

Pediatric benign transient hyperphosphatasemia: Clinical course and inflammatory ratios

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ABSTRACT

Objective: Benign transient hyperphosphatasemia (BTH) is a self-limited condition characterized by marked isolated serum alkaline phosphatase (ALP) elevation in children without evidence of bone or hepatobiliary disease. This study aimed to describe the clinical course of pediatric BTH and to test the hypothesis that Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) differ between children with BTH and healthy controls.

Materials and Methods: In this single-center retrospective study, we screened all pediatric ALP measurements (0–18 years) recorded between 2018 and 2025. Children were included if ALP was at least 2 times the age-specific upper reference limit, liver-related biochemical parameters were normal, there was no clinical evidence of bone or hepatobiliary disease, and ALP normalized during follow-up. NLR and PLR were compared with those of age and gender similar healthy controls without known chronic disease, medication use, or evidence of recent or ongoing infection or inflammatory conditions.

Results: Thirty-nine children met the inclusion criteria, with a mean age of 51.9±59.7 months (range, 3–166 months). Of these, 69.2% were younger than 3 years and 59.0% were female. Mean ALP at presentation was 1006.2±1061.9 U/L (range 504–6576). ALP normalized spontaneously within 8.5±3.9 week (range 3–17). Compared with controls, the BTH group had significantly lower NLR (0.85 vs 2.66; $p<0.001$) and PLR (83.76 vs 122.51; $p=0.047$).

Conclusion: BTH should be considered in clinically well children with isolated ALP elevation after exclusion of serious bone and hepatobiliary disorders. Lower NLR and PLR may provide supportive exploratory information, but require confirmation in larger prospective studies before clinical application.

Keywords: Alkaline phosphatase, benign transient hyperphosphatasemia, child, neutrophils, platelet count

Introduction

Serum alkaline phosphatase (ALP) comprises a group of isoenzymes mainly derived from bone, liver, intestine, kidney, placenta, and leukocytes (1). In healthy children, bone and liver fractions predominate, and ALP levels vary by age. ALP increases physiologically particularly during infancy and adolescence due to bone growth (2).

Six ALP isoenzymes have been described: high-molecular-weight ALP (ALP1), hepatic ALP (ALP2), bone ALP (ALP3), placental ALP (ALP4), intestinal ALP (ALP5), and IgG-bound ALP (ALP6) (3). When ALP is elevated beyond age-expected ranges, differential diagnoses should include rickets, fractures, hepatic disease, tubulopathies, and medication-related causes. Notably, ALP3 activity in children is several-fold higher than in adults. Therefore, even with age adjustment, pediatric patients with markedly elevated ALP are occasionally encountered.

Although ALP is physiologically higher in childhood than adulthood, a pronounced and transient elevation in ALP without evidence of bone or liver disease is termed benign transient hyperphosphatasemia (BTH) and is often detected incidentally (4).

The diagnostic framework based on Kraut's historical criteria and updates by Chu and Rothschild can be summarized as: a tendency to be detected in children <5 years of age, absence of clinical and laboratory evidence of bone or liver disease, elevation in both bone and liver isoenzymes, and normalization within 3–4 months (5,6).

In one study, 87% of cases were ≤24 months of age, ALP frequently exceeded 1000 U/L, and a substantial proportion of patients resolved within 4–12 weeks; increased detection in autumn and winter was also reported (4). The etiology of BTH remains uncertain; studies have suggested associations with respiratory syncytial virus (RSV), Epstein-Barr virus (EBV),

human bocavirus, rotavirus, HIV, and SARS-CoV-2 (1,7-9). Case reports from Turkey have similarly emphasized that BTH is commonly observed after viral infections in children, requires no treatment, and that unnecessary investigations should be avoided (10,11). More recently, BTH has also been described in toddlers with COVID-19 infection, further supporting the possibility that viral triggers may contribute to transient ALP elevation in susceptible children (12).

The aim of this study was to describe the clinical and laboratory characteristics of BTH cases aged 0–18 years at our center, including seasonal distribution and time to normalization, and to provide practical management recommendations in light of the existing literature.

Materials and Methods

This single-center retrospective analysis was conducted by screening all pediatric ALP measurements (0–18 years) performed in the laboratory information system for patients evaluated at the Department of Pediatrics at Çanakkale Onsekiz Mart University between 2018 and 2025. The index presentation was defined as the first elevated ALP result recorded for an individual patient.

Inclusion criteria were: (i) ALP $\geq 2\times$ the age-expected upper reference limit, (ii) concurrently normal alanine aminotransferase/aspartate aminotransferase (ALT/AST), gamma-glutamyl transferase (GGT), and bilirubin, (iii) no evidence in clinical records of bone disease/fracture, rickets, hepatobiliary disease, malignancy, overt renal tubulopathy/bone-mineral disorder, or use of medications known to increase ALP (phenobarbital, phenytoin, carbamazepine, and valproic acid, or systemic corticosteroids), and (iv) documented normalization of ALP to the age-appropriate range within the classical expected period of 3–4 months, with an upper allowance of 6 months in cases where repeat testing was delayed in routine retrospective follow-up.

From electronic medical records, we extracted sociodemographic variables (age, sex, season of presentation), symptoms or history suggestive of infection within the preceding 4–6 weeks, ALP values and follow-up measurements, liver-related biochemical parameters (ALT, AST, GGT, and bilirubin), complete blood count parameters required for the calculation of NLR and PLR, and the date of ALP normalization. Additional biochemical parameters relevant to the differential diagnosis of elevated ALP, including calcium, phosphorus, magnesium, 25-hydroxyvitamin D [25(OH)D], parathyroid hormone (PTH), creatinine, thyroid-stimulating hormone (TSH), and C-reactive protein (CRP), as well as imaging findings, were reviewed when available as part of the clinical assessment. Viral testing, when available, was performed according to routine clinical indications rather than a standardized protocol and included tests documented in the medical records (RSV, influenza A and B, adenovirus, SARS-CoV-2, EBV, CMV, and hepatitis A, B, and C). Because viral testing was not systematically performed in all patients, virologic data were incomplete and were not used as diagnostic criteria for BTH.

For analysis of NLR and PLR, the control group was composed of age- and sex-similar children who presented to

the outpatient clinic for routine evaluation and had available complete blood count data. Controls were retrospectively selected from existing outpatient clinic records and were not specifically recruited for this study. Controls were included only if they had no known chronic disease, no regular medication use, and no clinical or documented laboratory evidence of acute or recent infection, inflammatory condition, or other systemic illness at the time of assessment. Children with symptoms or records suggestive of recent infection, inflammatory disease, or any condition potentially affecting hematologic inflammatory indices were excluded. NLR and PLR were calculated using absolute cell counts expressed in the same unit; NLR was defined as neutrophil count/lymphocyte count, and PLR as platelet count/lymphocyte count. Both ratios are dimensionless, but values should be converted to the same unit when hematological parameters are reported differently across laboratories or countries.

Statistical analyses

Were performed using the Statistical Package for the Social Sciences (SPSS) for Windows, version 27 (IBM SPSS Corp.; Armonk, NY, USA). Continuous variables were summarized as mean and standard deviation (SD) and minimum and maximum, as appropriate, and categorical variables were presented as number and percentage. The distribution of continuous variables was assessed using visual and The distribution of continuous variables was assessed using visual methods (histograms and Q–Q plots) and the Shapiro–Wilk test. For between-group comparisons, Student's t-test was used for normally distributed variables. A two-sided p value of <0.050 was considered statistically significant. For the comparison of NLR and PLR between groups, effect size was additionally expressed using Cohen's d.

Results

A total of 39 pediatric BTH cases meeting the inclusion criteria were included. Mean age was 51.87 ± 59.68 months, ranging from 3 months to 13.8 years (Table I). BTH cases were predominantly young children; 69.2% were younger than 3 years. Females comprised 59.0% of cases (Table I). BTH was observed in all seasons, with slightly more presentations in summer (28.2%) BTH was observed in all seasons, with the highest proportion of presentations occurring in summer (28.2%), followed by spring and autumn (25.6% each), and the lowest proportion in winter (20.5%) (Table I). ALP elevation was mostly detected incidentally. None of the patients had symptoms or signs suggestive of bone or hepatobiliary disease at presentation. Recent infection-related complaints, mainly respiratory tract infection or gastroenteritis within the preceding 4–6 weeks, were recorded in 8 patients (Table I).

ALP levels at presentation varied widely. Mean ALP was 1006.20 U/L (SD 1061.87; range 504–6576) (Table I). Peak ALP exceeded 1000 U/L in 25.6% of cases. Liver function tests and other relevant biochemical parameters were within normal limits, with mean ALT 18.23 ± 12.70 U/L, AST 31.02 ± 12.43 U/L, and GGT 20.69 ± 17.60 U/L (Table I). Mean NLR and PLR in the BTH group were 0.85 ± 0.76 and 83.76 ± 32.37 , respectively (Table I). In all children diagnosed with BTH, ALP values returned spontaneously to the normal range

Table I: Sociodemographic and laboratory data

Variable	Values
Total number of patients	39
Age (month)*	51.87±59.68 (3-166)
Gender†	
Female	23 (59.0)
Male	16 (41.0)
Season of presentation†	
Spring	10 (25.6)
Summer	11 (28.2)
Autumn	10 (25.6)
Winter	8 (20.5)
Recent infection history (past 4-6 weeks)†	
No	31 (79.5)
Yes	8 (20.5)
Time to ALP normalization (weeks)*	8.48±3.85 (3-17)
Laboratory parameters*	
ALP (U/L)	1006.20±1061.87 (504-6576)
ALT (U/L)	18.23±12.70 (4-68)
AST (U/L)	31.02±12.43 (9-64)
GGT (U/L)	20.69±17.60 (4-69)
NLR	0.85±0.76 (0.06-3.11)
PLR	83.76±32.37 (20.47-181.11)

*: mean±SD (min-max), †: n(%), **NLR**: Neutrophil to lymphocyte ratio, **PLR**: Platelet to lymphocyte ratio

Table II: Comparison of BTH and control groups

	BTH *	Control *	p	t	Cohen's d
Total number of patients	39	39	-	-	-
NLR	0.85±0.76	2.66±2.87	<0.001	-3.784	0.862
PLR	83.76±32.37	122.51±113.63	0.047	-2.048	0.462

*: mean±SD (Independent samples *t*-test), **BTH**: Benign transient hyperphosphatasemia, **NLR**: Neutrophil-to-lymphocyte ratio, **PLR**: Platelet-to-lymphocyte ratio

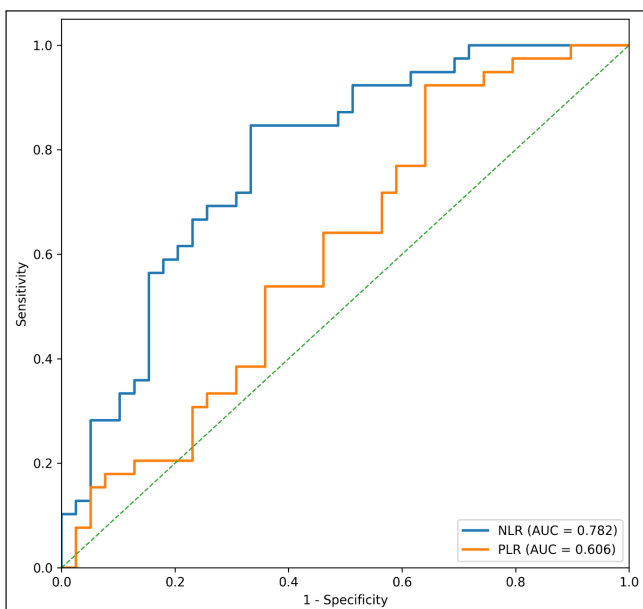


Figure 1: ROC curves of NLR and PLR for distinguishing BTH from controls.

within 8.48±3.85 weeks (range, 3–17) (Table I). Abdominal ultrasonography was performed in 10 patients, and a viral

panel was available in seven patients only, reflecting selective testing based on clinical indication in routine practice; all available results were reported as negative/normal in the medical records.

When the BTH group was compared with an age-similar healthy control group, significant differences were observed in NLR and PLR. NLR was significantly lower in the BTH group than in controls (0.85 vs 2.66; $p<0.001$) (Table II). Similarly, PLR was lower in the BTH group (83.76 vs 122.51; $p=0.047$) (Table II). These differences were statistically significant; the effect size was larger for NLR (Cohen's $d=0.862$).

ROC analysis demonstrated that NLR had moderate discriminatory ability for BTH, with an AUC of 0.782 (95% CI: 0.672–0.879, $p<0.001$). An NLR cut-off of ≤ 1.35 yielded 84.6% sensitivity and 66.7% specificity. ROC analysis showed limited and statistically nonsignificant discriminatory ability for PLR (AUC = 0.606, 95% CI: 0.474–0.727, $p=0.099$). Therefore, PLR findings were interpreted as exploratory.

Discussion

This study describes the clinical and laboratory profile and follow-up characteristics of pediatric BTH cases aged 0–18 years at our center. The great majority of BTH cases were detected in children ≤ 3 years of age. In a cohort of 382 cases, Shkalim et al. (4) reported that 87% were younger than 2 years, while Behúlová et al. (13) found that 96% of cases were under 5 years. A systematic review by Gualco et al. reported that 82% of cases were younger than 3 years and that ALP normalized within 4 months in 81% of patients (15). Consistent with these reports, most of our cases were under 5 years, and ALP elevations generally resolved spontaneously within a few months.

Regarding sex distribution, the literature suggests a slight male predominance. Regarding sex distribution, Shkalim et al. (4) reported that 54% of cases were male, whereas females comprised 59% of our cohort. Although these findings suggest some variability in sex distribution across studies, no consistent sex predominance has been clearly established in BTH.

The etiology of BTH has not been fully elucidated, and viral infections have been proposed as a potential contributing factor. In our study, 20.5% of cases had recent infection-related complaints, mainly upper or lower respiratory tract infection or gastroenteritis, within the preceding 4–6 weeks. The literature similarly describes associations with various viral infections, including sinusitis, bronchiolitis and viruses such as EBV and CMV (2,8,9). Some studies have also reported that cases cluster in autumn and winter (4). In our data, BTH cases were distributed throughout the year, with the highest proportion observed in summer (28.2%), followed by spring and autumn (25.6% each), and the lowest proportion in winter (20.5%). This relatively even distribution suggests that a clear seasonal pattern was not evident in our cohort. Increased testing during periods of higher infection activity in young children may nevertheless contribute to incidental detection. Because viral testing was not performed systematically and was available only in a limited number of patients, the possible association

between BTH and recent infection could not be evaluated in a standardized manner. Accordingly, infection history in this study should be interpreted cautiously, and no causal inference regarding specific viral pathogens can be made. Viral infection has been discussed in the BTH literature, but incomplete virologic testing in retrospective cohorts inherently limits pathogen-specific conclusions.

Biochemically, BTH has been described as involving elevations in both hepatic and bone ALP isoenzymes. Proposed mechanisms include transient increased release from liver and/or bone or decreased clearance due to changes in ALP glycosylation. Some groups have investigated a possible role for vitamin D and reported higher 25(OH)D levels, but definitive evidence is lacking (4,16). In our cohort, liver-related biochemical parameters were within normal limits, and no clinical findings suggestive of bone disease were identified. In classical descriptions of BTH, ALP isoenzyme analysis has often been used to demonstrate the characteristic contribution of both bone and liver fractions and thereby support the diagnosis. In the present cohort, isoenzyme fractionation was not available; therefore, our interpretation relied primarily on the overall clinical pattern, including isolated ALP elevation, absence of clinical and biochemical evidence of hepatobiliary or bone disease, and spontaneous normalization during follow-up. This point is important when interpreting our findings, as biochemical subtype confirmation could have provided additional support for diagnostic classification.

Similarly, a recent single-center pediatric cohort reported BTH in 95 of 249 children evaluated for elevated ALP, supporting that BTH represents a frequent benign explanation after exclusion of hepatic and bone disease (14). From a clinical perspective, unnecessary invasive procedures and extensive diagnostic workup should be avoided in children with suspected BTH, in order to reduce patient burden and prevent undue family anxiety. One study reported that among 62 children with ALP >1000 U/L who were later diagnosed with BTH, 25% underwent unnecessary further investigations and 13% were referred to tertiary centers without clear need (17). Recent data also suggest that greater awareness of BTH may reduce unnecessary referrals, investigations, and healthcare costs (18). Therefore, a “watchful waiting” approach with repeat ALP testing is recommended in clinically well children with unremarkable examination and otherwise normal laboratory/imaging assessment (10).

To our knowledge, this study is the first to examine NLR and PLR in BTH and to explore the potential relevance of these inflammatory indices. Recent pediatric studies have evaluated hematology-derived inflammatory ratios, particularly NLR and lymphocyte-to-monocyte ratio, in the context of respiratory infections and viral pneumonia, suggesting that these indices may provide supportive but nonspecific information regarding infection-related immune response patterns (19). Our results showed that children with BTH had significantly lower NLR and PLR values than healthy controls. One possible explanation is that BTH may occur in a biological setting characterized by minimal systemic inflammation, particularly in otherwise well-appearing children. Lower NLR may reflect relative lymphocyte

predominance and the absence of a marked neutrophil-driven inflammatory response, while lower PLR may similarly be consistent with a mild inflammatory milieu rather than an active systemic inflammatory process. From a clinical perspective, these findings suggest that low NLR and PLR may provide supportive contextual information when isolated ALP elevation is identified in a child with otherwise reassuring clinical and biochemical findings. However, both NLR and PLR are nonspecific indices and may be influenced by age, transient infections, physiologic hematologic variation, and the retrospective nature of control group selection; therefore, age-similar control selection is particularly important in pediatric studies (20). Therefore, these parameters should not be interpreted as diagnostic biomarkers for BTH, but rather as preliminary and hypothesis-generating observations that require confirmation in larger prospective studies.

Limitations

Our study adds to the literature by including a broad pediatric age range and by evaluating novel parameters such as NLR and PLR. However, several limitations should be acknowledged. However, due to the retrospective design, laboratory confirmation of viral etiologies was not available for all cases, as viral testing was performed only in selected patients according to routine clinical indications rather than a standardized protocol. Therefore, the association between BTH and specific viral pathogens could not be assessed systematically. In addition, ALP isoenzyme fractions were not specifically measured. The modest sample size may also limit statistical power in subgroup analyses. Despite these limitations, our findings support prior work indicating that BTH is a benign condition with spontaneous resolution within a few months. We also acknowledge that the requirement for documented ALP normalization may have introduced selection bias by favoring inclusion of cases with a typical transient course. While this criterion was used to improve diagnostic confidence in a retrospective setting, it may have excluded children with incomplete follow-up or less straightforward presentations. Additional hematological indices, such as neutrophil/(lymphocyte + monocyte) ratio or (absolute lymphocyte + monocyte count)/white blood cell count, were not analyzed because they were not part of the predefined exploratory hypothesis, and viral testing was not systematically performed. Future prospective studies with standardized virological assessment may evaluate these parameters more comprehensively. Serial complete blood count data at the time of ALP normalization were not available, as routine follow-up primarily focused on confirming ALP normalization. Therefore, longitudinal changes or normalization patterns of NLR and PLR could not be evaluated. Future prospective studies should include simultaneous ALP and complete blood count measurements during follow-up.

Conclusion

In this cohort, ALP levels in children with BTH normalized spontaneously within a mean of 8.48 ± 3.85 weeks. Compared with age and gender similar healthy controls, children with BTH had lower NLR and PLR values, with NLR showing

moderate discriminatory performance. These hemogram-derived indices may provide supportive exploratory information in clinically well children with isolated ALP elevation; however, they should not be interpreted as diagnostic biomarkers and require confirmation in larger prospective studies.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Çanakkale Onsekiz Mart University (24.09.2025, reference number: 2025-14/14-16).

Contribution of the authors

The authors confirm their contribution to the paper: study conception and design: TK; data collection: TK, SCT, KY; analysis and interpretation of results: TK, HS, KY; draft manuscript preparation: TK, KY, SCT, HS. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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