Metabolic Bone Disease and Bone Mineral Density in Very Preterm Infants

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Objectives To evaluate bone mineral density (BMD) in preterm neonates at discharge and identify the optimum cutoff values for serum alkaline phosphatase (ALP) and phosphorus (P) concentrations to diagnose the severity of metabolic bone disease of prematurity.

Study design A total of 336 preterm neonates (≤31 weeks' gestation and birth weight ≤1500 g) were prospectively evaluated for BMD before discharge using dual-energy X-ray absorptiometry.

Results BMD reference values (at ALP ≤500 IU/L) were measured in 279 patients. BMD was classified as poor (<10th percentile) at <0.068 g/cm^2, fair (10th-25th percentile) at 0.068-0.081 g/cm^2, good (25th-75th percentile) at 0.081-0.112 g/cm^2, and very good (>75th percentile) at >0.112 g/cm^2. Increased BMD was associated with a higher birth weight, short duration of parenteral nutrition, and the absence of small for gestational age status, patent ductus arteriosus, intraventricular hemorrhage, and other clinical variables. Metabolic bone disease of prematurity was absent (ALP ≤500 IU/L) in 279 cases (83.0%), mild (ALP >500 IU/L and P ≥4.5 mg/dL) in 46 cases (13.7%), and severe (ALP >500 IU/L and P <4.5 mg/dL) in 11 cases (3.3%).

Conclusions A BMD >0.068 g/cm^2 at discharge indicated a 90.3% probability of not developing metabolic bone disease of prematurity. The factors independently associated with increased BMD included higher birth weight, short duration of parenteral nutrition, absence of intraventricular hemorrhage, exclusive feeding of fortified breast milk, and older age at discharge. *(J Pediatr 2014;164:499-504)*.

Metabolic bone disease of prematurity is a new designation for osteopathy of prematurity that highlights the biochemical and metabolic aspects of the disorder, including the blood concentrations of alkaline phosphatase (ALP), calcium (Ca), phosphorus (P), parathyroid hormone (PTH), and vitamin D.[1] Metabolic bone disease of prematurity occurs in up to 23% of newborns weighing <1500 g at birth and in 55% of those weighing <1000 g who have not received fortified breast milk or formula with high Ca and P content.[2] The severity of the alterations of Ca-P metabolism in metabolic bone disease of prematurity correlate with the degree of ALP elevation at age 1 month[3] and with a decrease in serum P level and, in some cases, Ca level. The expression of metabolic bone disease of prematurity in the bones is quantified by bone mineral density (BMD) analysis.

Bone mineralization can be expressed as bone mineral content (based on grams of hydroxyapatite; rarely used), bone mineral content per centimeter cubed, or BMD (the most widely used measurement). BMD is generally assessed by dual-energy X-ray absorptiometry (DXA) scanning, which measures the Ca content in the bones, expressed as grams of hydroxyapatite per centimeter squared. The exposure to ionizing radiation is minimal (effective dose, 0.001 mSv; <0.1 mrem). The technique is precise and reproducible, and takes only 5 minutes. The trabecular bone is preferred, and the lumbar region is generally used in neonates. Modern portable machines can analyze the forearm and the calcaneus. BMD measurement is the method of choice for children, because the results are independent of anthropometric variables and gestational age.[4] Moreover, according to Yeste et al,[5] there are no significant sex-based differences in BMD.

Our aims in the present study were to evaluate BMD at discharge in preterm infants of ≤31 weeks' gestation with birth weight ≤1500 g, and to identify the optimum cutoff values for serum ALP and P concentrations to diagnose and grade metabolic bone disease of prematurity. We also analyzed the factors influencing BMD.

ALP	Alkaline phosphatase
BMD	Bone mineral density
BPD	Bronchopulmonary dysplasia
Ca	Calcium
DXA	Dual-energy X-ray absorptiometry
P	Phosphorus
PTH	Parathyroid hormone
SGA	Small for gestational age

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Methods

Preterm infants with a gestational age of ≤31 weeks and a birth weight ≤1500 g who were admitted to our neonatal unit between March 2002 and December 2011 and underwent bone densitometry before discharge were included in this analysis. Infants with malformations, chromosomal abnormalities, or metabolopathies, and those for whom parental consent was not obtained, were excluded. The study was approved by our institution's Neonatology Ethics Committee.

Bone densitometry was measured by DXA (Lunar Prodigy; GE Healthcare, Wauwatosa, Wisconsin) and processed using enCore version 8.10.027 software (GE Healthcare). The results were based on the traversal of a low-dose radiograph beam with 2 different energy peaks through the lumbar spine. One peak was absorbed primarily by the soft tissue, and the other was absorbed by bone tissue. The amount of soft tissue was subtracted from the total tissue, and the result was recorded as the BMD. Image acquisition was performed in the lumbar spine in the "thin" mode (default setting).[5,6] The BMD values of the L1-L4 vertebrae were measured, and the average value of the L2-L4 segment was used for the final quantification.

Serum Ca, P, and ALP levels and tubular P reabsorption were determined at discharge, at approximately the same time as bone densitometry was performed.

Following the standard practice for breastfed infants, the mother's milk was enriched using Enfamil Human Milk Fortifier (Mead Johnson, Glenview, Illinois). A standard preterm formula (Alprem; Nestle, Vevey, Switzerland) was given to the formula-fed infants.

The independent variables were year of birth; birth weight; gestational age; small for gestational age (SGA) status; prenatal steroid use; sex; postmenstrual age at discharge; neonatal complications, such as respiratory distress syndrome, patent ductus arteriosus, intraventricular hemorrhage, periventricular leukomalacia, necrotizing enterocolitis, cholestasis, late hemoculture-positive sepsis, bronchopulmonary dysplasia (BPD), and retinopathy of prematurity; treatments administered, such as parenteral nutrition, diuretics, xanthines, feedings, and mechanical ventilation; and serum Ca, P, and ALP and tubular P reabsorption values. Year of birth was analyzed because of the long duration of the study. SGA status was defined as birth weight below the 10th percentile for gestational age and sex, based on the neonatal curves of Olsen et al.[7] BPD was defined as a requirement for supplemental oxygen at 28 days of life. The dependent variables (or result) were BMD (quantitative) and metabolic bone disease of prematurity (categorical: 0, none; 1, mild; 2, severe).

The normal distribution of the quantitative variables was analyzed using the Kolmogorov-Smirnov test before the parametric tests. When the distribution was not normal or a difference in variance (Snedecor F distribution) was observed, nonparametric techniques were used. Parametric variables were recorded as mean ± SD; nonparametric variables, as median (IQR). The categories of the qualitative variables were abstracted as frequency and percentage. For the quantitative variables, nonparametric comparisons were performed using the Kruskal-Wallis test to compare more than 2 groups. Associations between qualitative variables were analyzed using the χ^2 test with the "linear-by-linear association" option when the categories were progressive. Correlations were evaluated using the nonparametric Spearman rho test. Quantitative variables and qualitative variables with progressive categories were included. Linear regression was used for the multivariate analysis, and the dependent and independent variables were quantitative or qualitative with progressive categories. A P value <.05 was considered statistically significant.

Results

A total of 336 preterm infants who underwent biochemical analyses and BMD assessment were included (Table I). The distributions of all quantitative variables except weight were abnormal, and thus nonparametric tests were always applied.

The closest correlations between BMD and any other variables were seen for ALP (n = 333, rho = −0.235; $P < .001$) and P (n = 322; rho = 0.327; $P < .001$). A preliminary analysis identified the best cutoff points for serum ALP and P levels for categorizing the presence and severity of metabolic bone disease of prematurity. After sorting the cases into different groups that were theoretically related to metabolic bone disease of prematurity (Table II), the classification that showed the highest correlation with the BMD value was selected. The concentration threshold of ALP to indicate metabolic bone disease of prematurity was 500

Table I. Demographic and clinical characteristics of the study cohort (n = 336)

Characteristic	Value
BMD, g/cm^2, median (IQR) [range]	0.092 (0.078-0.111) [0.01-0.36]
Birth weight, g, median (IQR) [range]	970 (821-1120) [460-1500]
Gestational age, wk, median (IQR) [range]	28 (26-29) [24 wk 1 d-31 wk 6 d]
SGA (<10th percentile), n (%)	75 (22.3)
Prenatal steroid use, n (%)	302 (92.4)
Male sex, n (%)	163 (48.5)
Respiratory distress syndrome, n (%)	174 (52.4)
Patent ductus arteriosus, n (%)	113 (33.6)
Surgical closure, n (%)	23 (7.1)
Intraventricular hemorrhage, n (%)	63 (19.0)
Cystic periventricular leukomalacia, n (%)	11 (3.3)
Necrotizing enterocolitis, n (%)	9 (2.7)
Cholestasis, n (%)	11 (3.3)
Early sepsis (hemoculture positive), n (%)	3 (0.9)
Late sepsis (hemoculture positive), n (%)	56 (16.9)
BPD (oxygen at 28 days of life), n (%)	28 (8.4)
Retinopathy of prematurity, n (%)	145 (43.7)
Degree 2-3, n (%)	68 (20.5)
Postmenstrual age at densitometry, wk, median (IQR) [range]	36.1 (34.6-38.3) [30-49]

Table II. Ordinal correlations between BMD and metabolic bone disease of prematurity according to cutoff values for serum ALP (300, 500, 700, and 900 IU/L) and P (4.5 and 5.5 mg/dL)

	Metabolic bone disease of prematurity category				
Correlation with BMD	None	Mild	Moderate	Severe	rho; *P* value
According to ALP	ALP ≤300	ALP 301-700	ALP >700		−0.169; .002
	ALP ≤500	ALP 501-700	ALP >700		−0.264; <.001
	ALP ≤500	ALP 501-700	ALP 701-900	ALP >900	−0.264; <.001
According to ALP and P (4 groups)	ALP ≤300	ALP >300 P ≥5.5	ALP >300 P 4.5-5.5	ALP >300 P <4.5	−0.238; <.001
	ALP ≤500	ALP >500 P ≥5.5	ALP >500 P 4.5-5.5	ALP >500 P <4.5	−0.272; <.001
	ALP ≤700	ALP >700 P ≥5.5	ALP >700 P 4.5-5.5	ALP >700 P <4.5	−0.098; .074
	ALP ≤900	ALP >900 P ≥5.5	ALP >900 P 4.5-5.5	ALP >900 P <4.5	−0.055; .319
According to ALP and P (3 groups)	ALP ≤500	ALP >500 P ≥5.5	ALP >500 P <5.5		−0.271; <.001
	ALP ≤500	ALP >500 P ≥4.5	ALP >500 P <4.5		−0.290; <.001

IU/L, because the absolute values of the ordinal correlations with BMD were highest when using this cutoff point (0.264, 0.272, and 0.290; Table II). The maximum value of the correlation (0.290) was obtained by associating the ALP and P concentrations with a cutoff point of 4.5 mg/dL to differentiate mild from severe metabolic bone disease of prematurity. The classification included 3 groups: none (ALP ≤500 IU/L), mild (ALP >500 IU/L and P ≥4.5 mg/dL), and severe (ALP >500 IU/L and P <4.5 mg/dL). The distribution of these categories in our cohort was 279 none (83.0%), 46 mild (13.7%), and 11 severe (3.3%).

To determine the reference BMD values, 279 patients with a serum ALP level ≤500 IU/L were evaluated. In these patients, the 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles were 0.059, 0.068, 0.081, 0.095, 0.112, 0.134, and 0.147 g/cm^2, respectively. Bone density was classified as poor (<10th percentile), fair (10th-25th percentile), good (25th-75th percentile), or very good (>75th percentile). Mean BMD was lower in the 57 patients with ALP >500 IU/L compared with those with ALP ≤500 IU/L ($P < .001$).

A good BMD was associated with higher birth weight; absence of SGA; a short period of parenteral nutrition (which implies increased enteral nutrition); absence of patent ductus arteriosus, intraventricular hemorrhage, cholestasis, and late sepsis; reduced need for mechanical ventilation; exclusive feeding of fortified breast milk; and normal Ca-P metabolism (high Ca, high P, and low ALP) (Table III).

On multivariate linear regression of 299 preterm infants, BMD was independently associated with higher birth weight, no history of intraventricular hemorrhage, a short period of parenteral nutrition, exclusive feeding of fortified breast milk, and older corrected postmenstrual age at discharge.

Only 1 of the 11 patients (9.1%) with severe metabolic bone disease of prematurity had a BMD value above the 25th percentile, and only 27 of the 279 patients (9.7%) without metabolic bone disease of prematurity had a BMD value below the 10th percentile (Table IV). A BMD >0.068 g/cm^2 (10th percentile) at discharge was associated with a 90.3% probability of not developing metabolic bone disease of prematurity. As expected, BMD, ALP, P, and Ca values differed significantly among the 3 groups (Table IV).

Discussion

None of the evaluated metabolites (Ca, P, ALP, PTH, and vitamin D) alone can be considered a marker of metabolic bone disease of prematurity.[8] Serum Ca and P levels may be normal despite reduced storage levels, because of the effect of PTH.[9] The most widely accepted marker of metabolic bone disease of prematurity is ALP,[10] but cutoff points for defining osteopenia vary widely among studies, from 300 IU/L (the maximum normal level in newborns[10]) to 900 IU/L.[11] According to Hung et al,[3] an ALP level >700 IU/L at 3 weeks postnatal age is predictive of osteopenia at term, with a sensitivity of 73% and a specificity of 74%. In our study, an ALP level of 500 IU/L was chosen as the threshold value, similar to that reported by Harrison et al,[1] because it was associated with the best division of the total patient sample according to BMD.

Assessing BMD with entire body and spine studies is recommended. For the entire body results, it is suggested that the value of the head not be taken into account because of the different bone evolution of the head relative to the rest of the skeleton. The software version available at the time of this study was enCore version 8. We tested this software in neonates and identified problems linked to cell size (4.8 × 6.5 mm) and faster acquisition, which resulted in lower spatial resolution. The software did not allow exclusion of results for the head/cranium from the overall BMD results or correction for the influence of immobilization devices on the results. The resulting variability was decreased in children weighing >15 kg. Thus, we decided to discontinue the use of this software in newborn patients. The spinal assessment allowed better bone edge recognition and reliable monitoring of the bone limits, and eliminated potential artifacts.[5,6]

Table III. Factors influencing BMD

Factor	BMD category (n = 336)				*P* value*
	Poor (n = 46)	Fair (n = 53)	Good (n = 158)	Very good (n = 79)	
BMD, g/cm^2, median (IQR)	0.059 (0.051-0.063)	0.076 (0.071-0.079)	0.094 (0.087-0.102)	0.127 (0.119-0.143)	-
Year of birth, median (IQR)	2008 (2006-2010)	2009 (2007-2010)	2008 (2007-2010)	2009 (2007-2010)	.027
Birth weight, g, median (IQR)	910 (770-1020)	840 (760-970)	990 (860-1125)	1070 (885-1200)	.000
Gestational age, wk, median (IQR)	28 (26-29)	27 (26-29)	28 (27-29)	28 (27-29)	.224
SGA <10th percentile, n (%)	15 (32.6)	16 (30.2)	22 (13.9)	8 (10.1)	.000
Prenatal steroids, n (%)	40 (90.9)	48 (90.5)	143 (93.5)	71 (92.2)	.912
Male sex, n (%)	28 (60.9)	30 (56.6)	68 (43.0)	37 (46.8)	.103
Respiratory distress syndrome, n (%)	18 (43.8)	33 (68.8)	78 (54.2)	33 (49.3)	.808
Patent ductus arteriosus, n *%)	20 (43.5)	18 (34.0)	57 (36.1)	18 (22.8)	.031
Surgical closure, n (%)	4 (9.8)	7 (14.9)	11 (7.8)	1 (1.5)	.067
Intraventricular hemorrhage, n (%)	12 (29.3)	14 (29.2)	23 (16.0)	10 (14.9)	.016
Cystic periventricular leukomalacia, n (%)	1 (2.4)	0	8 (5.6)	2 (3.0)	.452
Necrotizing enterocolitis, n (%)	2 (4.9)	2 (4.2)	1 (0.7)	1 (1.5)	.102
Cholestasis, n (%)	3 (7.3)	5 (10.4)	1 (0.7)	1 (1.5)	.007
Late sepsis hemoculture positive, n (%)	11 (26.8)	10 (20.8)	22 (15.3)	8 (11.9)	.030
BPD, n (%)	6 (13.0)	7 (13.2)	10 (6.3)	5 (6.3)	.237
Retinopathy of prematurity, n (%)	18 (43.9)	32 (66.7)	65 (45.1)	23 (34.3)	.049
Degree 2-3, n (%)	9 (22.0)	16 (33.3)	27 (18.8)	10 (15.0)	.093
Parenteral nutrition, d, median (IQR)	9 (8-13)	8 (7-10)	7 (6-9)	7 (5.5-9)	.000
Diuretic use, d, median (IQR)	0 (0-0)	0 (0-2)	0 (0-2)	0 (0-2)	.879
Xanthine use, d, median (IQR)	40 (24-65)	47 (33-60)	40 (23-52)	39 (26-52)	.465
Breast milk with/without formula, n (%)	37 (80.4)	50 (94.3)	138 (87.3)	76 (96.2)	.019
Exclusively fortified breast milk, n (%)	22 (47.8)	34 (64.2)	113 (71.5)	60 (75.9)	.007
Mechanical ventilation, d, median (IQR)	1 (0-5)	2 (0-5)	0 (0-2)	0 (0-2)	.012
Postmenstrual age at densitometry, wk, median (IQR)	37.2 (36.1-38.6)	36.4 (34.8-38.4)	35.7 (34.6-37.6)	35.4 (34.9-38.3)	.031
Serum Ca, mg/dL, median (IQR)	9.5 (9.1-9.8)	9.8 (9.4-10.2)	9.8 (9.4-10.1)	9.9 (9.6-10.2)	.004
Serum P, mg/dL, median (IQR)	6 (5-6.5)	6 (5.3-6.8)	6.6 (6.1-7.3)	6.9 (6.1-7.3)	.000
Serum ALP, IU/L, median (IQR)	455 (320-568)	368 (275-504)	316 (255-391)	318 (259-414)	.000
Tubular P reabsorption, %, median (IQR)	81 (66-92)	79 (69-90)	85 (75-91)	85 (76-89)	.340

*χ^2 or Kruskal-Wallis test.

Published studies related to BMD are limited for children[5,12] and infants, particularly preterm infants.[4,5,13,14] BMD is typically assessed in infants before discharge or during the first month after discharge. Measurements of BMD at discharge invariably reflect any effects of neonatal complications and the type of nutrition and treatments administered, which reflects the actual clinical situation of these infants. BMD is not associated with sex[5,15] and increases with age.[5] Rigo et al[4] studied 80 preterm infants weighing <1500 g at the time of discharge who were at appropriate weight for gestational age and found a mean bone mineral content of 30.8 g and a bone area of 221 cm^2, with a ratio of 0.139 g/cm^2. The mean DXA value measured in the lumbar region in our preterm population (0.09 g/cm^2) was less than the lowest value reported previously (0.14 g/cm^2),[4,13] and did not reach the value reported for infants at near to term.[16] This finding may be related to our infants' shorter gestational time (an average of 28.2 weeks vs 31.2 weeks[13]), lower birth weight (average of 1001 g vs 1480 g[13]), and evaluation at a younger corrected age (36 weeks, 1 month corrected age vs 0-1.5 months[17]), with less time for catch-up. Yeste et al[13] reported correlations between BMD at 0-1.5 months and gestational age ($r = 0.63$; $P < .001$) and birth weight ($r = 0.31$; $P = .02$).

In our study, birth weight was the clinical variable with the highest positive correlation with BMD at discharge. Rigo

Table IV. Characteristics by metabolic bone disease of prematurity category

Characteristic	Metabolic bone disease of prematurity category			*P* value*
	None	Mild	Severe	
Densitometry, g/cm^2, median (IQR)	0.094 (0.081-0.112)	0.082 (0.065-0.093)	0.060 (0.059-0.071)	<.001
BMD category, n (%)				<.001
Poor (<10th percentile)	27 (9.7)	13 (28.3)	6 (54.5)	
Fair (10th-25th percentile)	39 (14.0)	10 (21.7)	4 (36.4)	
Good (25th-75th percentile)	141 (50.5)	16 (34.8)	1 (9.1)	
Very good (>75th percentile)	72 (25.8)	7 (15.2)	0	
Serum ALP, IU/L, median (IQR)	314 (250-377)	568 (525-688)	568 (552-645)	<.001
Serum P, mg/dL, median (IQR)	6.7 (6.0-7.3)	6.1 (5.6-6.6)	3.9 (3.65-4.15)	<.001
Serum Ca, mg/dL, median (IQR)	9.8 (9.4-10.2)	9.6 (9.3-10.0)	9.4 (9.0-9.75)	.020

*χ^2 or Kruskal-Wallis test.

et al[4] reported an identical finding for stillbirths and term and preterm neonates.[14] These findings suggest that BMD is conditioned primarily by prenatal mineralization. Mineral accretion at the time of discharge is reportedly greater in preterm infants fed formula enriched with Ca and P.[18,19] We did not observe this effect, because our preterm infants received fortified breast milk or formula designed for preterm infants. The infants receiving fortified breast milk had higher BMD values, and fortified breast milk feeding was a significant independent variable in our linear regression analysis. Fewtrell et al[20] reported that supplementation of breast milk in preterm infants was not associated with a higher bone mineral content at age 20 years. Other variables, including gestational age, protein content,[21] and solubility of Ca and P salts, may influence BMD. Breast milk Ca is absorbed at a rate of 70%, compared with 25%-30% for formula Ca. Lactose encourages absorption.[22] Rigo et al[4] reported the maximum retention of Ca (91 mg/kg/day) and higher bone accretion at discharge in 9 preterm infants who received breast milk with a fortifier containing 170 mg/kg/day of highly soluble Ca glycerophosphate. Rigo et al[23] recommended administering 100-160 mg/kg/day of highly bioavailable Ca salts with 60-90 mg/kg/day of P and 800-1000 IU/day of vitamin D. The European Society of Paediatric Gastroenterology, Hepatology, and Nutrition's Committee on Nutrition advises a Ca intake of 120-140 mg/kg/day.[24] Our results also suggest that SGA preterm infants have reduced BMD. Lapillonne et al[25] reported decreased BMD in 20 intrauterine growth-restricted infants at term.

Generally, preterm infants recover from low BMD by age 2 years,[13] or by 6-12 months with the use of enriched formula.[4] Studies of patients aged 8-12 years have revealed delayed stature in children who have recovered from low BMD.[4] Although metabolic bone disease of prematurity is a self-limiting process, the benefits of rapid recovery include the avoidance of fractures, a lower rate of dolichocephaly, and improved growth[26] in addition to long-term benefits, such as increased bone mass[20] and reduced osteopenia in adulthood.

In a preterm infant, the diagnosis of metabolic bone disease of prematurity (ALP >500 IU/L) or low BMD at discharge (<0.068 g/cm^2), or during hospitalization if ALP and P are assessed periodically, justifies the application of clinical interventions that may include provision of sufficient Ca and P in parenteral nutrition (75 mg/kg/day of Ca and 44 mg/kg/day of P)[27] over the shortest period possible; provision of sufficient Ca and P in enteral nutrition[2]; fortification of breast milk or use of a specific formula for preterm infants[28]; changing of furosemide to chlorothiazide as early as possible; reduction in the use of dexamethasone; administration of oral vitamin D at 400-800 IU/day; physiotherapy to mobilize the upper and lower extremities in stable preterm infants to promote bone mineralization[29]; and careful management of preterm infants with severe metabolic bone disease of prematurity to prevent fractures. In addition, in our neonatal unit, infants with severe metabolic bone disease of prematurity are treated with vitamin D (800-1200 IU/day), Ca (100-150 mg/kg/day), and P (90 mg/kg/day), with the highest doses given to those with a BMD value <0.068 g/cm^2.

A weakness of the present study is its long duration (almost 10 years). However, postnatal steroids were never used to treat BPD for more than 5 days, and the same artificial formula and human milk fortifier was used throughout the study period. Birth year did not affect BMD in the multivariate analysis. An additional weakness is the assumption that all infants with a serum ALP level ≤500 IU/L have normal bone density. Although this assumption may be reasonable in clinical practice, BMD decreases in virtually all preterm infants from birth to discharge,[4,14] and serum ALP level appears to be of only limited value in predicting bone mineralization in preterm infants.[10] The closest correlations seen in the present study were between BMD and ALP and P levels, and thus we decided to diagnose and grade metabolic bone disease of prematurity based on the combined values. Our results agree with those reported by Backström et al,[30] although we identified different cutoff values (ALP >500 IU/L vs 900 IU/L and P <4.5 mg/dL vs 5.5 mg/dL). ■

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