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Original Article

Factors affecting chemotherapy response after the first relapse of B-cell acute lymphoblastic leukemia in pediatric patients

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Abstract: Objective: To investigate the factors affecting chemotherapy efficacy following first relapse in pediatric B-cell acute lymphoblastic leukemia (B-ALL). Methods: A retrospective investigation was conducted on the clinical data from 254 pediatric patients with B-ALL treated at the First Affiliated Hospital of Xinjiang Medical University, Red Star Hospital of the 13th Division of Xinjiang Production and Construction Corps and Chengdu Women's and Children's Central Hospital between August 2016 and September 2022. Patients were divided into a Good Response (GR) group and a Poor Response (PR) group based on minimal residual disease (MRD) levels post-relapse treatment. The demographic data, blood and cytokine profiles, cytogenetic/molecular alterations, and therapeutic interventions were analyzed. Factors influencing response were screened using univariate and multivariate logistic regression models. Results: The GR group showed significantly higher white blood cell (WBC) counts (8.24 ± 2.21 × 10^3/μL) compared to the PR group (7.50 ± 1.88 × 10^3/μL; P = 0.004). Elevated levels of tumor necrosis factor-alpha (TNF-α) (22.78 ± 4.31 vs. 20.94 ± 4.28 pg/mL; *P* < 0.001) and interleukin-6 (IL-6) (112.48 ± 21.09 vs. 106.31 ± 20.77 pg/mL; *P* = 0.020) were linked to poor outcome. Hypodiploidy and combined genetic alterations in Ikaros family zinc finger 1 (IKZF1), nuclear receptor subfamily 3 group C member 1 (NR3C1), and B-cell translocation gene 1 (BTG1) were associated with poor response (*P* = 0.032 and *P* = 0.003, respectively). Blinatumomab usage was associated with improved outcome (*P* = 0.030). Multivariate analysis revealed that higher TNF-α and IL-6 levels were independent risk factors of PR, while higher WBC count was a protective factor. Conclusion: Chemotherapy efficacy in relapsed pediatric B-ALL is influenced by hematologic, cytokine, and genetic factors.

Keywords: B-cell acute lymphoblastic leukemia, pediatric oncology, chemotherapy resistance, minimal residual disease, cytokines, genetic alterations

Introduction

Acute lymphoblastic leukemia (ALL) is the most common cancer among children, responsible for roughly 1/4 of all cancer cases in individuals under the age of 15 [1-3]. Among its subtypes, B-cell acute lymphoblastic leukemia (B-ALL) is the most prevalent type [4-6]. Significant advancements in therapeutic strategies over the past several decades have led to high survival rates, with over 90% of patients achieving complete remission (CR) following initial treatment [7-9]. Despite these advancements, approximately 15-20% of pediatric patients experience relapse, which remains a formidable challenge and is associated with poorer outcome [10]. Understanding the factors influencing the efficacy of chemotherapy after the first relapse is critical for enhancing survival rates and overall quality of life in affected children.

Relapse in pediatric B-ALL is often characterized by aggressive disease biology and resistance to standard therapy [11-13]. The reemer-

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gence of leukemic blasts in bone marrow or extramedullary sites after achieving CR marks the onset of a more refractory disease phase. At this stage, treatment typically involves intensive chemotherapy regimens, often supplemented by immunotherapy in high-risk cases [14, 15]. However, treatment responses are heterogenous and influenced by a variety of clinical and biological factors. Identifying these factors is essential for tailoring treatment approaches and improving outcome.

Recent studies have highlighted several key factors that influence chemotherapy efficacy after relapse in pediatric B-ALL patients. For instance, minimal residual disease (MRD) status at the time of relapse is a strong predictor of outcome, with higher MRD levels associated with poorer prognosis [16]. Genetic alterations, such as mutations in Tumor Protein p53 (TP53), Ikaros family zinc finger 1 (IKZF1), as well as nuclear receptor subfamily 3 group C member 1 (NR3C1), have been linked to treatment resistance [17]. Moreover, the presence of specific cytogenetic abnormalities, like hypodiploidy, has been linked to a poor response to therapy [18]. Elevated levels of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), have also been correlated with less favorable treatment outcomes [19].

Understanding the complexity of relapsed B-ALL requires an exploration of multiple domains, ranging from host-related factors such as immune status and performance metrics, to intrinsic tumor features, including genetic mutations and cytogenetic abnormalities. In light of these complexities, the current study endeavors to evaluate comprehensively the diverse factors influencing chemotherapy efficacy following the first relapse of pediatric B-ALL.

Materials and methods

Case selection

This retrospective analysis involved 254 pediatric patients diagnosed with B-ALL who were treated at the First Affiliated Hospital of Xinjiang Medical University, Red Star Hospital of the 13th Division of Xinjiang Production and Construction Corps and Chengdu Women's and Children's Central Hospital between August 2016 and September 2022. Patient data were collected through our medical record system, including demographic information, blood test results, cytokine levels, and data on cytogenetic and genetic alterations. Additionally, patient performance was assessed using the ECOG Performance Status and the Lansky Performance Score, along with details of other therapies received.

The Medical Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University granted approval for this study. Informed consent was waived due to the retrospective nature of the study with anonymized data, ensuring no risk or effect on patient care.

Inclusion and exclusion criteria

Inclusion Criteria: 1) Diagnosis of B-ALL confirmed through bone marrow histology, flow cytometry, and/or cytogenetic examinations, adhering to the National Comprehensive Cancer Network (NCCN) guidelines (Version 1.2018) for pediatric ALL [20]; 2) First relapse of B-ALL, defined as the recurrence of leukemic blasts exceeding 5% in the blood, bone marrow, or any extramedullary site after achieving CR [21]; 3) Completion of induction therapy and all cycles of standard consolidation chemotherapy; 4) Aged between 1-18 years; 5) Availability of comprehensive medical records and follow-up data.

Exclusion Criteria: 1) Down syndrome, due to its association with a distinct subtype of B-ALL that may introduce bias due to unique genetic and clinical features, including higher incidence of GATA1 mutations and generally more favorable prognosis; 2) Philadelphia chromosome-positive ALL, as it requires distinct treatment protocols, including tyrosine kinase inhibitors, which were not the focus of this study; 3) History of previous transplant or treatment with blinatumomab, as these interventions can significantly alter immune function and disease biology, potentially confounding treatment responses; 4) Optic nerve involvement or elevated creatinine levels (> 1.7 mg/dL), as these conditions may represent more aggressive disease or renal dysfunction, affecting drug metabolism and chemotherapy efficacy; 5) Co-existing lymphoma or other malignancies, as these conditions could confound the study outcomes; 6) Active hepatitis B or hepatitis C infection, which could affect treatment outcomes; 7) Patients who died during chemotherapy (**Figure 1**).

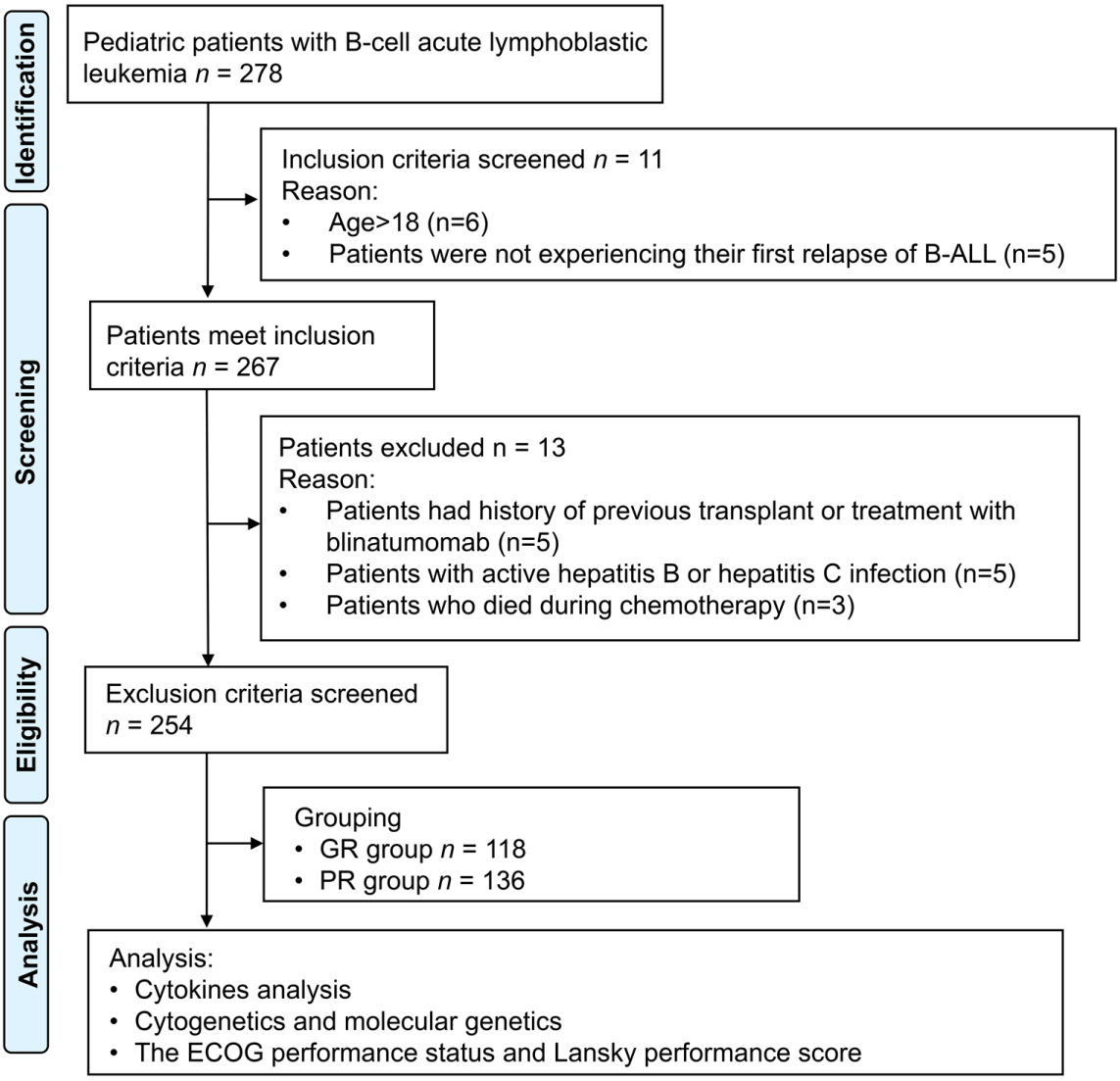

Figure 1. Experimental design flowchart.

Grouping and treatment methods

Based on the outcomes following chemotherapy after the first relapse in children with B-ALL, we categorized patients into two groups: The Good Response (GR) group (n = 118): this group included patients who had a minimal residual disease (MRD) level of less than 10^-4 [22] at the end of induction (EOI), or those with MRD levels between 10^-4 and 10^-3 at EOI who subsequently achieved an MRD level of < 10^-4 after further induction. The Poor Response (PR) group (n = 136): this group comprised patients with MRD levels greater than 10^-4 at EOI. MRD was assessed following induction therapy and, for some patients, after each block of therapy.

All patients underwent a 4-week regimen of reinduction chemotherapy in conjunction with risk-adjusted intrathecal chemotherapy. The standard treatment protocol for a first relapse involves 4 weeks of reinduction chemotherapy, succeeded by consolidation therapy. For patients with early bone marrow relapses (occurring within 36 months of initial diagnosis), consolidation included two cycles of intensive multi-agent chemotherapy, followed by a hematopoietic stem cell transplantation. However, many patients with early relapse were unable to proceed to transplantation due to adverse events during chemotherapy, such as severe infections, or failure to achieve a second remission characterized by MRD negativity, which is

essential for optimal transplant outcome. In cases of late first bone marrow relapse (occurring 36 months or more after diagnosis), consolidation therapy included intensive chemotherapy followed by transplantation. All patients received the same chemotherapy cycles and frequencies.

Assessment tool

Minimal residual disease (MRD): Bone marrow samples (3 ml) were collected from pediatric patients prior to the initiation of chemotherapy, with heparin used as an anticoagulant. DNA was extracted from the samples utilizing a DNA extraction kit (MagMAX, Thermo Fisher Scientific, USA). The extracted DNA underwent real-time polymerase chain reaction (PCR) amplification using the CFX96 Touch Real-Time PCR Detection System (Bio-Rad Laboratories, USA). The MRD level was determined based on the Cycle Threshold (Ct) value and was typically expressed as the number of leukemic cells per 10^4 normal cells. In the two-parameter flow cytometry diagram, the presence of cells in the region corresponding to leukemia cells indicated minimal residual leukemia, and the proportion of these residual cells among the total bone marrow mononuclear cells provided the MRD monitoring result.

Eastern Cooperative Oncology Group (ECOG) performance status and Lansky performance score: The ECOG Performance Status is a widely recognized scoring system used to assess the overall health and daily activity capabilities of patients with cancer or chronic diseases. This system classifies a patient's functional ability into five grades, from Grade 0: Fully active, capable of performing all pre-disease activities without restriction, to Grade 5: Deceased. The inter-rater reliability for this assessment was represented by Cohen's κ value of 0.486 [23].

The Lansky Performance Score was used to evaluate the functional status of children's cancer, based on parental assessment of their usual play activities during the preceding week. The scale extends from "unresponsive" at 0% and "no play; remains in bed" at 10%, up to "limited restrictions in physically demanding activities" at 90% and "completely active, normal" at 100%. A Pearson correlation of 0.71 was observed between the scores reported by mothers and fathers [24].

Blood test: Blood samples (3 ml) were collected by venipuncture and analyzed using an automated hematology analyzer (ADVIA 2120i, Siemens Healthineers, Germany) to measure levels of white blood cells (WBC), red blood cells (RBC), hemoglobin (Hb), platelets (PLT), and lymphocytes. In addition, an automated biochemistry analyzer (AU5800, Beckman Coulter, Inc., USA) was employed to assess various biochemical indicators in the blood, including alanine aminotransferase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), total bilirubin (TBIL), creatinine (Cr), blood urea nitrogen (BUN), and lactate dehydrogenase (LDH).

Cytokines analysis, cytogenetics, and molecular genetics: To analyze cytokines, 4 ml of fasting venous blood was collected into a single-use vacuum blood collection tube. The sample was incubated at 37°C until clot formation was complete, then centrifuged at 3,000 g for 10 minutes at 4°C. The resulting serum was stored at -20°C until further analysis. Interferon gamma (IFN-γ) levels were measured using an enzyme-linked immunosorbent assay (ELISA) with the Human IFN-γ ELISA Kit (88-7316-22, Thermo Fisher Scientific, USA). Additionally, concentrations of TNF-α, interleukin-8 (IL-8), granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-6, and monocyte chemoattractant protein-1 (MCP-1) were assessed using specific Quantikine ELISA Kits from R&D Systems, USA, namely: Human TNF-alpha Quantikine ELISA Kit (DTA00D), Human CXCL8/IL-8 Quantikine ELISA Kit (DX800), Human IL-6 Quantikine ELISA Kit (D6050), Human GM-CSF Quantikine ELISA Kit (DGM00), and Human MCP-1/CCL2 Quantikine ELISA Kit (DCP00), respectively.

For cytogenetics and molecular genetics, the SALSA multiplex ligation-dependent probe amplification (MLPA) kit P335 was employed to evaluate the copy number variation of several genes. Deletions in TP53 were identified using the P007 or P056 kit (MRC Holland, The Netherlands). Key gene exon mutations were analyzed using denaturing high-performance liquid chromatography (DHPLC) and/or Sanger sequencing techniques.

Statistical analysis

Data were reported as mean ± standard deviation or median with interquartile range, according to the normality of distribution. Categorical

Table 1. Comparison of general information between the two groups

Data	GR group (n = 118)	PR group (n = 136)	t/χ^2	P
Gender (F/M)	50 (42.37%)/68 (57.63%)	55 (40.44%)/81 (59.56%)	0.097	0.755
Age [n (%)]			0.002	0.965
1-12 (years)	83 (70.34%)	96 (70.59%)		
13-18 (years)	35 (29.66%)	40 (29.41%)		
BMI (kg/m^2)	17.56 ± 3.62	17.84 ± 3.47	0.646	0.519
Age at initial diagnosis (years)	6.32 ± 1.95	6.66 ± 2.04	1.347	0.179
Site of relapse [n (%)]			0.012	0.912
Bone marrow isolated	40 (33.9%)	47 (34.56%)		
Bone marrow combined	78 (66.1%)	89 (65.44%)		
Time from first diagnosis to relapse [n (%)]			0.120	0.942
< 18 (months)	57 (48.31%)	67 (49.26%)		
≥ 18 and ≤ 30 (months)	37 (31.36%)	40 (29.41%)		
> 30 (months)	24 (20.34%)	29 (21.32%)		
MRD at start of therapy [n (%)]			2.074	0.355
$< 10^{-4}$	82 (69.49%)	84 (61.76%)		
$\geq 10^{-4}$ to $< 10^{-3}$	24 (20.34%)	38 (27.94%)		
$\geq 10^{-3}$	12 (10.17%)	14 (10.29%)		
Percentage of blasts in bone marrow [n (%)]			0.427	0.514
< 5%	0	0		
≥ 5% and < 25%	43 (36.44%)	55 (40.44%)		
≥ 25%	75 (63.56%)	81 (59.56%)		
Testicular disease [n (%)]	11 (9.32%)	13 (9.56%)	0.004	0.949
CNS leukemia (CNS3) [n (%)]	24 (20.34%)	26 (19.12%)	0.060	0.807
Hepatic dysfunction [n (%)]	9 (7.63%)	11 (8.09%)	0.019	0.892
Renal dysfunction [n (%)]	7 (5.93%)	8 (5.88%)	0.000	0.987
Heart failure [n (%)]	5 (4.24%)	6 (4.41%)	0.005	0.946
Follow-up (months)	15.54 ± 3.58	15.45 ± 3.39	0.202	0.840
Chemotherapeutic agents [n (%)]				
Methotrexate	87 (73.73%)	105 (77.21%)	0.414	0.520
Cytarabine	59 (50%)	69 (50.74%)	0.014	0.907
Chemotherapeutic dosages				
Methotrexate (single dose) (g/m^2)	4.98 ± 0.23	5.02 ± 0.27	1.350	0.178
Cytarabine (single dose) (g/m^2)	1.04 ± 0.14	1.07 ± 0.18	1.212	0.227

GR, Good Response; PR, Poor Response; F, female; M, male; BMI, body mass index; MRD, minimal residual disease; CNS, central nervous system.

data were presented as frequencies and percentages. To compare continuous variables between two groups, unpaired t-tests were utilized. Univariate and multivariate logistic regression analyses were conducted to calculate the odds ratio (OR) and 95% confidence interval (CI) for each continuous variable. A *p*-value of less than 0.05 was considered significant. Additionally, correlation analyses were performed to explore relationships between key variables. The univariate and multivariate analysis specifically included the following factors: WBC, TNF-α, IL-6, Hypodiploid (< 40 Chr), IKZF1/NR3C1/BTG1, and CD19 CAR-T therapy-Blinatumomab. Statistical analyses were conducted utilizing SPSS version 19 (SPSS Inc., Chicago, IL, USA) along with R software version 3.0.2 (Free Software Foundation, Inc., Boston, MA, USA).

Results

General information

In this study, we examined various factors influencing the efficacy of chemotherapy following the first relapse in pediatric B-ALL patients by comparing general information between the GR group (n = 118) and the PR group (n = 136) (**Table 1**). No significant differences were found between the two groups regarding gender dis-

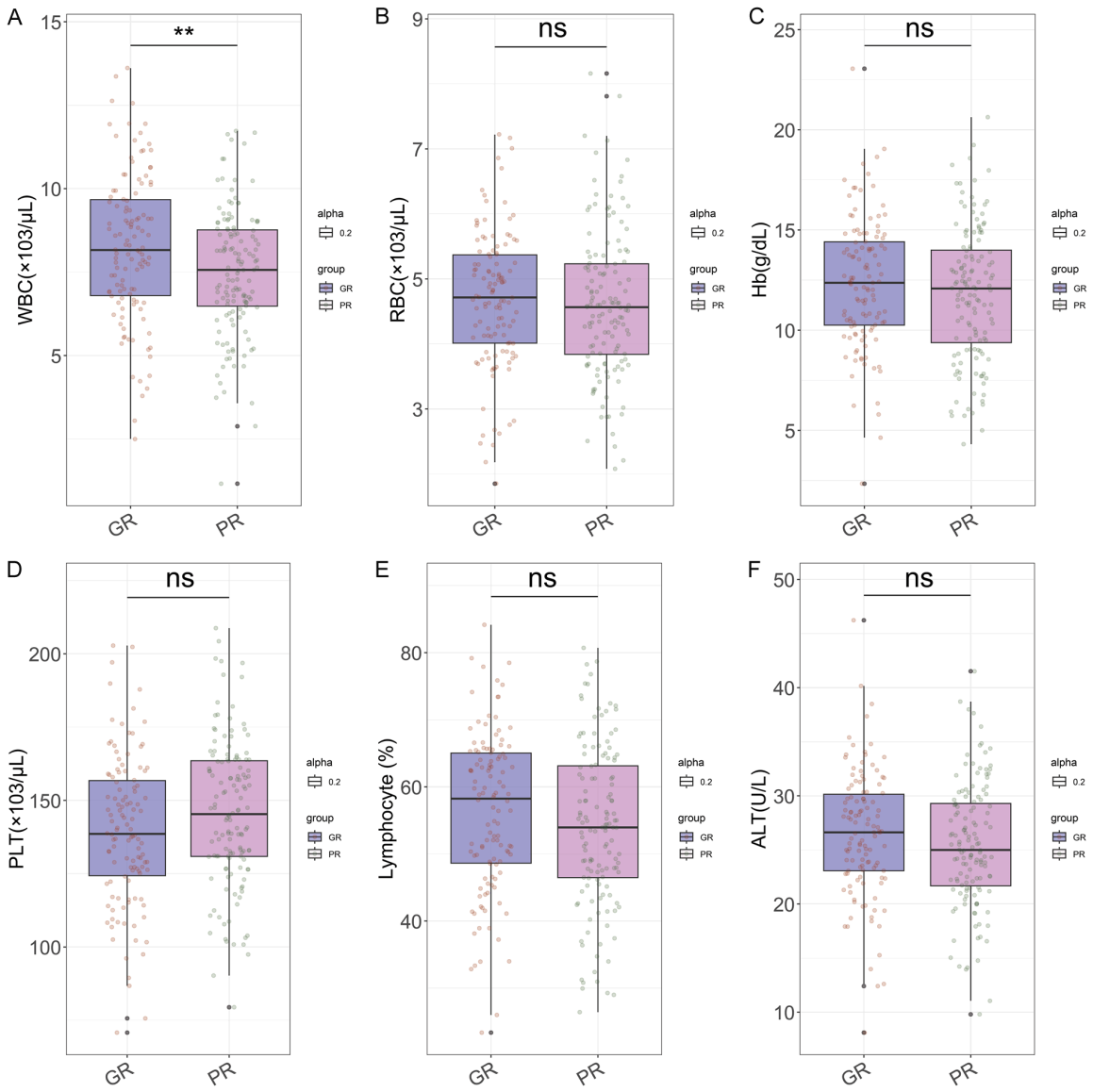

Figure 2. Comparison of blood test results between the two groups. (A) WBC, (B) RBC, (C) Hb, (D) PLT, (E) Lymphocytes, (F) ALT, $^{**}P < 0.01$, ns: no significant difference. Note: WBC, white blood cells; RBC, red blood cells; Hb, hemoglobin; PLT, platelets; ALT, alanine aminotransferase.

tribution (female/male: 42.37%/57.63% in GR vs. 40.44%/59.56% in PR; χ^2 = 0.097, P = 0.755), age categories (1-12 years: 70.34% in GR vs. 70.59% in PR; 13-18 years: 29.66% in GR vs. 29.41% in PR; χ^2 = 0.002, P = 0.965), or body mass index (BMI) (17.56 ± 3.62 kg/m^2 in GR vs. 17.84 ± 3.47 kg/m^2 in PR; t = 0.646, P = 0.519). No significant differences were found between the two groups regarding age at initial diagnosis, site of relapse, time from first diagnosis to relapse, MRD at the start of therapy, percentage of blasts in bone marrow, testicular disease, CNS leukemia, hepatic dysfunction, renal dysfunction, heart failure, follow-up duration, chemotherapeutic agents, or chemotherapeutic dosages (all $P > 0.05$). Overall, no significant differences were detected across all parameters assessed, indicating comparability between the GR and PR groups in baseline demographics and clinical characteristics.

Blood test

In comparing the blood test results between the GR group and PR group following the first relapse in pediatric B-ALL, a significant differ-

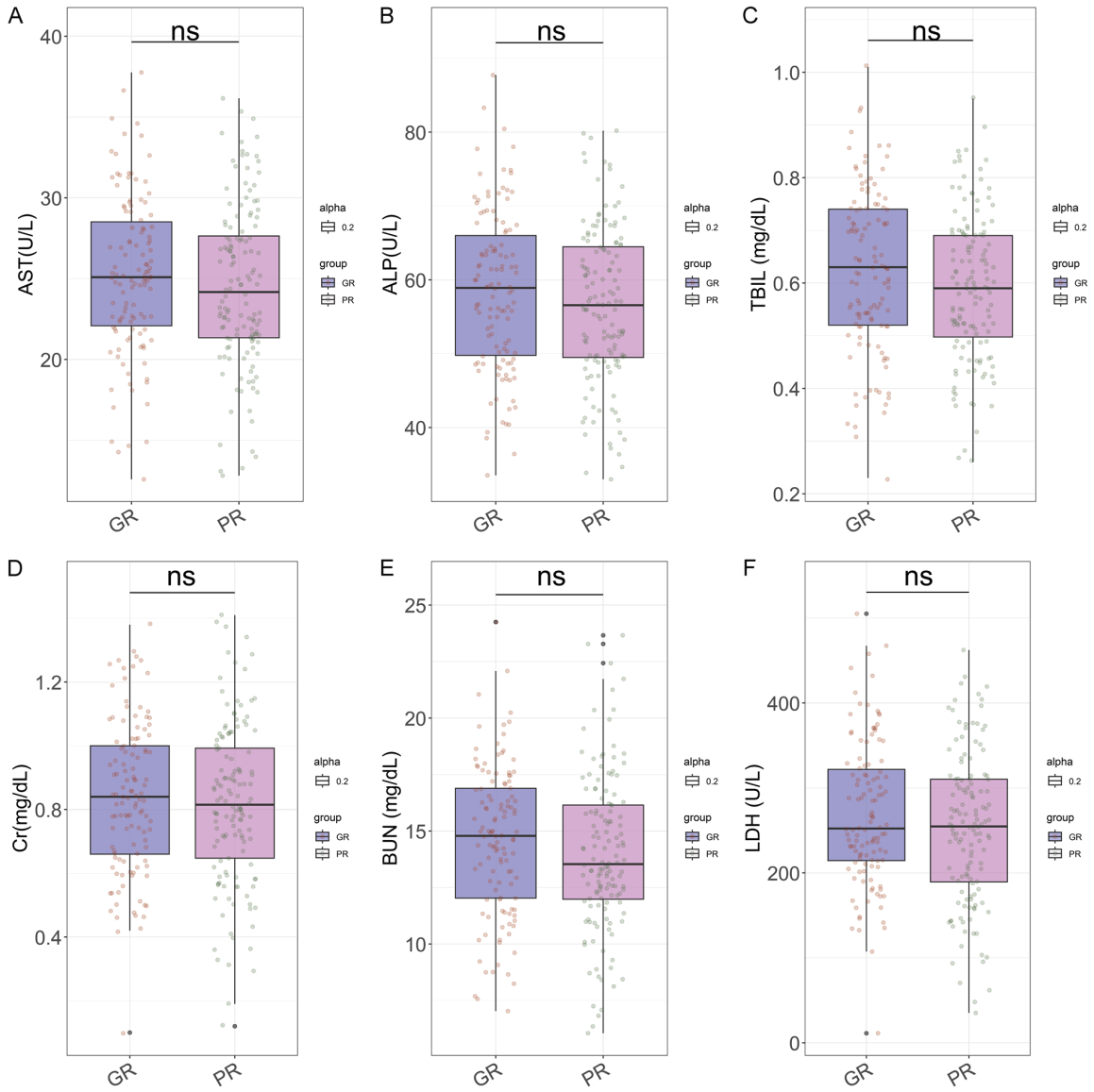

Figure 3. Comparison of blood test results between the two groups. (A) AST, (B) ALP, (C) TBIL, (D) Cr, (E) BUN, (F) LDH, ns: no significant difference. Note: AST, aspartate aminotransferase; ALP, alkaline phosphatase; TBIL, total bilirubin; Cr, creatinine; BUN, blood urea nitrogen; LDH, lactate dehydrogenase.

ence was observed in the mean WBC count, with the GR group showing higher levels (8.24 ± 2.21 × 10^3/μL) compared to the PR group (7.50 ± 1.88 × 10^3/μL; t = 2.899, P = 0.004) (**Figure 2**). No significant differences were found in the other parameters, including red blood cell (RBC) count, Hb levels and platelet (PLT) counts (P > 0.05). Additionally, measures such as lymphocyte percentage, liver function tests (ALT, ALP, AST), total bilirubin, renal function markers (creatinine and BUN), and lactate dehydrogenase (LDH) displayed no significant differences between the groups (all P > 0.05) (**Figure 3**). These findings suggest that while WBC count was notably different, other hematologic and biochemical markers did not significantly differ between the GR and PR groups.

Cytokines

TNF-α levels were significantly higher in the PR group (22.78 ± 4.31 pg/mL) compared to the GR group (20.94 ± 4.28 pg/mL; t = 3.403, P < 0.001) (**Figure 4**). Additionally, IL-6 levels were elevated in the PR group (112.48 ± 21.09 pg/mL) compared to the GR group (106.31 ± 20.77

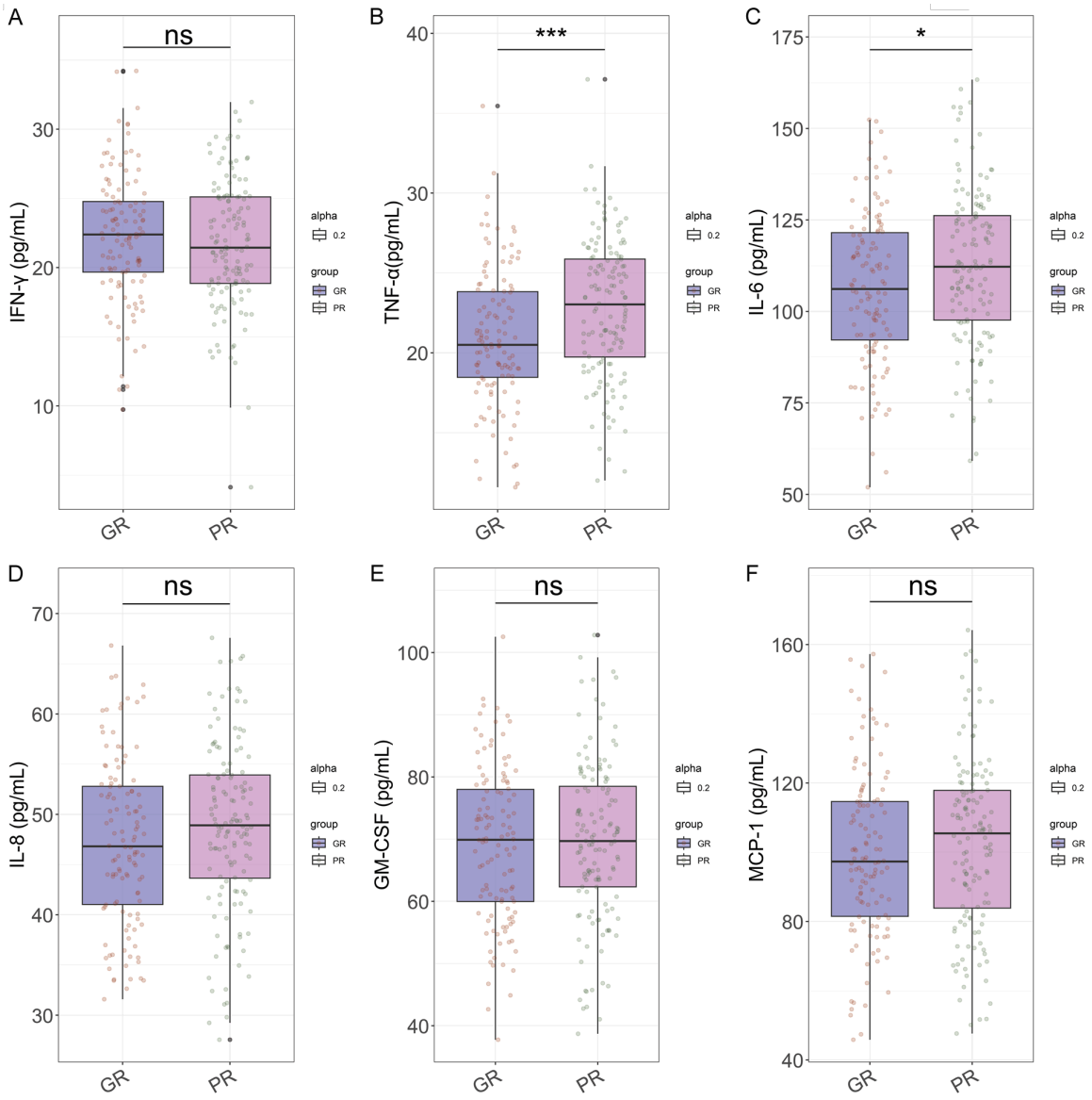

Figure 4. Comparison of cytokine levels between the two groups. (A) IFN-γ, (B) TNF-α, (C) IL-6, (D) IL-8, (E) GM-CSF, (F) MCP-1, *P < 0.05, ***P < 0.001, ns: no significant difference. Note: IFN-γ, interferon-γ; TNF-α, Tumor Necrosis Factor-alpha; IL-6, interleukin-6; IL-8, interleukin-8; GM-CSF, granulocyte-macrophage colony-stimulating factor; MCP-1, monocyte chemoattractant protein 1.

pg/mL; t = 2.342, P = 0.020). No significant differences were observed between the two groups for interferon-γ (IFN-γ), IL-8, GM-CSF, and monocyte chemoattractant protein 1 (MCP-1) (all P > 0.05). These results highlight significant elevations in TNF-α and IL-6 among patients with PR, suggesting their potential role in influencing chemotherapy efficacy.

Cytogenetic alterations

The comparison of cytogenetic alterations between the two groups revealed a significant difference in the incidence of hypodiploid karyotype (less than 40 chromosomes), which was more frequent in the PR group (10.29%) compared to the GR group (3.39%) (χ^2 = 4.574, P = 0.032) (**Table 2**). Other cytogenetic features, including ETS Variant 6 - Runt-related Transcription Factor 1 (ETV6-RUNX1) fusion, Lysine MethylTransferase 2A (KMT2A) fusions, the prevalence of Transcription Factor 3 - Hepatic Leukemia Factor (TCF3-HLF) and Transcription Factor 3 - Pre-B-cell Leukemia Homeobox (TCF3-PBX) translocations, and the

Table 2. Comparison of the cytogenetic alteration data between the two groups

Data	GR group (n = 118)	PR group (n = 136)	χ^2	P
ETV6-RUNX1 fusion [n (%)]	6 (5.08%)	5 (3.68%)	0.302	0.582
KTM2A fusions [n (%)]	10 (8.47%)	9 (6.62%)	0.315	0.575
TCF3-HLF, TCF3-PBX [n (%)]	17 (14.41%)	20 (14.71%)	0.005	0.946
High-hyperdiploid [n (%)]	14 (11.86%)	15 (11.03%)	0.044	0.835
Hypodiploid (< 40 Chr) [n (%)]	4 (3.39%)	14 (10.29%)	4.574	0.032

GR, Good Response; PR, Poor Response; ETV6, ETS Variant Transcription Factor 6; KTM2A, Lysine Methyltransferase 2A; TCF3, Transcription Factor 3; HLF, Hepatic Leukemia Factor; PBX1, Pre-B Cell Leukemia Homeobox 1.

Table 3. Comparison of the genetic alterations between two groups

Data	GR group (n = 118)	PR group (n = 136)	χ^2	P
IKZF1 [n (%)]	35 (29.66%)	36 (26.47%)	0.319	0.572
CDKN2A/B [n (%)]	54 (45.76%)	70 (51.47%)	0.824	0.364
ETV6 [n (%)]	16 (13.56%)	19 (13.97%)	0.009	0.924
PAX5 [n (%)]	28 (23.73%)	30 (22.06%)	0.100	0.752
BTG1 [n (%)]	11 (9.32%)	5 (3.68%)	3.412	0.065
RB1 [n (%)]	2 (1.69%)	4 (2.94%)	0.057	0.812
NR3C1 [n (%)]	16 (13.56%)	21 (15.44%)	0.180	0.672
IKZF1/NR3C1/BTG1 [n (%)]	46 (38.98%)	78 (57.35%)	8.533	0.003
TP53 alteration [n (%)]	24 (20.34%)	27 (19.85%)	0.009	0.923

GR, Good Response; PR, Poor Response; IKZF1, Ikaros Family Zinc Finger 1; CDKN2A/B, Cyclin Dependent Kinase Inhibitor 2A/2B; ETV6, ETS Variant Transcription Factor 6; PAX5, Paired Box 5; BTG1, B-Cell Translocation Gene 1; RB1, Retinoblastoma 1; NR3C1, Nuclear Receptor Subfamily 3 Group C Member 1; TP53, Tumor Protein p53.

high-hyperdiploid karyotype, showed no significant differences was similar between the two groups ($P > 0.05$). These findings indicate that while the presence of hypodiploidy significantly differed between the groups, other cytogenetic alterations were not significantly associated with response to chemotherapy.

Genetic alterations

The combination of TCF3-HLF and TCF3-PBX alterations was more prevalent in the PR group (57.35%) compared to the GR group (38.98%) ($\chi^2 = 8.533$, $P = 0.003$) (**Table 3**). Individually, alterations in IKZF1 were observed in 29.66% of the GR group and 26.47% of the PR group ($\chi^2 = 0.319$, $P = 0.572$). Similarly, CDKN2A/B deletions occurred in 45.76% of the GR group versus 51.47% of the PR group ($\chi^2 = 0.824$, $P = 0.364$). ETV6 alterations was noted in 13.56% of the GR group and 13.97% of the PR group ($\chi^2 = 0.009$, $P = 0.924$). PAX5 alterations were found in 23.73% of the GR group compared to 22.06% of the PR group ($\chi^2 = 0.100$, $P = 0.752$), while BTG1 alterations were seen in 9.32% of the GR group and 3.68% of the PR group, approaching significance ($\chi^2 = 3.412$, $P = 0.065$). Alterations in RB1 and NR3C1, as well as TP53, did not show significant differences between the two groups. Overall, the combined alterations of IKZF1, NR3C1, and BTG1 were significantly associated with a poorer response to chemotherapy.

The ECOG performance status and Lansky performance score

The distribution of ECOG performance status showed no significant variation between the two groups ($P = 0.987$) (**Table 4**). Similarly, the mean Lansky performance score was slightly lower in the GR group compared to the PR group ($P = 0.059$). These findings indicate that performance status, as measured by ECOG and Lansky scores, was not significantly associated with the efficacy of chemotherapy following the first relapse in these patients.

Other therapy

The GR group had a higher proportion of patients receiving Blinatumomab (23.73%) compared to the PR group (13.24%) ($\chi^2 = 4.691$, $P = 0.030$) (**Table 5**). There were no significant differences between the groups for other therapeutic modalities such as the use of Hyperfractionated Cyclophosphamide, Vincristine, Adriamycin, and Dexamethasone (Hyper-CVAD) chemotherapy, management of cytokine release syndrome (CRS) with Tocilizumab, corticosteroids, administered prophylactic antibiotics and prophylactic antivirals ($P > 0.05$). These results suggest a significant asso-

Table 4. Comparison of the ECOG performance status and Lansky performance score between two groups

Data	GR group (n = 118)	PR group (n = 136)	t/χ^2	P
ECOG performance status [n (%)]			0.026	0.987
0-1	38 (32.2%)	45 (33.09%)		
2	48 (40.68%)	55 (40.44%)		
3-5	32 (27.12%)	36 (26.47%)		
Lansky performance score	69.74 ± 10.54	72.31 ± 10.98	1.896	0.059

GR, Good Response; PR, Poor Response; ECOG, Eastern Cooperative Oncology Group.

Table 5. Comparison of other therapies between two groups

Data	GR group (n = 118)	PR group (n = 136)	χ^2	P
CD19 CART therapy				
Blinatumomab [n (%)]	28 (23.73%)	18 (13.24%)	4.691	0.030
Hyper-CVAD [n (%)]	38 (32.2%)	42 (30.88%)	0.051	0.821
Management of CRS				
Tocilizumab [n (%)]	28 (23.73%)	31 (22.79%)	0.031	0.860
Corticosteroids [n (%)]	41 (34.75%)	45 (33.09%)	0.078	0.781
Infection Prevention				
Prophylactic Antibiotics [n (%)]	55 (46.61%)	54 (39.71%)	1.229	0.268
Prophylactic Antivirals [n (%)]	57 (48.31%)	55 (40.44%)	1.585	0.208

GR, Good Response; PR, Poor Response; CD19 CART, CD19-specific chimeric antigen receptor T cell; CRS, Cytokine Release Syndrome.

ciation of Blinatumomab with better response outcomes, while other therapeutic approaches did not show significant differences between the two groups.

Correlation analysis

Both TNF-α and IL-6 levels were positively correlated with poor chemotherapy response (rho = 0.221, $P < 0.001$; rho = 0.141, $P = 0.025$) (**Figure 5**). Additionally, the presence of hypodiploidy (< 40 chromosomes) (rho = 0.134, $P = 0.033$) and the combined genetic alterations of IKZF1, NR3C1, and BTG1 (rho = 0.183, $P = 0.003$) were significantly correlated with PR. Conversely, WBC count showed a negative correlation with PR, indicating that higher WBC counts were associated with a better chemotherapy response (rho = -0.172, $P = 0.006$). The use of Blinatumomab, a CD19 CART therapy, was also negatively correlated with PR, suggesting its association with improved clinical outcome (rho = -0.136, $P = 0.030$). These findings highlight the significance of inflammatory cytokines, genetic factors, and specific therapies in influencing chemotherapy efficacy.

Univariate logistic regression analysis of the factors and chemotherapy response in pediatric B-ALL

Univariate logistic regression analysis identified several significant factors associated with poor chemotherapy response in pediatric B-ALL (**Table 6**). A higher WBC count was significantly associated with a lower likelihood of PR, with an odds ratio (OR) of 0.835 (95% CI, 0.734-0.944; $P = 0.005$), indicating a protective effect. Conversely, elevated levels of TNF-α were associated with an increased likelihood of PR (OR = 1.106; 95% CI, 1.043-1.177; $P = 0.001$). Similarly, higher IL-6 levels were also linked to poor outcome (OR = 1.014; 95% CI, 1.002-1.027; $P = 0.021$). The presence of hypodiploidy (< 40 chromosomes) showed a strong association with PR, with an OR of 3.27 (95% CI, 1.135-11.799; $P = 0.042$). Genetic alterations involving IKZF1, NR3C1, and BTG1 were significant predictors of PR (OR = 2.105; 95% CI, 1.278-3.495; $P = 0.004$). Additionally, the use of Blinatumomab, a CD19 CART therapy, was associated with a reduced risk of PR (OR = 0.490; 95% CI, 0.252-0.935; $P = 0.032$), sug-

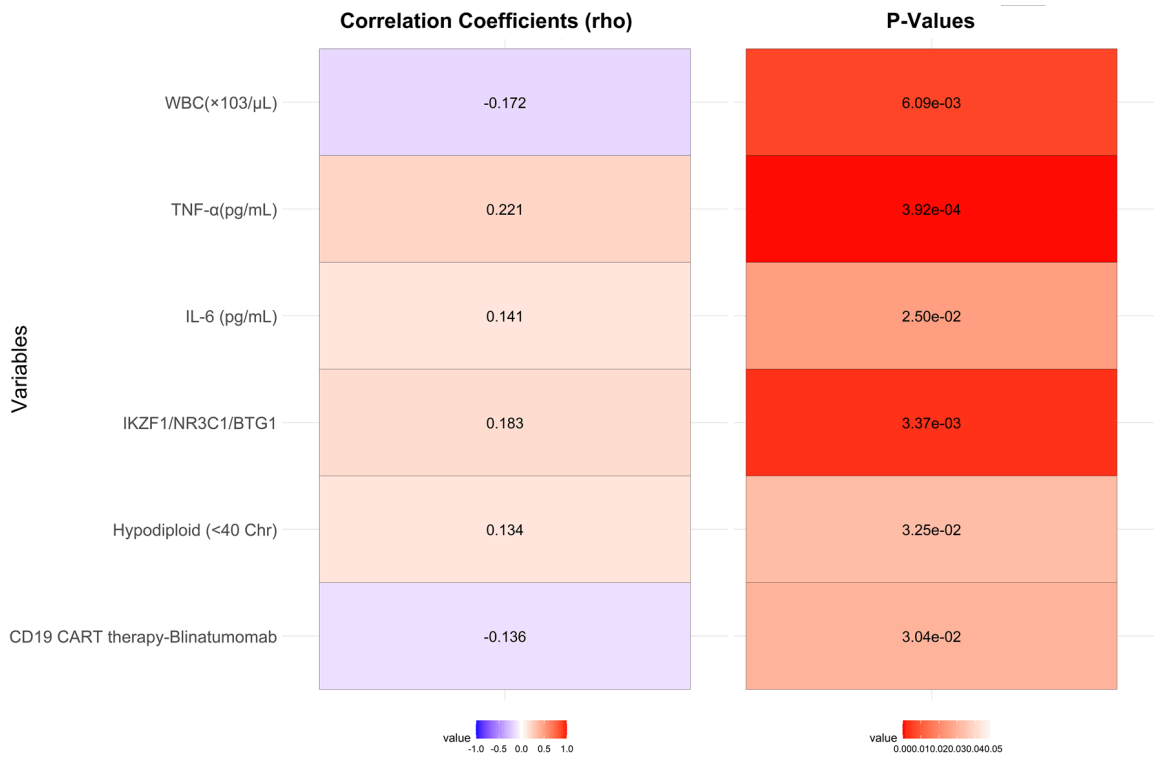

Figure 5. Correlation analysis heatmap of the factors and poor chemotherapy response in pediatric B-ALL patients. Note: B-ALL, B-cell Acute Lymphoblastic Leukemia.

Table 6. Univariate logistic regression analysis of the factors and chemotherapy response in pediatric patients with B-cell acute lymphoblastic leukemia (B-ALL)

Data	Std. Error	Wald	*P*-Value	OR	95% CI
WBC (× 10^3/μL)	0.064	2.816	0.005	0.835	0.734-0.944
TNF-α (pg/mL)	0.031	3.271	0.001	1.106	1.043-1.177
IL-6 (pg/mL)	0.006	2.302	0.021	1.014	1.002-1.027
Hypodiploid (< 40 Chr)	0.582	2.037	0.042	3.27	1.135-11.799
IKZF1/NR3C1/BTG1	0.256	2.904	0.004	2.105	1.278-3.495
CD19 CART Therapy-Blinatumomab	0.333	2.141	0.032	0.490	0.252-0.935

GR, Good Response; PR, Poor Response; WBC, White Blood Cells; TNF-α, Tumor Necrosis Factor-alpha; IL-6, Interleukin-6; IKZF1, Ikaros Family Zinc Finger 1; NR3C1, Nuclear Receptor Subfamily 3 Group C Member 1; BTG1, B-cell Translocation Gene 1; CD19 CART, CD19-specific chimeric antigen receptor T cell.

gesting its efficacy as a therapeutic intervention. These findings underscore the effect of cytokine levels, genetic factors, and targeted therapies on treatment outcome.

Multivariate logistic regression analysis of the factors and chemotherapy outcomes in pediatric B-ALL

Multivariate logistic regression analysis identified several independent factors significantly influencing chemotherapy outcomes in pediatric B-ALL following first relapse (**Table 7**). A higher WBC count was inversely correlated with PR (OR = 0.819; 95% CI, 0.717-0.937; *P* = 0.004), indicating a protective role. Elevated levels of TNF-α were positively associated with PR (OR = 1.105; 95% CI, 1.035-1.179; *P* = 0.003), as were higher IL-6 levels (OR = 1.018; 95% CI, 1.005-1.031; *P* = 0.007). Although hypodiploidy (< 40 chromosomes) was associated with poor outcome in the univariate analysis, it did not reach statistical significance in the multivariate analysis (OR = 2.622; 95% CI,

Table 7. Multivariate logistic regression analysis of the factors and chemotherapy outcomes in B-ALL

Data	Std. Error	Wald	P	OR	OR CI Lower	OR CI Upper
WBC (× 10^3/μL)	0.068	-2.918	0.004	0.819	0.717	0.937
TNF-α (pg/mL)	0.033	3.007	0.003	1.105	1.035	1.179
IL-6 (pg/mL)	0.007	2.674	0.007	1.018	1.005	1.031
Hypodiploid (< 40 Chr)	0.630	1.529	0.126	2.622	0.762	9.022
IKZF1/NR3C1/BTG1	0.277	2.675	0.007	2.097	1.219	3.607
CD19 CART Therapy-Blinatumomab	0.360	-1.511	0.131	0.580	0.286	1.176

GR, Good Response; PR, Poor Response; WBC, White Blood Cells; TNF-α, Tumor Necrosis Factor-alpha; IL-6, Interleukin-6; IKZF1, Ikaros Family Zinc Finger 1; NR3C1, Nuclear Receptor Subfamily 3 Group C Member 1; BTG1, B-cell Translocation Gene 1; CD19 CART, CD19-specific chimeric antigen receptor T cell.

0.762-9.022; P = 0.126). The concurrent genetic alterations involving IKZF1, NR3C1, and BTG1 remained a significant predictor of PR (OR = 2.097; 95% CI, 1.219-3.607; P = 0.007). The use of Blinatumomab was not significant in the multivariate model, although it showed a trend towards improving outcomes (OR = 0.580; 95% CI, 0.286-1.176; P = 0.131). These results highlight the critical influence of cytokine levels and specific genetic alterations on the efficacy of chemotherapy in this patient population.

Discussion

This study provides a comprehensive analysis of the factors influencing the efficacy of chemotherapy following the first relapse in pediatric patients with B-ALL. By examining hematologic, biochemical, and genetic data, we identified several key indicators that are associated with chemotherapy response. These findings not only highlight the complexity of the disease but also suggest potential therapeutic targets and strategies for improving treatment outcome.

The WBC count emerged as a critical measure inversely correlated with poor chemotherapy response. This suggests that a higher WBC count, often associated with better hematopoietic reserve and immune competence, might enhance the body's ability to endure and respond to intensive chemotherapy regimens. It is conceivable that patients with a higher WBC count have a more robust bone marrow reserve, enabling them to recover more effectively from the myelosuppressive effects of chemotherapy, thereby achieving a more favorable therapeutic outcome. Additionally, a higher WBC count may reflect underlying biological factors such as better mobilization and engagement of immune cells, which may help target and eliminate leukemic blasts [25, 26].

Moreover, inflammatory cytokines such as TNF-α and IL-6 were found to be significantly elevated in the PR group. TNF-α is a pro-inflammatory cytokine that can induce apoptosis in cancer cells; however, chronic elevation may promote an unfavorable microenvironment conducive to leukemic cell proliferation and survival [27, 28]. IL-6, a cytokine known for its pleiotropic effects, can promote leukemic cell growth and resistance to chemotherapy by activating signaling pathways such as the JAK/STAT3 and PI3K/AKT pathways [29, 30]. The positive correlation between these inflammatory cytokines and poor chemotherapy response suggests likely cytokine-mediated modulation of the leukemic microenvironment, which may impede chemotherapeutic efficacy. These results suggest that therapeutic targeting of these cytokines with anti-inflammatory agents may improve treatment outcome, highlighting an area for further research.

The cytogenetic analysis identified hypodiploidy as a significant feature associated with poor response in the univariate logistic regression model. Hypodiploidy, characterized by a chromosomal number less than the typical diploid number, has been associated with poor prognosis in leukemia due to its association with aggressive disease phenotypes and treatment resistance [31-33]. These observations affirm the adverse prognostic implications of hypodiploidy and underscore the need for tailored therapeutic strategies that address the genetic complexity of hypodiploid B-ALL. However, its lack of statistical significance in the multivariate analysis suggests the complexity of interactions with other genetic and environmental fac-

tors that together modulate the treatment response.

The study also highlights specific genetic alterations, particularly the combination of IKZF1, NR3C1, and BTG1 changes, as significant predictors of poor chemotherapy response. IKZF1 deletion has been implicated in compromising normal B-cell development and confers a high risk of relapse in B-ALL, potentially through impairing the regulation of genes crucial for lymphoid differentiation and survival [34, 35]. NR3C1 encodes the glucocorticoid receptor, vital for the efficacy of corticosteroid treatment in ALL, and mutations or alterations may contribute to steroid resistance [36, 37]. BTG1 is involved in cell cycle regulation and apoptosis, and its role in leukemogenesis might be linked to dysregulated cell proliferation and impaired apoptotic pathways [38]. The combination of these genetic alterations suggests a compounded negative effect, indicating that they might confer an additive or synergistic impact on leukemic cell biology, thereby reducing chemotherapy efficacy. It is critical to elucidate the molecular pathways perturbed by these genetic alterations to design targeted interventions that can circumvent the resistance mechanisms.

In contrast, the use of Blinatumomab, a bispecific T-cell engager antibody that targets CD19-positive B cells, was associated with improved responses, highlighting the potential of immunotherapy for treating relapsed B-ALL. Blinatumomab's mechanism of engaging T-cells to recognize and eliminate leukemia cells represents a promising approach that overcomes some of the resistance mechanisms inherent to conventional chemotherapy. While its significance in the multivariate analysis was not maintained, possibly due to sample size limitations or complex interactions with other variables, the observed trend affirms the promise of integrating immunotherapeutic agents into relapse management protocols. This therapy's ability to improve outcomes warrants further investigation with larger patient cohorts and exploration in combination with other targeted therapies [39-41].

The present study examined the relationship between various biological values, including blood and cytokine profiles, cytogenetic/molecular alterations, and treatment efficacy in relapsed B-ALL. The analysis of these factors provides a comprehensive understanding of the underlying mechanisms that influence chemotherapy response. Blood and cytokine profiles, such as the WBC count and levels of TNF-α and IL-6, are indicative of the patient's hematopoietic reserve and immune status. Cytogenetic and molecular alterations, such as hypodiploidy and genetic changes in IKZF1, NR3C1, and BTG1, provide insights into the genetic complexity of the disease. By integrating these measurements, we can gain a more nuanced understanding of the multifaceted nature of relapsed B-ALL and develop more effective, targeted therapy.

While our study provides valuable insight into the factors influencing chemotherapy response in relapsed B-ALL, there are several limitations that should be acknowledged. Firstly, the relatively small sample size might have constrained the ability to identify significant associations in the multivariate analysis. Secondly, since the study was conducted at a single institution, the findings may not be widely generalizable. Future studies should aim to validate these findings in larger, multicenter cohorts and explore the potential for integrating novel biomarkers and therapeutic approaches into clinical practice. Furthermore, longitudinal studies that follow patients over time could provide important information on the long-term outcome and evolution of the disease, as well as the impact of different treatment strategies. Finally, relapse itself is a relatively complex issue with considerable diversity. Incorporating a more detailed understanding of relapse patterns and the diverse treatment approaches could provide a more nuanced perspective on the factors affecting chemotherapy response. Longitudinal studies that follow patients over time and incorporate detailed clinical and molecular data would be particularly valuable.

The study underscores the need for a holistic approach to treatment, emphasizing the interactions between various biologic parameters and their contributory roles towards the chemotherapy response. Future research should focus on integrating molecular profiling into routine clinical practice to identify high-risk

patients who may benefit from more aggressive or alternate treatment strategies. Moreover, exploring the roles of immune modulation and biologic therapeutic interventions could provide new avenues for enhancing treatment efficacy in relapsed pediatric B-ALL patients. For example, combining immunotherapy with traditional chemotherapy or targeted therapies may overcome resistance and improve long-term survival rates. Furthermore, creating predictive biomarkers from genomic, transcriptomic, and proteomic data could lead to personalized treatment plans, optimizing therapy effectiveness for each patient.

Conclusion

The diverse factors influencing chemotherapy outcomes underscore the importance of personalized medicine approaches in treating pediatric B-ALL relapse. By identifying specific biological mechanisms that contribute to poor response, these findings pave the way for developing tailored therapeutic strategies that not only target the leukemic cells more effectively but also modulate the host environment to enhance treatment success. The evolving understanding of cytokine involvement, genetic alterations, and innovative therapies such as Blinatumomab invites continuous exploration and validation in clinical trials, with the goal of improving survival and quality of life for affected children.

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Disclosure of conflict of interest

None.

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References

[1] Chang JH, Poppe MM, Hua CH, Marcus KJ and Esiashvili N. Acute lymphoblastic leukemia. Pediatr Blood Cancer 2021; 68 Suppl 2: e28371.
[2] Inaba H and Mullighan CG. Pediatric acute lymphoblastic leukemia. Haematologica 2020; 105: 2524-2539.
[3] Malard F and Mohty M. Acute lymphoblastic leukaemia. Lancet 2020; 395: 1146-1162.
[4] Jędraszek K, Malczewska M, Parysek-Wójcik K and Lejman M. Resistance mechanisms in pediatric B-cell acute lymphoblastic leukemia. Int J Mol Sci 2022; 23: 3067.
[5] Panuciak K, Nowicka E, Mastalerczyk A, Zawitkowska J, Niedźwiecki M and Lejman M. Overview on aneuploidy in childhood B-cell acute lymphoblastic leukemia. Int J Mol Sci 2023; 24: 8764.
[6] Yasuda T, Sanada M, Tsuzuki S and Hayakawa F. Oncogenic lesions and molecular subtypes in adults with B-cell acute lymphoblastic leukemia. Cancer Sci 2023; 114: 8-15.
[7] Gregory S. Adult acute lymphoblastic leukemia: treatment and management updates. Semin Oncol Nurs 2019; 35: 150951.
[8] Harvey RC and Tasian SK. Clinical diagnostics and treatment strategies for Philadelphia chromosome-like acute lymphoblastic leukemia. Blood Adv 2020; 4: 218-228.
[9] Hunger SP and Raetz EA. How I treat relapsed acute lymphoblastic leukemia in the pediatric population. Blood 2020; 136: 1803-1812.
[10] Rafei H, Kantarjian HM and Jabbour EJ. Recent advances in the treatment of acute lymphoblastic leukemia. Leuk Lymphoma 2019; 60: 2606-2621.
[11] Kantarjian HM, Logan AC, Zaman F, Gökbuget N, Bargou RC, Zeng Y, Zugmaier G and Locatelli F. Survival outcomes in patients with relapsed/refractory or MRD-positive B-cell acute lymphoblastic leukemia treated with blinatumomab. Ther Adv Hematol 2023; 14: 20406207231201454.
[12] Davis K, Sheikh T and Aggarwal N. Emerging molecular subtypes and therapies in acute lymphoblastic leukemia. Semin Diagn Pathol 2023; 40: 202-215.
[13] DeAngelo DJ, Jabbour E and Advani A. Recent advances in managing acute lymphoblastic leukemia. Am Soc Clin Oncol Educ Book 2020; 40: 330-342.
[14] Śliwa-Tytko P, Kaczmarska A, Lejman M and Zawitkowska J. Neurotoxicity associated with

treatment of acute lymphoblastic leukemia chemotherapy and immunotherapy. Int J Mol Sci 2022; 23: 5515.
[15] Pui CH. Precision medicine in acute lymphoblastic leukemia. Front Med 2020; 14: 689-700.
[16] Winick N, Martin PL, Devidas M, Shuster J, Borowitz MJ, Paul Bowman W, Larsen E, Pullen J, Carroll A, Willman C, Hunger SP, Carroll WL and Camitta BM. Randomized assessment of delayed intensification and two methods for parenteral methotrexate delivery in childhood B-ALL: Children's Oncology Group Studies P9904 and P9905. Leukemia 2020; 34: 1006-1016.
[17] Esmeray E and Küçük C. Genetic alterations in B cell lymphoma subtypes as potential biomarkers for noninvasive diagnosis, prognosis, therapy, and disease monitoring. Turk J Biol 2020; 44: 1-14.
[18] Shetty D, Amare PK, Mohanty P, Talker E, Chaubal K, Jain H, Tembhare P, Patkar N, Chaturvedi A, Subramanian PG, Moulik N, Dhamne C, Jain H, Bagal B, Narula G, Sengar M, Khattry N and Banavali S. Investigating the clinical, hematological and cytogenetic profile of endoreduplicated hypodiploids in BCP-ALL. Blood Cells Mol Dis 2020; 85: 102465.
[19] Broto GE, Silva PRB, Trigo FC, Victorino VJ, Bonifácio KL, Pavanelli WR, Tomiotto-Pelissier F, Garbim MR, Oliveira ST, Jumes JJ, Panis C and Barbosa DS. Impact of the induction phase chemotherapy on cytokines and oxidative markers in peripheral and bone marrow plasma of children with acute lymphocytic leukemia. Curr Res Immunol 2021; 2: 163-168.
[20] O'Reilly R, Pui CH, Kernan N, Sallan S, Sanders J, Steinherz P, Wharam M and Zipf T. NCCN pediatric acute lymphoblastic leukemia practice guidelines. The National Comprehensive Cancer Network. Oncology (Williston Park) 1996; 10: 1787-1794.
[21] Locatelli F, Schrappe M, Bernardo ME and Rutella S. How I treat relapsed childhood acute lymphoblastic leukemia. Blood 2012; 120: 2807-2816.
[22] Biondi A, Valsecchi MG, Seriu T, D'Aniello E, Willemse MJ, Fasching K, Pannunzio A, Gadner H, Schrappe M, Kamps WA, Bartram CR, van Dongen JJ and Panzer-Grümayer ER. Molecular detection of minimal residual disease is a strong predictive factor of relapse in childhood B-lineage acute lymphoblastic leukemia with medium risk features. A case control study of the International BFM study group. Leukemia 2000; 14: 1939-1943.
[23] Neeman E, Gresham G, Ovasapians N, Hendifar A, Tuli R, Figlin R and Shinde A. Comparing Physician and Nurse Eastern Cooperative Oncology Group Performance Status (ECOG-PS) ratings as predictors of clinical outcomes in patients with cancer. Oncologist 2019; 24: e1460-e1466.
[24] Lansky SB, List MA, Lansky LL, Ritter-Sterr C and Miller DR. The measurement of performance in childhood cancer patients. Cancer 1987; 60: 1651-1656.
[25] Zhang R, Zhu H, Yuan Y, Zhao J, Yang X and Tian Z. Risk factors for relapse of childhood B cell acute lymphoblastic leukemia. Med Sci Monit 2020; 26: e923271.
[26] Li Y, Gong XY, Zhao XL, Wei H, Wang Y, Lin D, Zhou CL, Liu BC, Wang HJ, Li CW, Li QH, Gong BF, Liu YT, Wei SN, Zhang GJ, Mi YC, Wang JX and Liu KQ. Rituximab combined with short-course and intensive regimen for Burkitt leukemia: efficacy and safety analysis. Zhonghua Xue Ye Xue Za Zhi 2020; 41: 502-505.
[27] Agarwal P, Li H, Choi K, Hueneman K, He J, Welner RS, Starczynowski DT and Bhatia R. TNF-α-induced alterations in stromal progenitors enhance leukemic stem cell growth via CXCR2 signaling. Cell Rep 2021; 36: 109386.
[28] Ávila Ávila A, Nuantang K, Oliveira ML, Druillennec S, Zaniboni B, Lengliné E, Asnafi V, Ghysdael J and Tran Quang C. Targeting the TNF/IAP pathway synergizes with anti-CD3 immunotherapy in T-cell acute lymphoblastic leukemia. Blood 2024; 143: 2166-2177.
[29] Bella YF, Oliveira CR, Mateus-Silva JR, Brandao-Rangel MAR, Silva-Reis A, Santos JMB, Albertini R, Lopes-Martins RAB, de Oliveira LVF and Vieira RP. A phytotherapic blend immunity-6™ inhibits myeloid leukemic cells 2 activation involving purinergic signaling. Biomed Pharmacother 2023; 159: 114263.
[30] Mei Y, Ren K, Liu Y, Ma A, Xia Z, Han X, Li E, Tariq H, Bao H, Xie X, Zou C, Zhang D, Li Z, Dong L, Verma A, Lu X, Abaza Y, Altman JK, Sukhanova M, Yang J and Ji P. Bone marrow-confined IL-6 signaling mediates the progression of myelodysplastic syndromes to acute myeloid leukemia. J Clin Invest 2022; 132: e152673.
[31] Hammer ASB, Juul-Dam KL, Sandahl JD, Abrahamsson J, Czogala M, Delabesse E, Haltrich I, Jahnukainen K, Kolb EA, Kovács G, Leverger G, Locatelli F, Masetti R, Noren-Nyström U, Raimondi SC, Rasche M, Reinhardt D, Taki T, Tomizawa D, Zeller B, Hasle H and Kjeldsen E. Hypodiploidy has unfavorable impact on survival in pediatric acute myeloid leukemia: an I-BFM Study Group collaboration. Blood Adv 2023; 7: 1045-1055.
[32] Molina O, Bataller A, Thampi N, Ribera J, Granada I, Velasco P, Fuster JL and Menéndez P. Near-haploidy and low-hypodiploidy in B-cell acute lymphoblastic leukemia: when less is too much. Cancers (Basel) 2021; 14: 32.

[33] Yeh W and Tirado C. Hypodiploidy in AML. J Assoc Genet Technol 2021; 47: 122-126.
[34] Lopes BA, Meyer C, Bouzada H, Külp M, Maciel ALT, Larghero P, Barbosa TC, Poubel CP, Barbieri C, Venn NC, Pozza LD, Barbaric D, Palmi C, Fazio G, Saitta C, Aguiar TF, Lins MM, Ikoma-Colturato MRV, Schramm M, Chapchap E, Cazzaniga G, Sutton R, Marschalek R and Emerenciano M. The recombinome of IKZF1 deletions in B-cell precursor ALL. Leukemia 2023; 37: 1727-1731.
[35] Paolino J, Tsai HK, Harris MH and Pikman Y. IKZF1 alterations and therapeutic targeting in B-cell acute lymphoblastic leukemia. Biomedicines 2024; 12: 89.
[36] Lopez-Millan B, Rubio-Gayarre A, Vinyoles M, Trincado JL, Fraga MF, Fernandez-Fuentes N, Guerrero-Murillo M, Martinez A, Velasco-Hernandez T, Falgàs A, Panisello C, Valcarcel G, Sardina JL, López-Martí P, Javierre BM, Del Valle-Pérez B, García de Herreros A, Locatelli F, Pieters R, Bardini M, Cazzaniga G, Rodríguez-Manzaneque JC, Hanewald T, Marschalek R, Milne TA, Stam RW, Tejedor JR, Menendez P and Bueno C. NG2 is a target gene of MLL-AF4 and underlies glucocorticoid resistance in MLLr B-ALL by regulating NR3C1 expression. Blood 2024; 144: 2002-2017.
[37] Wu T, Shao Y, Li X, Wu T, Yu L, Liang J, Zhang Y, Wang J, Sun T, Zhu Y, Chang X, Wang S, Chen F and Han X. NR3C1/Glucocorticoid receptor activation promotes pancreatic β-cell autophagy overload in response to glucolipotoxicity. Autophagy 2023; 19: 2538-2557.
[38] de Albuquerque A, Lopes BA, Fernandes RA, Gimba ERP and Emerenciano M. IKZF1 and BTG1 silencing reduces glucocorticoid response in B-cell precursor acute leukemia cell line. Hematol Transfus Cell Ther 2024; 46 Suppl 6: S163-S170.
[39] He RR, Nayer Z, Hogan M, Cuevo RS, Woodward K, Heyer D, Curtis CA and Peterson JF. Immunotherapy- (Blinatumomab-) related lineage switch of KMT2A/AFF1 rearranged B-lymphoblastic leukemia into acute myeloid leukemia/myeloid sarcoma and subsequently into B/myeloid mixed phenotype acute leukemia. Case Rep Hematol 2019; 2019: 7394619.
[40] Brown P, Zugmaier G, Gore L, Tuglus CA and von Stackelberg A. Day 15 bone marrow minimal residual disease predicts response to blinatumomab in relapsed/refractory paediatric B-ALL. Br J Haematol 2020; 188: e36-e39.
[41] Apel A, Ofran Y, Wolach O, Shimony S, Ram R, Levi I, Zektser M and Koren-Michowitz M. Safety and efficacy of blinatumomab: a real world data. Ann Hematol 2020; 99: 835-838.