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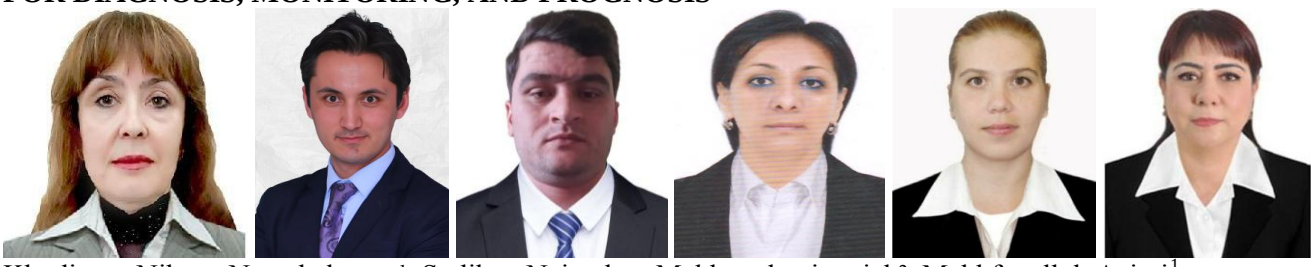
ROLE OF INFLAMMATORY BIOMARKERS IN PEDIATRIC ACUTE LEUKEMIAS: INSIGHTS FOR DIAGNOSIS, MONITORING, AND PROGNOSIS



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БОЛАЛАРДА ЎТКИР ЛЕЙКОЗЛАРДА ЯЛЛИҒЛАНИШ БИОМАРКЕРЛАРИНИНГ РОЛИ: ДИАГНОСТИКА, МОНИТОРИНГ ВА ПРОГНОЗ УЧУН ТУШУНЧА

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РОЛЬ БИОМАРКЕРОВ ВОСПАЛЕНИЯ ПРИ ОСТРЫХ ЛЕЙКОЗАХ У ДЕТЕЙ: ПОНИМАНИЕ ДЛЯ ДИАГНОСТИКИ, МОНИТОРИНГА И ПРОГНОЗА

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Резюме. *Яқинда AL (60% ALL, 40% AML) ташхиси қўйилган 50 нафар болада проспектив когорт тадқиқоти 2023 йилдан 2025 йилгача ўтказилди. Биомаркерлар даражаси биокимёвий таҳлиллар ва хемилюминессент иммунтаҳлил (CLIA) ёрдамида бошланғич даражада, терапиянинг 14- ва 28-кунларида ўлчанди. Статистик таҳлил SPSS в26.0 ёрдамида амалга оширилди, аҳамиятлилик P<0,05 да аниқланди. Дастлабки ҳолатда АЛ билан оғриган болаларда НА (назоратда 1,1 ± 0,2 мг/л га нисбатан 2,8 ± 0,6 мг/л), РСТ (АЛЛ да 0,96 ± 0,24 нг/мл, АМЛ да 1,12 ± 0,31 нг/мл назоратда 0,03 ± 0,02 нг/мл га нисбатан) ва ИЛ-6 (АЛЛ да 35 ± 8 пг/мл, АМЛ да 45 ± 10 пг/мл назоратда 3 ± 1 пг/мл га нисбатан) даражаси сезиларли даражада ошди. Терапия ушбу маркерларнинг аста-секин пасайишига олиб келди, бу эса клиник яхшиланиш билан боғлиқ эди. Педиатрик АЛЛда яллиғланиш биомаркерларини кузатиш эрта ташхис қўйиш, хавф даражасини табақалаштириш ва даволашни баҳолашни яхшилайди, даволашга индивидуал ёндашувни қўллаб-қувватлайди.*

Калит сўзлар: *Педиатрик ўткир лейкоз, яллиғланиш биомаркерлари, гиалурон кислотаси, прокалситонин, интерлейкинлар, прогнози.*

Abstract. *A prospective cohort study of 50 children with newly diagnosed AL (60% ALL, 40% AML) was conducted from 2023 to 2025. Biomarker levels were measured at baseline, day 14, and day 28 of therapy using biochemical assays*

and chemiluminescent immunoassays (CLIA). Statistical analysis was performed using SPSS v26.0, with significance set at P< 0.05. At baseline, children with AL showed significantly elevated levels of HA (2.8 ± 0.6 mg/L vs 1.1 ± 0.2 mg/L in controls), PCT (0.96 ± 0.24 ng/mL in ALL, 1.12 ± 0.31 ng/mL in AML vs 0.03 ± 0.02 ng/mL in controls), and IL-6 (35 ± 8 pg/mL in ALL, 45 ± 10 pg/mL in AML vs 3 ± 1 pg/mL in controls). Therapy led to a progressive decline in these markers, correlating with clinical improvement. Monitoring inflammatory biomarkers in pediatric AL enhances early diagnosis, risk stratification, and treatment evaluation, supporting a personalized approach to therapy.

Keywords: *Pediatric acute leukemia, inflammatory biomarkers, hyaluronic acid, procalcitonin, interleukins, prognosis.*

Introduction. Acute leukemias (AL) are a leading cause of morbidity in pediatric oncohematology, with acute lymphoblastic leukemia (ALL) accounting for 75–80% of childhood hemoblastoses and acute myeloblastic leukemia (AML) comprising 15–20% [1,2]. Despite diagnostic and therapeutic advancements, survival outcomes remain disparate, with five-year survival rates of 85–90% for ALL and 60–70% for AML [3]. These disparities underscore the need for novel biomarkers to predict disease progression and tailor therapy.

Table 1. Dynamics of Inflammatory and Tumor Growth Biomarkers in Children With Acute Leukemia and Healthy Controls

No.	Biomarker	Group	At Admission, Mean ± SD	Day 14, Mean ± SD	Day 28, Mean ± SD	Reference Range
1	Procalcitonin (PCT), ng/mL	ALL	0.96 ± 0.24	0.41 ± 0.12	0.15 ± 0.05	<0.05
		AML	1.12 ± 0.31	0.53 ± 0.15	0.22 ± 0.08	<0.05
		Healthy Controls	0.03 ± 0.02	0.02 ± 0.01	0.03 ± 0.02	<0.05
2	Hyaluronic Acid (HA), µg/L	ALL	210 ± 45	150 ± 32	95 ± 25	<100
		AML	250 ± 60	190 ± 45	120 ± 30	<100
		Healthy Controls	65 ± 20	68 ± 21	67 ± 19	<100
3	Laminin, ng/mL	ALL	120 ± 25	80 ± 18	60 ± 15	<50
		AML	150 ± 30	100 ± 25	75 ± 20	<50
		Healthy Controls	35 ± 10	36 ± 11	37 ± 10	<50
4	Interleukin-1β (IL-1β), pg/mL	ALL	15 ± 4	7 ± 2	4 ± 1	<2
		AML	20 ± 5	10 ± 3	6 ± 2	<2
		Healthy Controls	1 ± 0.5	1 ± 0.6	1 ± 0.4	<2
5	Interleukin-6 (IL-6), pg/mL	ALL	35 ± 8	18 ± 5	10 ± 3	<5
		AML	45 ± 10	22 ± 6	15 ± 4	<5
		Healthy Controls	3 ± 1	4 ± 1	3 ± 1	<5
6	Interleukin-10 (IL-10), pg/mL	ALL	25 ± 6	35 ± 8	20 ± 5	<10
		AML	30 ± 7	40 ± 9	25 ± 6	<10
		Healthy Controls	5 ± 2	5 ± 2	5 ± 2	<10
7	C-reactive Protein (CRP), mg/L	ALL	27.5 ± 6.8	9.4 ± 3.2	3.8 ± 1.5	<5.0
		AML	34.2 ± 7.9	12.8 ± 4.5	5.2 ± 2.1	<5.0
		Healthy Controls	1.8 ± 0.9	1.7 ± 0.8	1.9 ± 1.0	<5.0

Table Notes: ALL = acute lymphoblastic leukemia; AML = acute myeloblastic leukemia.

Values are expressed as mean ± standard deviation (SD).

Statistical significance was determined with P< 0.05 compared to healthy controls (data not shown in table but referenced in text). Reference ranges are based on established laboratory standards.

The pathogenesis of AL involves profound immune dysregulation and bone marrow microenvironment alterations, characterized by overproduction of pro-inflammatory cytokines, suppression of anti-inflammatory mechanisms, and systemic inflammation [4]. Recent research highlights the role of interleukins (IL-1β, IL-6, IL-10), hyaluronic acid (HA) as a marker of extracellular matrix remodeling, and procalcitonin (PCT) as an early indicator of systemic inflammation and sepsis in AL [5,6].

IL-6 drives T-lymphocyte activation, acute-phase protein synthesis, and B-cell differentiation, with elevated levels correlating with disease severity and poor prognosis in leukemia [7]. Conversely, IL-10 exerts anti-inflammatory effects but may contribute to immunosuppression and infectious complications when overproduced [8]. PCT, traditionally a marker of bacterial sepsis, is often elevated in AL patients even without overt infection, reflecting systemic inflammation [9]. HA, a key extracellular matrix component, indicates tissue damage and angiogenesis, correlating with blast infiltration and inflammation in AL [10].

This study investigates the utility of these biomarkers in early diagnosis, monitoring, and prognosis of pediatric AL, aiming to inform personalized therapeutic strategies.

Materials and methods. This prospective cohort study was conducted at a pediatric hematology unit in a national medical center from 2023 to 2025. The study included 50 children with newly diagnosed AL, comprising 60% males (n=30) and 40% females (n=20). Morphologic and immunophenotypic analysis confirmed ALL in 60% (n=30) and AML in 40% (n=20). Age distribution was as follows: 36% (n=18) aged ≤4 years, 44% (n=22) aged ≤10 years, and 20% (n=10) aged ≤14 years at diagnosis.

A control group of 20 healthy children was included for comparison. The study analyzed both retrospective and prospective data, focusing on infection history (viral and bacterial episodes prior to diagnosis) extracted from medical records. Biomarker levels (HA, PCT, IL-1β, IL-6, IL-10, laminin, and C-reactive protein [CRP]) were measured at baseline (admission), day 14, and day 28 of therapy using biochemical assays and CLIA with certified reagent kits.

Statistical analysis was performed using SPSS v26.0 (IBM Corp., Armonk, NY). Data were analyzed with Student's t-test, Mann-Whitney U test, and Spearman's correlation coefficient, with significance defined as $P< 0.05$.

Results. Of the 50 children enrolled, 48 completed the study (36 ALL, 12 AML). At baseline, HA levels were significantly elevated in AL patients (2.8 ± 0.6 mg/L) compared to controls (1.1 ± 0.2 mg/L; $P< 0.001$), with higher levels in AML (250 ± 60 μg/L) than ALL (210 ± 45 μg/L). By day 28, HA decreased (95 ± 25 μg/L in ALL, 120 ± 30 μg/L in AML), reflecting treatment response.

PCT levels were also elevated at admission (0.96 ± 0.24 ng/mL in ALL, 1.12 ± 0.31 ng/mL in AML vs 0.03 ± 0.02 ng/mL in controls; $P< 0.001$), decreasing by day 28 (0.15 ± 0.05 ng/mL in ALL, 0.22 ± 0.08 ng/mL in AML), indicating reduced inflammatory activity.

Cytokine analysis revealed significant elevations in IL-6 (35 ± 8 pg/mL in ALL, 45 ± 10 pg/mL in AML vs 3 ± 1 pg/mL in controls; $P< 0.001$) and IL-1β (15 ± 4 pg/mL in ALL, 20 ± 5 pg/mL in AML vs 1 ± 0.5 pg/mL in controls; $P< 0.001$) at baseline, with reductions by day 28 (IL-6: 10 ± 3 pg/mL in ALL, 15 ± 4 pg/mL in AML; IL-1β: 4 ± 1 pg/mL in ALL, 6 ± 2 pg/mL in AML). IL-10 levels remained elevated throughout (25 ± 6 pg/mL in ALL, 30 ± 7 pg/mL in AML vs 5 ± 2 pg/mL in controls), suggesting a compensatory anti-inflammatory response.

Laminin levels were higher in AL patients (120 ± 25 ng/mL in ALL, 150 ± 30 ng/mL in AML vs 35 ± 10 ng/mL in controls; $P< 0.001$), decreasing by day 28 (60 ± 15 ng/mL in ALL, 75 ± 20 ng/mL in AML), indicating reduced tissue remodeling. CRP levels followed a similar trend (27.5 ± 6.8 mg/L in ALL, 34.2 ± 7.9 mg/L in AML vs 1.8 ± 0.9 mg/L in controls; $P< 0.001$), declining by day 28 (3.8 ± 1.5 mg/L in ALL, 5.2 ± 2.1 mg/L in AML).

General clinical parameters (hemoglobin, leukocytes, platelets) improved by day 28, reflecting treatment efficacy. All patients received standard chemotherapy per clinical protocols, including antimetabolites and alkylating agents.

Discussion. Elevated baseline levels of HA, PCT, IL-6, IL-1β, laminin, and CRP in children with AL highlight the role of systemic inflammation and tissue remodeling in disease pathogenesis. The higher biomarker levels in AML compared to ALL align with its more aggressive course and lower therapy response, consistent with survival data (60–70% for AML vs 85–90% for ALL). The progressive decline in these markers during therapy correlates with clinical improvement, supporting their utility in monitoring treatment response.

IL-6 and IL-1β emerged as potential prognostic markers, with their reduction reflecting suppression of inflammation by chemotherapy. Persistent IL-10 elevation suggests an ongoing immunoregulatory response, potentially linked to immunosuppression risks. Elevated PCT, even without bacterial infection, underscores its role as a marker of systemic inflammation in AL. HA and laminin levels indicate tissue damage and angiogenesis, offering insights into disease severity and vascular complications.

These findings advocate for integrating biomarker monitoring into routine clinical practice to enhance early diagnosis, risk stratification, and personalized therapy in pediatric AL.

Conclusion. This study demonstrates that inflammatory biomarkers (HA, PCT, IL-6, IL-1β, IL-10, laminin, CRP) provide valuable insights into the diagnosis, monitoring, and prognosis of pediatric AL. Their dynamic changes during therapy correlate with clinical outcomes, supporting their role in personalized treatment strategies. Future research should focus on larger cohorts and standardized cutoffs for clinical application.

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Резюме. *Проспективное когортное исследование 50 детей с недавно диагностированным AL (60% ALL, 40% AML) проводилось с 2023 по 2025 год. Уровни биомаркеров измерялись на исходном уровне, на 14-й и 28-й день терапии с помощью биохимических анализов и хемилюминесцентного иммуноанализа (CLIA). Статистический анализ проводился с помощью SPSS v26.0, значимость определялась при P<0,05. В исходном состоянии у детей с АЛ были значительно повышены уровни НА (2,8 ± 0,6 мг/л против 1,1 ± 0,2 мг/л в контроле), PCT (0,96 ± 0,24 нг/мл при АЛЛ, 1,12 ± 0,31 нг/мл при АМЛ против 0,03 ± 0,02 нг/мл в контроле) и ИЛ-6 (35 ± 8 пг/мл при АЛЛ, 45 ± 10 пг/мл при АМЛ против 3 ± 1 пг/мл в контроле). Терапия приводила к постепенному снижению этих маркеров, что коррелировало с клиническим улучшением. Мониторинг биомаркеров воспаления при педиатрическом АЛЛ улучшает раннюю диагностику, стратификацию риска и оценку лечения, поддерживая персонализированный подход к терапии.*

Ключевые слова: *Педиатрический острый лейкоз, биомаркеры воспаления, гиалуроновая кислота, прокальцитонин, интерлейкины, прогноз.*