROP, and NEC which are serious complications closely related to sepsis. These complications are associated with later disability, confirmed by many studies [20,66-69], thus the importance of calcium as prognostic marker [66,70]. Multiple pathophysiological changes can lead to the development of hypocalcemia in sepsis and many studies have shown that sepsis induces increased levels of various cytokines that can cause hypocalcemia [52-54,70]. There was no predictive value for any marker for the occurrence of ≥2 complications. For any isolated complication there was also no predictive or prognostic marker. Our study has several strengths. Being a prospective study, it was possible to design it with all the variables we wanted to collect, so there are few missing values, making it a valid study. We have also some limitations in our work: it is a single center study, so our sample is limited in size. This forced us to group all the pathologies in one major group (the poor outcome group). Only late sepsis allowed us to do an individual analysis. We also didn't register the diet implemented for each PTN, since they are not standardized diets, but individualized PN each day, for each PTN. The biochemical

study was not repeated at the time of discharge. Although it would have been useful for the study purpose, it was not possible for ethical reasons, since it would have been a clinical unnecessary blood draw. The complications analyzed in this study convey the disabilities in the short term, however, these complications bring consequences on the long run, due to the pathology itself and also their effect on growth and neurodevelopment. We do need to follow these babies and assess their growth, pathologies and neurodevelopment.

We know that neonatal nutritional status at birth is correlated with maternal nutritional status during pregnancy. Maternal nutritional markers were not measured, so, we did not analyze the correlation between our results maternal and neonatal total protein and albumin levels at birth, but improving the maternal nutritional status could be an important factor for decreasing the risk of respiratory support in the neonate during the first day of life [29].

Conclusion

This study highlights the importance of several nutritional markers with prognostic value in preterm outcomes. Anthropometric parameters can be easily and inexpensively measured, but objective laboratory markers should be used to make proper decisions in terms of nutritional support. The neurodevelopment of premature babies is very sensitive to nutrition in the first few weeks of life, and these effects may be long lasting. With the increase of survival of premature NB at the extremes of viability, future research needs to address how better growth and neurodevelopmental outcomes may be achieved. Adequate early nutrition may also attenuate the adverse effects of neonatal illness.

More research is needed to determine the best nutrition, growth rates and body composition in preterm infants that are associated with the best neurocognitive benefits, while minimizing the long-term risk of chronic diseases, making a major contribution to the lives of individuals, families and society. Further studies with larger study populations and a thorough investigation of morbidities will be needed to confirm these results. Each neonatal unit must have a robust and intensive detail orientated approach to monitoring nutrition and growth. Ensuring excellent nutrition is an essential part in everyday decision making and management plan of every infant on the NICU, yielding the best neonatal outcomes.

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