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Original Article

Descriptive Comparative Analysis of Acute Lymphoblastic Leukemia Treatment Standards

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Abstract

Background: Acute lymphoblastic leukemia (ALL) remains the most common malignancy in childhood and requires a multi-phase, resource-dependent treatment strategy. Despite overall progress in pediatric hematology-oncology, considerable disparities persist between countries in access to advanced diagnostic methods, targeted therapies, and supportive care. These differences may influence treatment costs and survival outcomes. This study compares national pediatric ALL treatment standards in Uzbekistan, Russia, and Kazakhstan to evaluate diagnostic capabilities, chemotherapy protocols, drug availability, and economic efficiency.

Materials and Methods: A descriptive comparative analysis was conducted using three national treatment protocols for pediatric ALL: Uzbekistan (Order No. 273, 2021), Russia (Protocol No. 1/3П/2020, 2020), and Kazakhstan (Protocol No. 187, 2023). Evaluation criteria included diagnostic procedures, functional examinations, specialist consultations, chemotherapy regimens, targeted therapy availability, and pharmacoeconomic indicators. The analysis also referenced widely applied international regimens (ALL-2009, Hyper-CVAD, and Helzer).

Results: Diagnostic costs were lowest in Uzbekistan (US$195.90), followed by Kazakhstan (US$473.60) and Russia (US$753.78). All countries used multi-phase chemotherapy, while Kazakhstan included a broader range of targeted therapies. Total direct medical costs were US$279.68 in Uzbekistan, US$801.63 in Kazakhstan, and US$1,272.66 in Russia.

Conclusion: Pediatric ALL protocols differed substantially in diagnostic scope, targeted therapy availability, and direct medical costs. Uzbekistan had the lowest overall costs, Kazakhstan included a broader range of targeted therapies with intermediate costs, and Russia had the highest costs. Further clinical and pharmacoeconomic studies are needed to assess the cost-effectiveness of these approaches.

Keywords: Acute Lymphoblastic Leukemia, Chemotherapy, Diagnostic Approaches, Targeted Therapy, Treatment Standards

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Introduction

Acute lymphoblastic leukemia (ALL) is the most common hematologic malignancy in children, comprising about one-third of pediatric cancers and 75% of acute leukemia cases in this population. Its global incidence is estimated at 2,500–3,500 cases annually (≈3.4 per 100,000 children) (1). Thanks to advances in diagnostics and treatment, the 5-year disease-free survival (DFS) rate now exceeds 90% in high-income countries. However, survival rates remain lower in developing regions due to limited access to care, inconsistent adherence to protocols, and systemic healthcare barriers.

ALL treatment is complex and multi-phased induction, consolidation, intensification, and maintenance with recent inclusion of targeted and immunotherapies. Yet, access to these innovations remains unequal, particularly due to economic and regulatory limitations.

This study presents a comparative analysis of ALL treatment protocols in Uzbekistan, Russia, and Kazakhstan, evaluating diagnostic procedures, therapeutic strategies, and drug availability. A pharmacoeconomic assessment will also be conducted to examine the cost-effectiveness of current approaches and their impact on healthcare systems.

The results aim to inform efforts to optimize treatment protocols, improve drug access, and support alignment with international standards, ultimately contributing to more equitable and effective ALL care in the region.

Despite advances in pediatric ALL treatment, significant disparities in diagnostic capabilities, therapeutic approaches, and healthcare financing remain across countries with differing healthcare infrastructures. Limited comparative research exists regarding how these differences influence both treatment costs and clinical outcomes in the pediatric population.

This study aims to fill this gap by comparing pediatric ALL treatment standards in Uzbekistan, Russia, and Kazakhstan, with an emphasis on diagnostic practices, chemotherapy protocols, targeted therapies, and pharmacoeconomic factors.

Specifically, it addresses the following research questions:

1. What are the major differences in pediatric ALL diagnostic and treatment protocols across the three countries?
2. How do the costs of diagnostics and treatments differ, and what systemic factors contribute to these variations?
3. What is the level of availability and use of targeted therapies?
4. How might these differences affect pediatric clinical outcomes, such as OS, DFS, and PFS?
5. What recommendations can be made to improve the standardization and cost-effectiveness of pediatric ALL care in the region?

Material and Methods

Study design

This study represents a descriptive comparative analysis of national clinical treatment guidelines for pediatric ALL. It is not a systematic review or meta-analysis, as no structured literature search, pooled outcome synthesis, or quality appraisal of clinical studies was performed. The analysis is based exclusively on officially approved national clinical protocols and standards, with international regimens used for contextual benchmarking only.

Data Sources

The primary data sources consisted of national pediatric ALL treatment protocols officially endorsed by governmental or professional oncology bodies:

- Uzbekistan: Order of the Ministry of Health of the Republic of Uzbekistan No. 273 (November 30, 2021);
- Russia: Clinical Protocol of the All-Russian National Union “Association of Oncologists of Russia” No. 1/3П/2020 (February 1, 2020);
- Kazakhstan: Clinical Protocol of the Ministry of Health of the Republic of Kazakhstan No. 187 (August 18, 2023).

For comparative context, selected internationally recognized treatment regimens were reviewed (ALL-2009, Hyper-CVAD, Helzer protocols). These international protocols were not treated as direct comparators but served as reference frameworks reflecting contemporary

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standards of care.

Eligibility and Selection Criteria

Protocols were included if they met the following criteria:

1. Official national approval or endorsement by a governmental or professional authority;

2. Explicit focus on pediatric acute lymphoblastic leukemia;

3. Availability of detailed sections describing:
   - diagnostic algorithms,
   - chemotherapy regimens,
   - use of targeted therapies,
   - supportive and monitoring procedures;

4. Publication or update within the period 2020–2023.

Protocols addressing adult ALL, experimental clinical trials, or institution-specific guidelines were excluded.

Population Definition

The population of interest was children and adolescents with acute lymphoblastic leukemia as defined by national pediatric oncology standards. All analyses, tables, and interpretations refer exclusively to pediatric ALL. Any prior inconsistencies between pediatric and adult terminology have been corrected.

Analytical Framework

A structured comparative framework was applied, evaluating protocols across four predefined domains:

1. Diagnostic strategy
   - laboratory diagnostics (hematology, cytochemistry, immunophenotyping, cytogenetics, molecular testing);
   - instrumental and functional examinations;
   - specialist consultations.

2. Therapeutic approach
   - chemotherapy phase structure (induction, consolidation, maintenance);
   - intensity and composition of regimens;
   - incorporation of targeted and immunotherapeutic agents.

3. Drug availability
   - access to conventional cytostatics;
   - availability of targeted agents (e.g., Blinatumomab, Venetoclax, tyrosine kinase inhibitors).

4. Economic characteristics
   - costs of diagnostic procedures, specialist consultations, and treatment components as listed in national standards.

Cost Analysis Methodology

The cost analysis conducted in this study was descriptive and comparative in nature and did not constitute a formal pharmacoeconomic evaluation, such as cost-effectiveness, cost-utility, or cost-benefit analysis.

Only direct medical costs were considered, including:

- costs of laboratory and instrumental diagnostic procedures;
- costs of specialist consultations;
- costs of pharmacotherapy specified in national clinical treatment protocols.

Pricing data were obtained from:

- official tariffs and cost schedules included in national clinical guidelines;
- annexes to state-regulated standards of medical care;
- officially regulated national price lists valid at the time of protocol approval.

All cost data were reported in US dollars (USD). Currency conversion from national currencies was performed using official exchange rates of national central banks applicable in the year of protocol approval or latest revision, which was used as the reference year. Indirect costs, non-medical expenses, and long-term economic outcome modeling were not included. The cost data were used solely for descriptive comparison of cost structures and not for assessing the economic efficiency of

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treatment strategies.

Data Extraction and Synthesis

Data were extracted manually from protocol texts and tabulated to enable cross-country comparison. Results are presented descriptively, emphasizing structural differences between national standards rather than clinical efficacy or survival outcomes.

Ethical Considerations

This study involved no patient-level data, clinical interventions, or personal information. Ethical approval was therefore not required (2,3,4,5,6,7).

Results

ALL is classified according to lymphoid cell origin into two major subtypes: B-lymphoblastic leukemia/lymphoblastic lymphoma (B-ALL/LBL) and T-lymphoblastic leukemia/lymphoblastic lymphoma (T-ALL/LBL). The disease presents as leukemia when tumor cells infiltrate the bloodstream and bone marrow, with more than 20% blasts in the bone marrow. When lymphoblast accumulation is predominantly extramedullary, the disease manifests as lymphoma.

Initial diagnostic evaluation begins with a detailed patient history and clinical examination, as these aspects significantly influence the accuracy of diagnosis and therapeutic decisions. The onset of ALL is typically acute, with symptoms progressing over several days or weeks. Clinical features primarily result from hematopoietic suppression and leukemic infiltration.

Extramedullary leukemic infiltration may result in hepatosplenomegaly, generalized or localized lymphadenopathy, and bone or joint pain, particularly in children, due to bone marrow and periosteal involvement. Recognizing this clinical profile supports timely diagnosis and promotes targeted therapeutic interventions.

Diagnostic Considerations

As shown in Table 1-2, the national clinical protocols demonstrate both shared elements and notable inter-country differences in diagnostic strategies for pediatric ALL. All countries include basic hematological and morphological assessments, reflecting a standardized approach to initial disease verification.

However, differences are observed in the extent of molecular genetic testing and access to advanced cytogenetic methods. Broader implementation of molecular diagnostics may enable more precise risk stratification and treatment adaptation, which is clinically relevant for personalized therapeutic decision-making.

Preliminary diagnosis of ALL is based on clinical presentation and initial laboratory tests. Physical examination may reveal pallor, petechiae, ecchymoses, gingival bleeding, fever, lymphadenopathy (including tonsillar hypertrophy), hepatosplenomegaly, renal enlargement, and bone tenderness.

Hematological studies include:

- complete blood count (CBC), typically showing varying degrees of anemia, thrombocytopenia, and leukocytosis or leukopenia;
- coagulation profile, with fibrinogen reduction possible in disseminated intravascular coagulation (DIC).

Confirmatory diagnostics consist of bone marrow aspiration and biopsy demonstrating ≥20% lymphoblasts. Flow cytometry and immunophenotyping are required for differentiation between B-ALL and T-ALL. Although skin involvement is rare, it occurs more often in pre-B-cell subtypes (5–8).

Laboratory Diagnostic Tests

The diagnostic program includes the following methods:

1. Morphological cytochemistry
2. Flow cytometry
3. Cytogenetic and FISH analysis
4. Molecular genetic testing
5. Routine hematological and biochemical investigations

According to treatment standards, CBC with differential must be performed 2–3 times weekly during diagnosis and therapy to monitor

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response and disease progression.

Regional variations exist:

-Uzbekistan and Russia routinely perform cytochemical analysis and endolumbar puncture with cerebrospinal fluid (CSF) testing.

Kazakhstan does not include cytochemical analysis and CSF testing in standard protocols.

Bone marrow examination through aspiration and/or biopsy is mandatory in all countries. Additional tests include urinalysis and screening for hepatitis B/C and HIV (performed routinely in Uzbekistan and Russia).

Cytogenetic testing is essential for detecting numerical and structural chromosomal abnormalities, including prognostically relevant hyperploidy (>46 chromosomes).

In addition to laboratory investigations, functional diagnostic procedures are performed for patients with ALL. According to treatment standards in Uzbekistan and Russia, all patients undergo electrocardiography (ECG) and echocardiography (EchoCG) to evaluate cardiac function, identify concomitant cardiovascular diseases, and prevent or manage potential cardiotoxic complications.

All national protocols recommend ultrasound examinations to assess peripheral and intra-abdominal lymph nodes, abdominal organs, pelvic organs in women, and the prostate gland in men. This approach enables early detection of comorbid conditions that may influence treatment outcomes.

Treatment standards in Kazakhstan and Russia additionally require computed tomography (CT) of the chest to identify infiltrative lung changes and intrathoracic lymphadenopathy. In Kazakhstan, fibroesophagogastroduodenoscopy (FGDS) is also performed to diagnose esophagitis, gastritis, bulbitis, or duodenitis.

The average cost of functional diagnostics varies significantly across countries. In Uzbekistan, the cost averages US$29.6; in Kazakhstan, US$144.4; and in Russia, US$306.8. These differences appear to reflect variations in healthcare infrastructure, resource availability, and economic factors influencing medical service pricing.

Consultations with Specialized Medical Professionals

Following completion of diagnostic procedures for suspected ALL, patients are referred to specialists for evaluation of comorbidities that may influence treatment safety or increase the risk of complications. Mandatory consultations across all treatment standards include neurologist, ophthalmologist, otolaryngologist, gynecologist (for female patients), and nephrologist. In Kazakhstan, the protocol additionally requires consultation with a thoracic surgeon to determine the need for lung or mediastinal biopsy.

The average cost of specialist consultations is US$54.18 in Uzbekistan, US$183.63 in Kazakhstan, and US$212.08 in Russia, reflecting differences in healthcare organization and reimbursement policies (Table 3).

Stages of Chemotherapeutic Treatment for ALL

Chemotherapeutic treatment of acute lymphoblastic leukemia follows a structured sequence consisting of remission induction, consolidation, maintenance therapy, and neuroleukemia prevention or treatment.

The comparative analysis of national pediatric ALL treatment protocols revealed differences in the structure and composition of chemotherapy regimens, while preserving a common phase-based treatment concept comprising induction, consolidation, and maintenance therapy.

National protocols vary in drug selection, treatment intensity, and the availability of modern targeted and immunotherapeutic agents. In some countries, broader access to contemporary treatment options may expand therapeutic possibilities for high-risk patients but is also associated with increased direct medical costs.

1. Induction of Remission.The goal of induction therapy is a rapid reduction of tumor burden and achievement of complete remission (CR). This phase consists of two consecutive cycles, each lasting four weeks, administered without a break. Cytostatic therapy reduces the

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number of leukemic cells in the bone marrow by approximately 100-fold. CR is confirmed when fewer than 5% blasts are seen during cytological evaluation.

2. Consolidation of Remission. The consolidation phase strengthens the antitumor response achieved during induction. It represents the most intensive component of modern ALL treatment, using high-dose chemotherapy to eradicate residual leukemic cells. Typically, one to two cycles are administered; however, protocols in Uzbekistan and Russia include five sequential intensive stages of three to four weeks each, followed by maintenance therapy using low-dose cytostatics to eliminate residual malignant cells.

Comparative Analysis of Treatment Standards

Comparative evaluation of ALL treatment protocols in Uzbekistan, Russia, and Kazakhstan demonstrates substantial differences in diagnostic approaches, chemotherapy selection, drug availability, and overall treatment costs.

Uzbekistan and Russia rely on cytochemical diagnostics and CSF analysis, while Kazakhstan omits these procedures but incorporates advanced diagnostic technologies such as immunophenotyping and spinal puncture. Diagnostic costs are lowest in Uzbekistan (US$195.9), moderate in Kazakhstan (US$473.6), and highest in Russia (US$753.78).

ECG and echocardiography are routinely used in Uzbekistan and Russia, whereas Kazakhstan substitutes these procedures with chest CT, FGDS, and mandatory consultation with a thoracic surgeon. Multi-phase chemotherapy is standard in all three countries, but drug availability differs significantly: Uzbekistan and Russia primarily use traditional cytostatics and have limited access to targeted agents, while Kazakhstan utilizes a broader range of modern antileukemic therapies, including Blinatumomab, Venetoclax, Dasatinib, Nilotinib, and Ponatinib.

Total treatment costs (diagnostics + therapy) are lowest in Uzbekistan (US$279.68), intermediate in Kazakhstan (US$801.63), and highest in Russia (US$1,272.66), underscoring differences in healthcare financing, procurement strategies, and access to innovative agents (Table 4-5).

Terminology Clarification

Throughout this manuscript, the term “targeted therapies” refers to agents such as monoclonal antibodies, tyrosine kinase inhibitors, and other molecularly targeted drugs. The term “molecular diagnostics” is used to describe genetic, cytogenetic, and molecular-based laboratory methods. Key survival outcomes are consistently reported using the standardized terms: overall survival (OS), event-free survival (EFS), and DFS.

This comparative analysis demonstrates pronounced variations in ALL diagnostic and treatment standards across Uzbekistan, Russia, and Kazakhstan. Uzbekistan follows a highly cost-efficient model relying on basic diagnostics and conventional multi-phase chemotherapy but lacks access to advanced technologies and targeted therapies. Kazakhstan adopts a more progressive strategy with high-cost diagnostic procedures and innovative therapeutics such as Blinatumomab, Venetoclax, and Ponatinib. Russia maintains a balanced approach, combining broad diagnostic capacities with diverse chemotherapeutic options, although costs remain the highest.

European countries (e.g., Germany, France, Italy, the Netherlands) follow protocols such as ALL. Together and BFM, which emphasize personalized and risk-adapted therapy using immunophenotyping, cytogenetic and molecular diagnostics, and minimal residual disease (MRD) monitoring. Targeted therapies—including monoclonal antibodies and CAR-T cell therapy—are increasingly integrated into frontline protocols, contributing to five-year pediatric survival rates exceeding 90%. These contrasts highlight the need for improved alignment of ALL treatment protocols across Eurasia.

It should be noted that the present study did not include an analysis of clinical outcomes such

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as OS, EFS, or DFS. References to these outcomes are provided for contextual purposes only and reflect their use within the respective clinical protocols.

Table I: Diagnostic procedures for laboratory diagnosis of acute lymphoblastic leukemia

Types of diagnostics	Uzbekistan USD		Kazakhstan USD		Russia USD	
General (clinical) blood test	+	2.4$	+	3.3$	+	8.51$
Myelogram	+	5.28$	+	22.2$	+	196.42$
Trephine biopsy	+	5.28$	-		+	196.42$
Cytochemical study	+	17.6$	-		+	157.14$
Endolumbar puncture with cerebrospinal fluid examination	+	14.24$	-		+	109.12$
Blood chemistry analysis	+	8$	+	54.0$	+	1.86$
Oagulogram	+	3.28$	-		+	17.24$
Urine analysis	+	2.48$	-		+	5.89$
Blood culture reservoir	+	8$	-		+	0,00
Determination of blood group and Rh factor, study of autoantibodies in erythrocytes	+	3.76$	-		+	5.11$
Blood test for hepatitis B	+	3.28$	-		+	5.11$
Blood test for hepatitis C	+	3.28$			+	5.70$
Blood test for AIDS	+	3.2$			+	2.70$
Immunophenotyping of bone marrow cells	-		+	52.9$	-	
Spinal tap	-		+	332.3$	-	
Cytogenetic studies	+	72$	+	8.9$	+	42.56$
Total cost		195.9$		473.6$		753.78$

Table note:
"+" indicates the presence of a diagnostic method, drug, or treatment component in the national clinical protocol;
"–" indicates the absence of the corresponding element;
"N/A" indicates that the item is not applicable within the given protocol.
All cost values represent direct medical costs and are reported in USD using official exchange rates applicable in the year of protocol approval.

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Table II: Non-laboratory Diagnostic Procedures of acute lymphoblastic leukemia

Types of diagnostics	Uzbekistan USD	Kazakhstan USD	Russia USD			
Electrocardiography	+	2.72 $	-		+	13.7 $
Echocardiography	+	5.6 $	-		+	40.4 $
Ultrasound examination of peripheral and intra-abdominal lymph nodes	+	4.48 $	+	3.7 $	+	18.6 $
Ultrasound examination of abdominal organs	+	4.48 $	+	26.6 $	+	37.3 $
Ultrasound examination of the pelvic organs in women	+	4.48 $	+	15.5 $	+	32.3 $
Ultrasound examination of the prostate gland in men	+	6.16 $	+	15.5 $	+	32.1 $
Chest X-ray	+	10 $	-		+	45.5 $
Computed tomography of the chest segment	-		+	56.5 $	+	86.9 $
Fibrogastroduodenoscopy	-		+	26.6 $	-	
Total cost		29.6 $		144.4 $		306.8 $

Table note:
"+" indicates the presence of a diagnostic method, drug, or treatment component in the national clinical protocol;
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Ultrasound examination of abdominal organs	+	4.48 $	+	26.6 $	+	37.3 $
Ultrasound examination of the pelvic organs in women	+	4.48 $	+	15.5 $	+	32.3 $
Ultrasound examination of the prostate gland in men	+	6.16 $	+	15.5 $	+	32.1 $
Chest X-ray	+	10 $	-		+	45.5 $
Computed tomography of the chest segment	-		+	56.5 $	+	86.9 $
Fibrogastroduodenoscopy	-		+	26.6 $	-	
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Table III: Consultation with specialists in a narrow field

Specialists in the field	Uzbekistan USD		Kazakhstan USD		Russia USD	
Gynaecologist consultation	+	7.11 $	+	22.4 $	+	24.2 $
Cardiologist consultation	+	3.9 $	+	22.4 $	+	36.3 $
Consultation with a nephrologist	+	5.8 $	+	22.4 $	+	24.2 $
Consultation with a neurologist	+	4.7 $	+	22.4 $	+	33.0 $
Ophthalmologist consultation	+	4.7 $	+	22.4 $	+	18.7 $
Consultation with an otolaryngologist	+	6.9 $	+	22.4 $	+	18.7 $
Consultation with a surgeon	+	4.7 $	+	22.4 $	+	27.5 $
Consultation with a thoracic surgeon	-		+	22.4 $	-	
Phthisiatrician consultation	+	15.9 $	+	4.5 $	+	29.6 $
Total cost		54.18 $		183.63 $		212.8 $

Table note:
"+" indicates the presence of a diagnostic method, drug, or treatment component in the national clinical protocol;
"–" indicates the absence of the corresponding element;
"N/A" indicates that the item is not applicable within the given protocol.
All cost values represent direct medical costs and are reported in USD using official exchange rates applicable in the year of protocol approval.

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Table IV: Chemotherapeutic therapy

Protocol				**ALL-MB 2009**	
Phase	Dose	Path	Weeks	Day (Days)	Dose
Induction I -phase					
Prednisolone				2-28	60mg/ m^2
Dexamethasone	6 mg / **m2**	RO	1-4	1-28	10 mg/ m^2
Vincristine	**1.5** mg/ **m2**	**vv**	1-6	8,15,22,	2 mg/ m^2
Daunorubicin	45 mg/ m^2	**vv**	1(3)	8,15,22	45 mg/ m^2
L - asparaginase	10000 mg/ m^2	**vm**	5.6	29.36	10000 U/ m^2
Induction II - phase					
Mercaptopurine				43-70	25 mg/ m^2
Cyclophosphamide				43	1000 mg/ m^2
Cytarabine				45-48, 59-62	75 mg/ m^2
L - asparaginase	10000 mg/ m^2	**vm**	5.6	50,57,64	10000 U / m^2
Intensification			**Consolidation 1 (MB)**		
Doxorubicin				71.85	30 mg/ m^2
Dexamethasone	6 mg/ m^2	RO	14-15	71-84	10 mg/ m^2
Vincristine	1.5mg / **m^2**	**vv**	14-15	71.85	2 mg/ m^2

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Table V: Chemotherapy therapy (Phase 4 and maintenance therapy)

Consolidation II				
Mercaptopurine	50 mg/ **m2**	RO	16-21	92-105
L - asparaginase	10000 U/ m2	VM	6-21	92.99
Consolidation III				
Mercaptopurine *	25 mg/ m2	RO	24-29	106-133
L - asparaginase	10000 units / m2	VM	24-29	163, 170, 177, 184, 191, 198
Cytarabine	75 mg/ m2			108-111,127
Cyclophosphamide	1000 mg/ m2			113,127
Consolidation IV				
Methotrexate	1.5 g / m2	VM	24-29	134
Dexamethasone	30 mg/m2	RO	30-31	134-136
L - asparaginase	10000 units / m2	VM	24-29	136
Consolidation V				
Cytarabine	2 g/m2 (2 times a day)			148
Dexamethasone	30 mg/m2	RO	30-31	148-150
L - asparaginase	10000 units / m2	VM	24-29	150
Supportive therapy				
Mercaptopurine	50 mg/ m2	RO	32-37,40-45, 48-53,56-61, 64-65,72-	4-28
Methotrexate	30 mg/ m2	VM		2,9,16,23
Dexamethasone	10 mg/ m2	RO	38-39,46-47, 54-55,62-	1-3
Vincristine	2 mg/ m2	**vv**		1
Daunorubicin	45 mg/ m2			1
L - asparaginase	10000 units / m2	VM	2 4-29	3.10

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Table VI: Drugs used to treat ALL

Drug group	International nonproprietary name of the drug	Uzbekistan	Kazakhstan	Russia
Antineoplastic drugs	Daunorubicin	1+	+	+
	Methotrexate	+	+	+
	Mercaptopurine	+	+	+
	Rituximab		+	+
	PEG - asparaginase		+	+
	L- asparaginase	+	+	+
	Etoposide		+	+
	Cyclophosphamide	+	+	+
	Cytarabine	+	+	+
Targeted therapy	Blinatumomab		+	
	Venetoclax		+	
	Dasatinib	+	+	
	Imatinib	+	+	+
	Nilotinib		+	
	Ponatinib		+	

Table note:
"+" indicates the presence of a diagnostic method, drug, or treatment component in the national clinical protocol;

Discussion

Comparative Analysis of Diagnostic Approaches and Treatment Protocols

The comparative analysis of pediatric ALL treatment protocols in Uzbekistan, Russia, and Kazakhstan demonstrates substantial differences in diagnostic requirements, therapeutic structures, and drug availability. These differences reflect variations in national healthcare organization, regulatory frameworks, and resource allocation rather than differences in demonstrated clinical effectiveness.

Diagnostic approaches vary across countries with respect to the scope of laboratory, functional, and specialist assessments, which is reflected in differences in reported diagnostic costs. Similarly, national protocols differ in their inclusion of targeted therapies, with Kazakhstan incorporating selected targeted agents alongside conventional chemotherapy, while Uzbekistan and Russia predominantly rely on classical cytotoxic regimens. These observations highlight structural heterogeneity among national treatment standards.

Clinical Implications of Diagnostic and Therapeutic Gaps

The observed variability in diagnostic and therapeutic components may have implications for clinical decision-making; however, the present study does not include an assessment of clinical outcomes, such as OS, EFS, or DFS. Therefore, any discussion of potential clinical impact should be interpreted as hypothetical and indirect.

The use of advanced diagnostic tools and targeted therapies may potentially support more refined risk stratification and treatment optimization, as suggested by previously published studies. Nevertheless, in the absence

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of patient-level outcome data, no conclusions regarding survival benefits can be drawn from the present analysis.Lessons from European ALLTogether Protocol

Economic Factors Behind Cost Differences

Differences in total treatment costs among the analyzed countries reflect variations in diagnostic scope, access to targeted therapies, pharmaceutical procurement policies, and healthcare financing mechanisms. While advanced diagnostics and targeted therapies are associated with higher upfront costs, the present study did not conduct a formal pharmacoeconomic evaluation, such as cost-effectiveness or cost-utility analysis.

Accordingly, any statements regarding potential long-term economic implications are extrapolated from international literature and published experience and should not be interpreted as direct economic conclusions within the analyzed national healthcare systems.

Contextual Reference to the European ALL Together Protocol

The European ALLTogether protocol is referenced in this study solely as a conceptual benchmark, illustrating contemporary approaches to pediatric ALL diagnosis and treatment. It was not used as a direct comparator, as the study lacks harmonized outcome data and formal benchmarking analysis.

Comparisons with ALLTogether are descriptive and contextual in nature and serve to highlight general trends in international pediatric hemato-oncology rather than to support conclusions regarding comparative effectiveness.

Policy Implications and Recommendations for the Region

Kazakhstan’s treatment model may serve as a practical reference for neighboring countries, including Iran, which face similar resource and infrastructure constraints. Incorporating targeted therapies and modern diagnostic methods represents a promising direction for improving pediatric ALL outcomes across the region.

Given financial limitations, countries such as Uzbekistan could adopt a phased approach by initially implementing high-cost diagnostics and targeted agents for high-risk pediatric subgroups, accompanied by systematic cost-effectiveness assessment. Future research should focus on quantitative analyses of the relationship between treatment expenditures and clinical outcomes to support evidence-based decision-making in healthcare planning and to promote sustainable progress in pediatric hematology-oncology

These findings highlight the importance of further pharmacoeconomic research to assess the cost-effectiveness of advanced therapies, including targeted agents and molecular diagnostic technologies. Harmonizing treatment protocols and expanding access to such innovations could reduce survival disparities across the region, promoting more standardized and equitable care for patients with leukemia.

From a clinical standpoint, the study offers actionable insights for pediatric hematology-oncology specialists. It emphasizes the need to integrate advanced diagnostics and targeted therapies into national treatment protocols where feasible, with the dual aim of improving survival outcomes and maintaining cost-effectiveness.

Limitations of the Study

This study has several limitations that should be considered when interpreting the findings. First, the analysis was based exclusively on officially published national treatment protocols and standards rather than on real-world clinical practice. Therefore, potential variations in protocol implementation at the institutional or regional level were not captured.

Second, the study did not include a direct comparison of clinical outcomes, such as OS, EFS, or DFS, as no patient-level data or clinical trial results were analyzed. Consequently, the impact of protocol differences on actual treatment effectiveness can only be inferred indirectly.

Third, the pharmacoeconomic evaluation was

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limited to listed diagnostic procedures, consultations, and therapeutic interventions as defined in national standards. Information on hospital-specific equipment, medical kits, consumables, and locally available instruments was not included, as such data were not consistently reported across protocols and vary substantially between healthcare institutions.

Additionally, cost estimates were based on average prices and do not account for fluctuations related to procurement mechanisms, regional pricing policies, or changes over time. Differences in healthcare financing systems and reimbursement models across countries may further influence cost comparability.

Finally, although international treatment regimens were referenced for contextual comparison, the study did not perform a full benchmarking analysis against European or North American protocols. Future studies incorporating real-world outcome data and prospective economic analyses would be necessary to validate and expand upon the conclusions of this work.

As the first systematic, cross-country comparison of pediatric ALL treatment protocols and costs in this region, the study provides a valuable foundation for future research, healthcare optimization, and evidence-based policy development. Drawing lessons from the European ALLTogether protocol, countries in the region could benefit from the gradual adoption of risk-adapted, MRD-guided treatment strategies, ensuring both clinical efficacy and long-term economic sustainability.

One of the main limitations of this study is the absence of clinical outcome analysis, including survival metrics. The study is descriptive and comparative in nature and is based exclusively on the analysis of national clinical protocols. The lack of patient-level outcome data precludes any conclusions regarding clinical effectiveness or survival, and the findings should be interpreted within the scope of protocol structure, treatment approaches, and cost comparison.

Conclusion

The findings of this study reflect differences in diagnostic, therapeutic, and economic approaches embedded in national pediatric ALL treatment protocols. The results are not intended to assess clinical effectiveness or survival outcomes and are limited to a descriptive comparison of protocol structures. Given the descriptive and comparative nature of this study, the findings may serve as a basis for future investigations incorporating clinical outcome and formal pharmacoeconomic analyses.

Future research should focus on harmonizing pediatric ALL diagnostic standards, improving access to targeted therapies, and incorporating pharmacoeconomic evaluations into treatment guidelines. Regional collaboration, data sharing, and multicenter outcome studies are also needed to enable robust comparisons and assess the feasibility of adapting effective treatment strategies across neighboring healthcare systems.

Availability of Data

The data that support the findings of this study are available from the corresponding author upon reasonable request

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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Ethical Considerations

This study did not involve direct patient participation, clinical trials, or personal data. Therefore, ethical approval was not required. The study was approved by the university administration and the local ethics committee,

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and was conducted in accordance with institutional and ethical standards (number).

Authors' Contributions

Concept and Design: All authors
Data Collection and Analysis: All authors
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