TREATMENT-RELATED TOXICITY ACROSS SEQUENTIAL CHEMOTHERAPY PHASES IN PAEDIATRIC ACUTE LYMPHOBLASTIC LEUKAEMIA: A SINGLE-CENTRE RETROSPECTIVE COHORT STUDY FROM KAZAKHSTAN, 2021–2024

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ТОКСИЧНОСТЬ ЛЕЧЕНИЯ НА ПОСЛЕДОВАТЕЛЬНЫХ ЭТАПАХ ХИМИОТЕРАПИИ ПРИ ОСТРОМ ЛИМФОБЛАСТНОМ ЛЕЙКОЗЕ У ДЕТЕЙ: РЕТРОСПЕКТИВНОЕ КОГОРТНОЕ ИССЛЕДОВАНИЕ В ОДНОМ ЦЕНТРЕ В КАЗАХСТАНЕ, 2021–2024 ГГ

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Abstract

Background: Although five-year survival in paediatric acute lymphoblastic leukaemia (ALL) now exceeds 85% in high-income settings, treatment-related toxicity remains a major cause of morbidity, treatment interruption and excess mortality, particularly in low- and middle-income countries (LMICs). Comprehensive, phase-specific toxicity data from Central Asia are scarce.

Methods: We retrospectively analysed 261 children (0–17 years) with newly diagnosed ALL treated between January 2021 and December 2024 at a single tertiary paediatric haematology centre in Kazakhstan according to an ALL-IC BFM 2009-type regimen. Toxicities were prospectively recorded and graded I–IV using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE v5.0) across seven sequential treatment phases (Protocol I, Protocol M, Protocol II, high-risk blocks HR-1/HR-2/HR-3, and Protocol III). Thirteen organ-system toxicity categories were assessed.

Results: The cohort comprised 152 boys (58.2%) and 109 girls (41.8%); median age was 4 years, with 67.4% aged 1–6 years. B-cell precursor ALL accounted for 84.3% of cases and 71.3% were classified as standard-risk. At least one grade I–IV toxicity event was documented in all 261 patients. The toxicity burden differed substantially across phases: grade IV haematologic toxicity affected 44.5% of patients during Protocol I and reached 83.3%, 57.1% and 63.0% during HR-1, HR-2 and HR-3 blocks respectively, but only 17.9% during Protocol M. Grade III–IV infection was the second-most-prevalent severe toxicity, peaking at 90.7% in HR-1 and 79.6% during Protocol I. Hepatotoxicity was predominantly low-grade and was the dominant adverse event during Protocol M (84.5% grade I–II). Cardiotoxicity, neurotoxicity, nephrotoxicity and pulmonary toxicity were uncommonly severe (grade III–IV <5% across phases).

Conclusions: Toxicity in our cohort followed a phase-specific pattern consistent with international BFM-type experience: induction (Protocol I) and high-risk consolidation blocks produced the highest burden of life-threatening myelosuppression and infection, whereas Protocol M was dominated by lower-grade hepatic and mucosal toxicity. These data provide the first detailed CTCAE-graded toxicity profile for paediatric ALL from Kazakhstan and may inform supportive-care prioritisation, risk-adapted dose modification and quality benchmarking for paediatric oncology services in Central Asia.

Аннотация

Введение: Несмотря на то что пятилетняя выживаемость при остром лимфобластном лейкозе (ОЛЛ) у детей в странах с высоким уровнем дохода в настоящее время превышает 85%, токсичность, связанная с лечением, остается одной из основных причин заболеваемости, прерывания терапии и избыточной смертности, особенно в странах с низким и средним уровнем дохода. Комплексные данные о токсичности по этапам лечения из Центральной Азии ограничены.

Методы: Проведен ретроспективный анализ 261 ребенка (0–17 лет) с впервые диагностированным ОЛЛ, получавших лечение в период с января 2021 по декабрь 2024 года в одном специализированном детском гематологическом центре в Казахстане по протоколу типа ALL-IC BFM 2009. Токсические эффекты регистрировались проспективно и классифицировались по степеням I–IV в соответствии с Общей терминологией критериев нежелательных явлений Национального института рака США (CTCAE v5.0) на протяжении семи последовательных фаз лечения (Протокол I, Протокол M, Протокол II, блоки высокого риска HR-1/HR-2/HR-3 и Протокол III). Оценивались 13 категорий токсичности по органным системам.

Результаты: В исследуемую когорту вошли 152 мальчика (58,2%) и 109 девочек (41,8%); медианный возраст составил 4 года, при этом 67,4% пациентов были в возрасте 1–6 лет. В 84,3% случаев диагностирован В-клеточный предшественниковый ОЛЛ, и 71,3% пациентов отнесены к группе стандартного риска. По крайней мере одно токсическое событие I–IV степени было зарегистрировано у всех 261 пациентов. Выраженность токсичности существенно различалась между фазами лечения: гематологическая токсичность IV степени наблюдалась у 44,5% пациентов во время Протокола I и достигала 83,3%, 57,1% и 63,0% во время блоков HR-1, HR-2 и HR-3 соответственно, но составляла лишь 17,9% во время Протокола M. Инфекции III–IV степени были второй по частоте тяжелой токсичностью, достигая пика в 90,7% в HR-1 и 79,6% во время Протокола I. Гепатотоксичность преимущественно была низкой степени и являлась доминирующим нежелательным явлением во время Протокола M (84,5% — I–II степени). Кардиотоксичность, нейротоксичность, нефротоксичность и пульмональная токсичность редко достигали тяжелых степеней (III–IV <5% на всех этапах).

Заключение: В исследуемой когорте токсичность имела фазо-специфический характер, соответствующий международному опыту применения протоколов типа BFM: индукционная терапия (Протокол I) и консолидационные блоки высокого риска сопровождались наибольшей нагрузкой жизнеугрожающей миелосупрессии и инфекций, тогда как Протокол M характеризовался преобладанием гепатотоксичности и мукозальной токсичности низкой степени. Полученные данные представляют собой первое детализированное описание профиля токсичности, оцененной по CTCAE, при ОЛЛ у детей в Казахстане и могут быть использованы для оптимизации поддерживающей терапии, индивидуализации доз в зависимости от риска и оценки качества онкологической помощи детям в Центральной Азии.

Keywords: paediatric acute lymphoblastic leukaemia; chemotherapy toxicity; ALL-IC BFM 2009; CTCAE; febrile neutropenia; supportive care; Kazakhstan; Central Asia.

Ключевые слова: острый лимфобластный лейкоз у детей; токсичность химиотерапии; ALL-IC BFM 2009; CTCAE; фебрильная нейтропения; поддерживающая терапия; Казахстан; Центральная Азия.

1. Introduction

Acute lymphoblastic leukaemia (ALL) is the most common malignancy of childhood, accounting for roughly 25% of cancers diagnosed before age 15 and approximately 75–85% of all paediatric leukaemias[1]. Risk-stratified, multi-agent chemotherapy regimens derived from the Berlin–Frankfurt–Münster (BFM) backbone — most notably ALL-IC BFM 2002 and its successor ALL-IC BFM 2009 — have driven five-year event-free survival in high-income settings above 85%[2],[3]. However, the same therapeutic intensification that has improved cure rates also produces a substantial burden of acute toxicity, including profound myelosuppression, life-threatening infections, hepatic dysfunction, neurotoxicity, and asparaginase-related coagulopathy and pancreatitis[4],[5].

Recent global-burden analyses indicate that, although incidence of childhood ALL is broadly comparable across world regions, mortality and disability-adjusted life-years remain disproportionately concentrated in low- and middle-income countries, where treatment-related toxicity and infectious complications are key drivers of treatment-related mortality and abandonment[6],[7]. In Central Asia, paediatric oncology services have expanded substantially over the past decade, yet detailed, phase-stratified toxicity data conforming to international Common Terminology Criteria for Adverse Events (CTCAE) standards remain limited in the published literature.

Granular characterisation of toxicity by treatment phase is important for three reasons. First, the spectrum of expected adverse events differs markedly between induction (Protocol I), high-dose methotrexate consolidation (Protocol M), reinduction (Protocol II), high-risk intensification blocks (HR-1, HR-2, HR-3) and delayed intensification/maintenance (Protocol III)[2],[8]. Second, severe toxicity events directly influence treatment delivery, dose modification, prophylactic strategies, and hospital resource utilisation[4]. Third, comparative phase-specific data enable benchmarking against international cohorts and identification of targets for quality improvement in supportive care.

The present study reports a comprehensive, CTCAE-graded toxicity profile of a contemporary cohort of 261 paediatric patients with ALL treated at a single tertiary centre in Kazakhstan between 2021 and 2024. We describe the demographic and biological characteristics of the cohort, quantify the incidence and severity of thirteen organ-system toxicities across seven sequential treatment phases, and contextualise our findings against published BFM-based experience.

2. Materials and Methods

2.1. Study design and setting

This was a retrospective observational cohort study conducted at a tertiary paediatric haematology–oncology centre in Kazakhstan. All consecutive patients aged 0–17 years with a newly diagnosed, morphologically and immunophenotypically confirmed diagnosis of ALL, who initiated frontline treatment between 1 January 2021 and 31 December 2024, were eligible for inclusion. Patients with mature B-cell ALL/Burkitt leukaemia, mixed-phenotype acute leukaemia treated on an acute myeloid leukaemia protocol, or those who received only palliative care, were excluded.

2.2. Treatment protocol

All patients were treated according to an ALL-IC BFM 2009-type regimen, with risk stratification into standard-risk (SR), intermediate-risk (IR), and high-risk (HR) categories based on age, presenting white-blood-cell count, central nervous system involvement,

immunophenotype, cytogenetic findings (including *BCR::ABL1* and *KMT2A* rearrangements) and minimal residual disease at days 15 and 33 of induction[2],[8]. Treatment phases assessed in this analysis comprised: (i) Protocol I — four-drug induction with vincristine, an anthracycline (daunorubicin), corticosteroid (prednisone or dexamethasone), and L-asparaginase; (ii) Protocol M — interim maintenance with four cycles of high-dose methotrexate (HD-MTX, 2–5 g/m²) and oral 6-mercaptopurine; (iii) Protocol II — reinduction analogous to Protocol I with dexamethasone, vincristine, doxorubicin and asparaginase, followed by cyclophosphamide/cytarabine/6-thioguanine consolidation; (iv) high-risk intensification blocks HR-1, HR-2 and HR-3, each comprising HD-MTX or HD-cytarabine, cyclophosphamide or ifosfamide, vincristine, daunorubicin or etoposide, and asparaginase, administered to high-risk patients; and (v) Protocol III — a shortened delayed intensification block used selectively.

2.3. Toxicity assessment

Adverse events were prospectively recorded by treating clinicians at every cycle and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 5.0[9]. Thirteen organ-system toxicity categories were assessed at each phase: haematologic, hepatic, dermatologic/mucosal, dyspeptic/gastrointestinal, performance-status decline (Karnofsky/Lansky), infection, cardiotoxicity, coagulologic, metabolic (including electrolyte disturbance and hyperglycaemia), neurotoxicity, nephrotoxicity, weight loss, and respiratory toxicity. For each patient and phase, the highest grade reached per category was recorded. Severe toxicity was defined as grade III–IV.

2.4. Statistical analysis

Categorical variables are presented as counts and percentages; continuous variables as medians and ranges. Because each patient could exhibit toxicity of more than one grade within a category during the same phase, row percentages within toxicity-by-grade tables refer to the proportion of patients in that phase exhibiting at least one episode of that grade. Analyses were descriptive and were performed in R version 4.3 (R Foundation for Statistical Computing, Vienna, Austria) and Jamovi 2.4 (The Jamovi Project, Sydney, Australia). No imputation of missing data was performed.

2.5. Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee. Because data were extracted retrospectively from anonymised clinical records, the requirement for individual informed consent was waived.

3. Results

3.1. Cohort characteristics

A total of 261 children with newly diagnosed ALL met inclusion criteria. Demographic and clinical characteristics are summarised in Table 1. The cohort comprised 152 boys (58.2%) and 109 girls (41.8%), yielding a male-to-female ratio of 1.39:1, which is consistent with the well-documented modest male preponderance in paediatric ALL[1],[6]. The median age at diagnosis was 4 years (range 0–17), with 67.4% of patients (n = 176) aged between 1 and 6 years — the well-described peak incidence window. Annual case numbers rose during the observation period from 37 in 2021 to 99 in 2024, reflecting both increased referral and the recovery of paediatric services following pandemic-related disruption.

B-cell precursor ALL was the dominant immunophenotype (n = 220, 84.3%), followed by T-cell ALL (n = 33, 12.6%); mixed-lineage, biphenotypic, and unclassified cases together accounted for 3.1%. Risk stratification yielded 186 standard-risk patients (71.3%), 61 high-risk (23.4%), 10 intermediate-risk (3.8%), 3 low-risk (1.1%) and 1 unspecified (0.4%).

Table 1.

Demographic and clinical characteristics of the cohort (N = 261).

Characteristic	n	%
Sex		
Male	152	58.2
Female	109	41.8
Age group (years)		
<1	6	2.3
1–6	176	67.4
7–12	49	18.8
13–17	30	11.5
Immunophenotype		
B-cell precursor	220	84.3
T-cell	33	12.6
Mixed / biphenotypic	6	2.3

Characteristic	n	%
Unknown / other	2	0.8
Risk group		
Standard	186	71.3
High	61	23.4
Intermediate	10	3.8
Low	3	1.1
Unspecified	1	0.4
Year of diagnosis		
2021	37	14.2
2022	69	26.4
2023	56	21.5
2024	99	37.9

3.2. Overall toxicity burden

At least one toxicity event of any grade was documented in every patient. The proportion of patients experiencing at least one grade III–IV (severe) event in each phase is summarised in Table 2. Severe toxicity was most concentrated during Protocol I (49.1% of patients with at least one grade IV event), the three high-risk blocks (grade IV: HR-1 85.2%, HR-2 59.2%, HR-3 65.2%), and Protocol II (grade IV 34.3%). Protocol M, despite its dose-intensive HD-MTX backbone, was characterised by a substantially lower share of grade IV events (22.2%), with toxicity concentrated in grades I–II.

Table 2.

Proportion of patients (%) experiencing at least one toxicity event of each maximum CTCAE grade, by treatment phase.

Phase	n	Gr I	Gr II	Gr III	Gr IV
Protocol I	262	93.2	80.8	87.9	49.1
Protocol M	207	99.0	89.9	75.4	22.2
Protocol II	204	95.6	84.8	88.2	34.3
Block HR-1	54	88.9	92.6	94.4	85.2
Block HR-2	49	95.9	77.6	89.8	59.2
Block HR-3	46	87.0	76.1	91.3	65.2
Protocol III	29	96.6	86.2	82.8	37.9

3**.3. Phase-specific toxicity profiles**

3.3.1. Protocol I (induction). During Protocol I, grade III–IV haematologic toxicity was nearly universal (101 patients [38.1%] grade III; 118 [44.5%] grade IV), reflecting both leukaemic marrow infiltration at diagnosis and intensive cytoreduction by the four-drug regimen (Table 3). Grade III infection occurred in 187 patients (70.6%) and grade IV in 24 (9.1%), making infection the second-most-prevalent severe toxicity. Hepatotoxicity was predominantly low-grade (grade I 37.7%, grade II 28.7%), with severe (grade III–IV) hepatotoxicity in 22.6%, consistent with the cumulative effect of asparaginase, dexamethasone and 6-mercaptopurine[5],[10]. Dermatologic/mucosal toxicity reached grade III in 89 (33.6%) and grade IV in 5 (1.9%) patients. Coagulopathy, including grade III in 15.9% and grade IV in 5.7% of patients, reflects the well-described impact of L-asparaginase on hepatic synthesis of antithrombin and fibrinogen[11],[12]. Cardiotoxicity, neurotoxicity, nephrotoxicity, and pulmonary toxicity remained predominantly low-grade.

Table 3.

CTCAE-graded toxicity during Protocol I (induction). Values are n (%) of patients in each toxicity category.

Toxicity category	Gr I	Gr II	Gr III	Gr IV	Any (Σ events)
Haematologic	8 (3.0)	31 (11.7)	101 (38.1)	118 (44.5)	258
Hepatic	100 (37.7)	76 (28.7)	51 (19.3)	9 (3.4)	236
Dermatologic	17 (6.4)	67 (25.3)	89 (33.6)	5 (1.9)	178
Dyspeptic/GI	54 (20.4)	82 (30.9)	101 (38.1)	2 (0.8)	239
Performance status	111 (41.9)	56 (21.1)	6 (2.3)	—	173
Infection	12 (4.5)	29 (10.9)	187 (70.6)	24 (9.1)	252
Cardiotoxicity	117 (44.2)	12 (4.5)	4 (1.5)	—	133
Coagulologic	65 (24.5)	64 (24.2)	42 (15.9)	15 (5.7)	186
Metabolic	144 (54.3)	76 (28.7)	19 (7.2)	1 (0.4)	240
Neurotoxicity	117 (44.2)	12 (4.5)	2 (0.8)	1 (0.4)	132
Nephrotoxicity	62 (23.4)	11 (4.2)	5 (1.9)	2 (0.8)	80
Weight loss	104 (39.3)	16 (6.0)	—	—	120
Respiratory	55 (20.8)	10 (3.8)	7 (2.6)	1 (0.4)	73

3.3.2. Protocol M (HD-MTX consolidation). Protocol M produced the broadest spread of low-grade events but the lowest share of grade IV toxicity (Table 4). Hepatic toxicity (any grade) affected 139 of 207 patients (67.1%), with grade III–IV in 15.0%; this profile is in keeping with HD-MTX hepatotoxicity, which is typically reversible and often related to delayed methotrexate clearance and pharmacogenomic variation in MTHFR, ABCB1 and SLCO1B1[13],[14]. Mucositis (dermatologic toxicity) was prevalent (any grade 79.7%) and grade III–IV in 30.0% — consistent with HD-MTX-related epithelial injury[15]. Infection remained an important burden, with grade III–IV in 44.9% of patients.

Table 4.

CTCAE-graded toxicity during Protocol M (n = 207).

Toxicity category	Gr I	Gr II	Gr III	Gr IV	Any (Σ)
Haematologic	125 (60.4)	102 (49.3)	88 (42.5)	37 (17.9)	186
Hepatic	120 (58.0)	55 (26.6)	25 (12.1)	6 (2.9)	139
Dermatologic	74 (35.8)	89 (43.0)	60 (29.0)	2 (1.0)	165
Dyspeptic/GI	99 (47.8)	115 (55.6)	58 (28.0)	1 (0.5)	195
Performance status	120 (58.0)	18 (8.7)	4 (1.9)	—	122
Infection	108 (52.2)	39 (18.8)	88 (42.5)	5 (2.4)	164
Cardiotoxicity	49 (23.7)	11 (5.3)	2 (1.0)	—	57
Coagulologic	35 (16.9)	8 (3.9)	2 (1.0)	2 (1.0)	44
Metabolic	137 (66.2)	24 (11.6)	3 (1.5)	1 (0.5)	146
Neurotoxicity	31 (15.0)	3 (1.5)	1 (0.5)	—	35
Nephrotoxicity	25 (12.1)	14 (6.8)	4 (1.9)	1 (0.5)	32
Weight loss	61 (29.5)	3 (1.5)	—	—	63
Respiratory	9 (4.4)	2 (1.0)	2 (1.0)	1 (0.5)	12

3.3.3. Protocol II (reinduction). Toxicity during Protocol II broadly mirrored Protocol I, with grade III–IV haematologic toxicity in 72.5% (grade III 42.7%, grade IV 29.9%) and grade III–IV infection in 69.1% (Table 5). The relatively higher rate of grade III–IV coagulopathy (11.3%) is again attributable to repeated asparaginase exposure[11]. Dyspeptic toxicity remained common (grade III 26.5%), reflecting the steroid- and cyclophosphamide-driven gastrointestinal injury characteristic of reinduction.

Table 5.

CTCAE-graded toxicity during Protocol II (n = 204).

Toxicity category	Gr I	Gr II	Gr III	Gr IV	Any (Σ)
Haematologic	18 (8.8)	36 (17.6)	87 (42.7)	61 (29.9)	199
Hepatic	87 (42.7)	59 (28.9)	25 (12.3)	2 (1.0)	172
Dermatologic	27 (13.2)	61 (29.9)	48 (23.5)	2 (1.0)	138
Dyspeptic/GI	54 (26.5)	82 (40.2)	54 (26.5)	—	189
Performance status	91 (44.6)	17 (8.3)	4 (2.0)	—	112
Infection	24 (11.8)	25 (12.3)	133 (65.2)	8 (3.9)	190
Cardiotoxicity	84 (41.2)	10 (4.9)	2 (1.0)	—	96
Coagulologic	50 (24.5)	33 (16.2)	16 (7.8)	7 (3.4)	106
Metabolic	116 (56.9)	57 (27.9)	9 (4.4)	1 (0.5)	181
Neurotoxicity	71 (34.8)	9 (4.4)	3 (1.5)	—	83
Nephrotoxicity	24 (11.8)	4 (2.0)	3 (1.5)	—	31
Weight loss	82 (40.2)	6 (2.9)	—	—	88
Respiratory	14 (6.9)	2 (1.0)	3 (1.5)	—	19

3.3.4. High-risk intensification blocks (HR-1, HR-2, HR-3). High-risk patients (n = 61) experienced the greatest absolute and relative burden of severe toxicity. During HR-1, 45 of 54 patients (83.3%) developed grade IV haematologic toxicity and 49 (90.7%) developed grade III–IV infection (Table 6). Severe dyspeptic toxicity (grade III–IV) reached 51.8% in HR-1. The HR-2 and HR-3 blocks produced a comparable pattern: grade IV haematologic toxicity in 57.1% and 63.0% respectively, and grade III–IV infection in 77.6% and 84.8%. Grade III–IV pulmonary toxicity, although infrequent overall, was disproportionately observed in HR-1 (7.4%). These findings are consistent with the published BFM experience that the HR triad of HD-MTX, HD-cytarabine and ifosfamide–etoposide combinations represents the period of highest treatment-related morbidity and mortality[2],[16].

Table 6.

Severe (grade III–IV) toxicity (%) across high-risk intensification blocks.

Toxicity category	HR-1 (n=54)	HR-2 (n=49)	HR-3 (n=46)
Haematologic	96.3	89.8	89.1
Hepatic	20.4	6.1	8.7
Dermatologic	31.5	24.5	13.0
Dyspeptic/GI	51.9	36.7	30.4
Infection	90.7	77.6	84.8
Coagulologic	14.8	8.2	6.5
Metabolic	7.4	8.2	0.0
Neurotoxicity	7.4	0.0	0.0
Respiratory	7.4	2.0	0.0

3.3.5. Protocol III (delayed intensification). In the 29 patients who received Protocol III, grade III–IV haematologic toxicity affected 82.8% and grade III–IV infection 69.0%. Hepatotoxicity remained mostly low-

grade (grade I 62.1%, grade II 37.9%; no grade IV). The smaller sample size of this phase limits statistical inference; nonetheless, the qualitative pattern was consistent with the rest of the cohort.

3.4. Cross-phase comparison of haematologic and infectious toxicity

Two organ systems — bone marrow and the infection axis — accounted for the great majority of severe toxicity in our cohort. Figure 1 (conceptual; data summarised in Table 7) shows the proportion of patients experiencing grade III or IV toxicity in each category across all seven phases. Grade IV myelosuppression rose sharply between Protocol M (17.9%) and the HR blocks (57.1–83.3%) and remained elevated during delayed intensification. Grade III–IV infection followed a parallel trajectory, with peak rates during HR-1 (90.7%), Protocol I (79.6%) and HR-3 (84.8%). In contrast, hepatic, cardiac, neurologic and renal toxicities showed a flatter distribution, with grade III–IV rates rarely exceeding 25% in any phase.

Table 7.

Grade III + IV (severe) toxicity rates (%) by phase and organ system. Cardiac, neuro, nephro and respiratory toxicities are abbreviated for layout.

Toxicity	Prot I	Prot M	Prot II	HR-1	HR-2	HR-3	Prot III
Haematologic	82.6	60.4	72.5	96.3	89.8	89.1	82.8
Hepatic	22.6	15.0	13.2	20.4	6.1	8.7	10.3
Dermatologic	35.5	30.0	24.5	31.5	24.5	13.0	13.8
Dyspeptic/GI	38.9	28.5	26.5	51.9	36.7	30.4	24.1
Infection	79.6	44.9	69.1	90.7	77.6	84.8	69.0
Cardiac	1.5	1.0	1.0	1.9	2.0	0.0	0.0
Coagulologic	21.5	1.9	11.3	14.8	8.2	6.5	17.2
Metabolic	7.5	1.9	4.9	7.4	8.2	0.0	10.3
Neurologic	1.1	0.5	1.5	7.4	0.0	0.0	3.4
Renal	2.7	2.4	1.5	0.0	2.0	0.0	0.0
Respiratory	3.0	1.4	1.5	7.4	2.0	0.0	3.4

4. Discussion

This study provides the first comprehensive, CTCAE-graded description of acute treatment-related toxicity in paediatric ALL from a Kazakhstani tertiary centre. Three findings deserve emphasis.

First, the demographic and biological profile of our cohort — male predominance, modal age at 4 years, B-cell precursor disease in 84.3%, and standard-risk classification in 71.3% — is broadly comparable to large international BFM-based series[1],[2],[6]. This supports the external generalisability of subsequent toxicity comparisons.

Second, the phase-specific toxicity pattern that we observed closely matches the spectrum reported in pooled BFM and AIEOP-BFM experience. Demidowicz and colleagues, in a 210-patient analysis of ALL IC-BFM 2002 and 2009 from a single Polish centre, reported that hepatic transaminitis, infection and mucositis dominated the non-haematologic toxicity profile, and that the introduction of ALL IC-BFM 2009 was associated with a relative shift from grade II to grade III events[4]. Our cohort shows the same hierarchy: infection and haematologic toxicity drive severe events, while hepatic and gastrointestinal toxicity contribute the bulk of grade I–II morbidity. Severe infection rates of 70–90% during induction and the HR blocks are at the upper end of the published range and probably reflect both intensive immunosuppression and the resource-limited supportive-care environment in which most patients in LMIC settings receive treatment[7],[17].

Third, the comparative profile of Protocol M is informative. Despite the well-known dose-dependent hepatotoxicity and mucositis of HD-MTX, our patients had the lowest share of grade IV toxicity during this phase (22.2%). This is consistent with the observation that HD-MTX-related toxicity, when monitored with leucovorin rescue, hyperhydration, alkalinisation and pharmacokinetic surveillance, is generally reversible and rarely life-threatening[13],[14]. The relatively high rate of grade I–II mucositis (43.0% grade II) is in line with published rates and supports continued investment in oral-care prophylaxis and nutritional support[15].

Coagulopathy emerged as a distinct, phase-specific toxicity. Grade III–IV coagulopathy was observed in 21.5% during Protocol I and 11.3% during Protocol II, with a near absence in Protocol M (1.9%). This pattern reflects asparaginase pharmacology: depletion of antithrombin, fibrinogen and other liver-synthesised coagulation proteins occurs almost exclusively during phases containing native or pegylated L-asparaginase[11],[12]. In this context, our findings reinforce international recommendations for routine coagulation monitoring and selective antithrombin or fibrinogen replacement during asparaginase-containing phases.

Several limitations should be acknowledged. First, this is a single-centre retrospective cohort study without a formal comparator arm; toxicity comparisons are

therefore descriptive. Second, although the cohort size (n = 261) is among the largest reported from Central Asia, the HR blocks (n = 46–54) have wider confidence intervals than the standard-risk arms. Third, CTCAE grading was performed clinically rather than by independent central review; misclassification, particularly at the grade II/III boundary, cannot be excluded. Fourth, we did not link toxicity events to treatment delays, intensive-care admissions, treatment-related mortality, or long-term outcomes; analyses of these clinically important endpoints are planned in a follow-up study. Finally, pharmacogenomic correlates of toxicity (e.g., *MTHFR*, *SLCO1B1*, *TPMT*, *NUDT15*) were not assessed and represent a priority for prospective work[13],[14],[18].

Despite these limitations, our data have direct clinical and policy relevance. They provide the first robust baseline against which future quality-improvement initiatives — for example, antimicrobial stewardship, supportive-care bundles, or therapeutic drug monitoring of HD-MTX — can be evaluated. They also confirm that, in a contemporary Kazakhstani paediatric oncology setting, BFM-type therapy is deliverable with a toxicity profile consistent with international experience, while highlighting infection control as the highest-impact target for further reduction in treatment-related morbidity.

5. Conclusions

In a retrospective cohort of 261 children with newly diagnosed ALL treated according to an ALL-IC BFM 2009-type regimen in Kazakhstan between 2021 and 2024, every patient experienced at least one treatment-related toxicity event. The burden was phase-specific: severe haematologic toxicity and infection dominated during Protocol I, Protocol II and the high-risk intensification blocks, while Protocol M was characterised by lower-grade hepatic and mucosal toxicity. Cardiac, neurologic, renal and pulmonary toxicities remained predominantly low-grade across all phases. These findings provide a reproducible benchmark for paediatric oncology services in Central Asia and identify infection prevention, asparaginase-related coagulopathy management, and HD-MTX monitoring as the most actionable targets for supportive-care improvement.

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Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee of the affiliated institution.

Informed Consent Statement

Patient consent was waived owing to the retrospective and anonymised nature of the data.

Data Availability Statement

De-identified data are available from the corresponding author upon reasonable request and subject to institutional approval.

Conflicts of Interest

The author declares no conflicts of interest.

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