Allogeneic haematopoietic stem cell transplantation might overcome the poor prognosis of adult T-lineage acute lymphoblastic leukaemia with CDKN2 deletion

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Article

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Abstract

The clinical significance of cyclin-dependent kinase inhibitor 2 (CDKN2) deletion in adult T-lineage acute lymphoblastic leukemia (T-ALL) is still a matter of debate. This study aimed to investigate the prognostic value of CDKN2 deletion and impact of allogeneic hematopoietic stem cell transplantation (allo-HSCT) in adult T-ALL. A total of 241 T-ALL patients were enrolled in this single-center retrospective study: 57 with CDKN2 deletion and 184 with CDKN2 wild-type (WT). CDKN2 deletion was associated with a higher white blood cell (WBC) count (P = 0.013), a greater proportion of high-risk disease (P = 0.004), and a complex karyotype (P = 0.004) than CDKN2 WT. The 5-year cumulative incidence of relapse (CIR) was 30.9% (95% CI 17.5-45.3) and 17.5% (95% CI 11.2-25.1) (P = 0.004), disease-free survival (DFS) was 39.7% (95% CI 25.6-53.4) and 53.8% (95% CI 45.1-61.7) (P = 0.002), and overall survival (OS) was 36.8% (95% CI 23.2-50.5) and 58.2% (95% CI 49.1-66.2) (P < 0.001) in patients with CDKN2 deletion and CDKN2 WT, respectively. In the multivariable analysis of the entire population, CDKN2 deletion was found to be an independent adverse prognostic factor for CIR (HR 2.79 (95% CI 1.3-6), P = 0.009), DFS (HR 1.76 (95% CI 1.1-2.79), P = 0.018), and OS (HR 1.91 (95% CI 1.19-3.07), P = 0.008). In the CDKN2 deletion subgroup, the 5-year CIR was
15.8% (95% CI 4.8-32.6) and 53.9% (95% CI 26.3-75.1) (P = 0.005), DFS was 51.8% (95% CI 30.9-69.1) and 21.1% (95% CI 7.2-39.8) (P < 0.001), and OS was 51.2% (95% CI 30.4-68.7) and 17.4% (95% CI 4.8-36.5) (P < 0.001) in patients with and without allo-HSCT, respectively.

**Conclusion**: CDKN2 deletion is associated with poor prognosis in adult patients with T-ALL. Patients with T-ALL and CDKN2 deletions may benefit from allo-HSCT.

**Keywords**: CDKN2 deletion, prognosis, T-lineage acute lymphoblastic leukaemia, allo-SCT

**Background**

Recently, significant advancements have improved the therapeutic response and long-term survival of patients with acute B-lineage lymphoblastic leukemia (B-ALL). These improvements are attributed to better risk assessment, application of pediatric chemotherapy protocols, and personalized treatment strategies [1, 2]. In contrast, adult T-lineage acute lymphoblastic leukemia (T-ALL) still presents a challenging prognosis because of the absence of consistent risk assessments and suitable treatment approaches [3-5]. Consequently, it is imperative to identify reliable biomarkers for the accurate risk assessment and customization of treatment plans for adult patients with T-ALL.

Deletion of cyclin-dependent kinase inhibitor 2 (CDKN2) is common in various lymphoid malignancies. It is reported to have a prevalence of 24-49% in adult B-ALL [6-9] and 23-55% in T-ALL [10-13]. Emerging evidence indicates that CDKN2 deletion is an adverse prognostic marker in adult B-ALL, and the utilization of pediatric chemotherapy and allogeneic hematopoietic stem cell transplantation (allo-HSCT) has yielded more favorable outcomes [8, 9, 14-17]. However, the prognostic significance of CDKN2 deletion in adult T-ALL remains contentious [3, 11, 18, 19]. While some studies have suggested a favorable prognosis for adult T-ALL patients with CDKN2 deletion, a recent study indicated that such patients have a poor prognosis and that allo-HSCT may ameliorate this negative impact. Nevertheless, it is worth noting that the latter study included a relatively small cohort of patients with CDKN2 deletion (n=23), with
only six patients undergoing allo-SCT. Consequently, further investigation is required to fully understand the clinical implications of CDKN2 deletion and the effects of different treatments on prognosis. In this retrospective analysis, we examined a larger cohort of 241 adult patients with T-ALL from our center and assessed their clinical characteristics, treatments, and prognoses. Our findings support the notion that CDKN2 deletion serves as an unfavorable prognostic factor. However, allo-HSCT may mitigate the adverse prognostic impact of CDKN2 deletion in patients with T-ALL.

2. Methods

2.1 Patients and data collection

This retrospective analysis included patients with T-ALL treated at the Nanfang Hospital, Southern Medical University, from January 2010 to December 2021. The diagnosis and risk stratification of T-ALL adhered to the WHO criteria[20], and patients who met the following criteria were eligible: 1) age 14 years or older, and 2) received more than one round of chemotherapy, including induction and consolidation chemotherapy. This study followed the ethical principles outlined in the Declaration of Helsinki and was approved by the Institutional Review Board of Nanfang Hospital. Patient medical records were comprehensively documented, including sex, age, white blood cell (WBC) count at onset, immune phenotype, cytogenetics, minimal residual disease(MRD) monitoring, treatment-related parameters, and survival outcomes.

2.2 Therapeutic protocol

Prior to January 2016, the primary treatment for adults consisted of chemotherapy regimens, including VDLP (vincristine, daunorubicin, idarubicin, L-asparaginase, and prednisone) administered for 1-2 cycles as induction therapy. Subsequently, consolidation regimens of hyper-CVAD-A (cyclophosphamide, vincristine, daunorubicin, and dexamethasone) and hyper-CVAD-B (high-dose methotrexate and cytarabine) were alternated for–2-4 cycles[21]. Starting in February 2016, patients newly diagnosed with T-ALL were treated with a pediatric-type chemotherapy regimen known as PDT-ALL-2016 (Supplemental Table 1). This
protocol is based on pegasparagase and antimetabolic drugs\textsuperscript{[22]}. Adult treatment protocols were also applied to patients who previously received treatment at other medical facilities.

**Supplemental Table 1: PDT-ALL-LBL Treatment Protocol**

<table>
<thead>
<tr>
<th>Element</th>
<th>Drug</th>
<th>Dose</th>
<th>Given Day(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VICLD</td>
<td>Vincristine/VCR</td>
<td>1.4 mg/m\textsuperscript{2}</td>
<td>day 1, 8, 15, 22</td>
</tr>
<tr>
<td></td>
<td>Idarubicin/IDA</td>
<td>10 mg/m\textsuperscript{2}</td>
<td>day 1, 8</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide/CTX</td>
<td>1 g/m\textsuperscript{2}</td>
<td>day 1</td>
</tr>
<tr>
<td></td>
<td>Pegasparagase/PEG-asp</td>
<td>2000 IU/m\textsuperscript{2}</td>
<td>day 1, 15</td>
</tr>
<tr>
<td></td>
<td>Dexamethasone</td>
<td>0.15 mg/m\textsuperscript{2}</td>
<td>day 1 - 24</td>
</tr>
<tr>
<td></td>
<td>Chidamide</td>
<td>10 mg</td>
<td>day 1 - 24</td>
</tr>
</tbody>
</table>

2.3 Transplantation

In accordance with our guidelines, once a patient achieved a complete response (CR), they underwent 2-4 cycles of consolidation chemotherapy, and the decision to proceed with allo-HSCT was determined based on the patient's preferences and donor availability\textsuperscript{[23]}. Patients in CR received a myeloablative conditioning regimen consisting of total body irradiation (TBI, 4.5 Gy/day, administered for 5 and 4 days), cyclophosphamide (CY, 60 mg/kg on days 1, 3, and 2 prior to transplantation), and etoposide (VP-16, 15 mg/kg on days 1, 3, and 2 prior to transplantation). For patients not in remission (NR), an intensified conditioning regimen was applied that included fludarabine (Flu, 35 mg/m\textsuperscript{2} on day 1, from 10 days prior to 6 days prior to transplantation), cytarabine (Ara-c, 1 g/m\textsuperscript{2}, on day 1, from 10 days before to 6 days prior to transplantation), TBI (4.5 Gy/day, administered for 5 and 4 days), CY (60 mg/kg on days 1, 3 days prior to transplantation, and 2 days prior to transplantation), and VP-16 (15 mg/kg on days 1, 3, and 2 days prior to transplantation)\textsuperscript{[24]}. Graft-versus-host disease (GVHD) prophylaxis for recipients with an HLA-matched sibling donor (MSD) comprises Cyclosporine A (CsA) and methotrexate (MTX). Patients undergoing haploidentical donor transplantation and those with unrelated donors were provided GVHD prophylaxis through Cyclosporin A (CsA), CsA, MTX, mycophenolate, and anti-thymocyte globulin\textsuperscript{[25-27]}. 


2.4 MRD

Minimal residual disease (MRD) was evaluated using multiparameter flow cytometry with eight colors (MFC). Identification involved the use of a panel of antibody combinations, including cytoplasmic CD3, surface CD3, CD4, CD5, CD7, CD8, CD10, CD34, CD45, CD56, CD99, and terminal deoxynucleotidyl transferase (TdT). MRD is characterized by the presence of clusters of cells with leukemia-associated immunophenotypes (LAIPs) or cells displaying an abnormal pattern of antigen expression, deviating from the norm during the senescence phase of specific cells in a normal or regenerative bone marrow environment. After one cycle of induction chemotherapy, a test value on day 21 or 28 exceeding 0.01% was considered MRD positive (referred to as MRD1-positive). A pre-transplant test value equal to or greater than 0.01% was deemed MRD-positive.

2.5 Fluorescence in situ hybridization (FISH)

Interphase fluorescence in situ hybridization (I-FISH) was employed to detect various genetic aberrations, including CDKN2 (covering a 193 kDa region of 9q21.3, extending from the 105 kDa telomere of the p16 gene to the 46 kDa centromere of CDKN2B), BCR/ABL, E2A/PBX1, TEL/AML1, MLL rearrangement, MYC (8q24.21) translocation, IGH (14q32) translocation, and hyperdiploidy (chromosomes 4, 10, and 17 regions) in the bone marrow cells of all patients. The results were analyzed according to the ISCN (2005) criteria. Two green-labeled chromosome 9 probes and two red-labeled CDKN2 probe kits (catalog no. LH009; Cytocell, Cambridge, UK) according to the manufacturer's protocol. The samples were initially treated with the pretreatment solution and incubated at 110°C for 1 min. Subsequently, the samples were digested with pepsin for 10 minutes at 37°C. The probes were denatured at 95°C for 5 min before hybridization. The slides were then allowed to hybridize at 37°C for 48 h and were stained with DAPI. FISH results identified deletions in CDKN2 and other genetic anomalies.

2.6 Definition and Statistical analysis

CR was defined as the presence of < 5% blasts in the bone marrow, absence of leukemia cells in the peripheral blood, and absence of extraordinary manifestations of
leukemia. NR was defined as > 20% blasts in the bone marrow. Relapse was characterized by the reappearance of leukemia cells in the peripheral blood or the presence of > 5% blasts in the bone marrow following the initial CR. Disease-free survival (DFS) was calculated as the duration from CR attainment to relapse or death, whereas overall survival (OS) was measured from the time of diagnosis to death from any cause. Categorical variables were analyzed for differences between groups using the chi-square test, whereas continuous variables were compared using either the Student's t-test or a nonparametric test. OS and DFS were evaluated using the Kaplan-Meier method with SPSS software (version 25.0; SPSS Inc., Chicago, IL, USA). The cumulative incidence of relapse (CIR) was calculated using the Gray (R) method, considering each event as a competing risk, and hazard ratios (HRs) with their corresponding 95% confidence intervals (CIs) were determined. Data analysis was conducted using R software (version 4.1.1 (R Development Core Team, Vienna, Austria). Variables with a significance level of $P \leq 0.1$ in univariate survival analysis were included in the multivariate analysis and assessed using the Cox regression model. Statistical significance was established at a two-sided $P$-value of less than 0.05.

3. Results

3.1 Basic characteristics

A total of 272 consecutive patients with newly diagnosed T-ALL were identified, ultimately resulting in the enrollment of 241 T-ALL patients for this study (refer to Fig. 1). The median age of the patients was 24 years (range: 14–63 years). Among them, 57 patients had CDKN2 deletions, whereas 184 had CDKN2 wild-type (WT) status. The baseline characteristics of the patients are summarized in Table 1. Patients with CDKN2 deletion demonstrated higher white blood cell (WBC) counts ($\geq 100 \times 10^9/L$) ($P = 0.013$), a greater proportion of complex karyotypes ($P = 0.004$), a higher prevalence of high-risk stratification ($P = 0.004$), and a larger percentage of non-early T-cell precursor (non-ETP) subtypes ($P = 0.038$) than those with CDKN2 WT. There were no significant differences in other variables, such as sex and age, between
CDKN2 deletion and CDKN2 WT.

Additional FISH abnormalities are summarized in Supplemental Table 2, revealing significantly higher rates of MYC translocation, MLL rearrangement, and E2A/PBX1 cytogenetic abnormalities in CDKN2 deletion patients.

<table>
<thead>
<tr>
<th>Table 1 Characteristics of T-ALL Patients</th>
<th>CDKN2 DEL (n=57)</th>
<th>CDKN2 WT (n=184)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>0.393</td>
</tr>
<tr>
<td>Female</td>
<td>14 (24.6%)</td>
<td>56 (30.4%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>43 (75.4%)</td>
<td>128 (69.6%)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td>0.996</td>
</tr>
<tr>
<td>14-35y</td>
<td>48 (84.2%)</td>
<td>155 (84.2%)</td>
<td></td>
</tr>
<tr>
<td>&gt;35y</td>
<td>9 (15.8%)</td>
<td>29 (15.8%)</td>
<td></td>
</tr>
<tr>
<td>Subtype</td>
<td></td>
<td></td>
<td>0.038</td>
</tr>
<tr>
<td>Non-ETP</td>
<td>33 (80.5%)</td>
<td>91 (63.2%)</td>
<td></td>
</tr>
<tr>
<td>ETP</td>
<td>8 (19.5%)</td>
<td>53 (36.8%)</td>
<td></td>
</tr>
<tr>
<td>WBC count</td>
<td></td>
<td></td>
<td>0.013</td>
</tr>
<tr>
<td>&lt;100×10⁹/L</td>
<td>36 (63.2%)</td>
<td>146 (79.3%)</td>
<td></td>
</tr>
<tr>
<td>≥100×10⁹/L</td>
<td>21 (36.8%)</td>
<td>38 (20.7%)</td>
<td></td>
</tr>
<tr>
<td>Risk stratification</td>
<td></td>
<td></td>
<td>0.004</td>
</tr>
<tr>
<td>SR</td>
<td>19 (33.3%)</td>
<td>102 (55.4%)</td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>38 (66.7%)</td>
<td>82 (44.6%)</td>
<td></td>
</tr>
<tr>
<td>Karyotype</td>
<td></td>
<td></td>
<td>0.004</td>
</tr>
<tr>
<td>Normal</td>
<td>32 (57.1%)</td>
<td>145 (78.8%)</td>
<td></td>
</tr>
<tr>
<td>Complex</td>
<td>11 (19.6%)</td>
<td>15 (8.2%)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>13 (23.2%)</td>
<td>24 (13%)</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td>0.996</td>
</tr>
<tr>
<td>Adult-type chemotherapy</td>
<td>26 (45.6%)</td>
<td>84 (45.7%)</td>
<td></td>
</tr>
<tr>
<td>Pediatric-chemotherapy</td>
<td>31 (54.4%)</td>
<td>100 (54.3%)</td>
<td></td>
</tr>
<tr>
<td>Non-HSCT</td>
<td>26 (45.6%)</td>
<td>50 (27.2%)</td>
<td>0.009</td>
</tr>
<tr>
<td>HSCT</td>
<td>31 (54.3%)</td>
<td>134 (72.8%)</td>
<td></td>
</tr>
</tbody>
</table>

Supplemental Table 2. CDKN2 Association with Other FISH Abnormalities

<table>
<thead>
<tr>
<th></th>
<th>CDKN2 DEL (n=57)</th>
<th>CDKN2 WT (n=184)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEL/AML1</td>
<td>5 (8.8%)</td>
<td>6 (3.3%)</td>
<td>0.388</td>
</tr>
<tr>
<td>MLL rearrangement</td>
<td>7 (12.3%)</td>
<td>3 (1.6%)</td>
<td>0.000</td>
</tr>
<tr>
<td>MYC translocation</td>
<td>10 (17.5%)</td>
<td>6 (3.3%)</td>
<td>0.000</td>
</tr>
<tr>
<td>IGH rearrangement</td>
<td>6 (10.5%)</td>
<td>10 (5.4%)</td>
<td>0.177</td>
</tr>
<tr>
<td>Hyperdiploidy</td>
<td>3 (5.3%)</td>
<td>2 (1.1%)</td>
<td>0.161</td>
</tr>
<tr>
<td>E2A/PBX1</td>
<td>9 (15.8%)</td>
<td>11 (6%)</td>
<td>0.019</td>
</tr>
</tbody>
</table>
3.2 Response and Treatment

The CR rates of the 241 patients were 68.4% and 78.8% (P = 0.052) after one cycle of induction chemotherapy, and 77.2% and 89.7% (P = 0.015) after two cycles of chemotherapy in patients with CDKN2 deletion and WT, respectively. Among the 184 patients who achieved CR1 after induction, 175 had available MRD1 data, of which 103 (58.6%) were MRD-negative (MRD1 −) (consisting of 26 with CDKN2 deletion and 77 with CDKN2 WT). The MRD negativity rates after one cycle of induction chemotherapy were 48.1% and 43.7% (P = 0.57) in patients with CDKN2 deletion and WT, respectively. Relapse occurred in 45 patients (14 with CDKN2 deletion and 31 with CDKN2 WT) after CR, with an MRD1-negative relapse rate of 15.5% (16/103) (8 with CDKN2 deletion and 8 with CDKN2 WT). The MRD1-negative relapse rates were 30.8% and 10.4% (P = 0.013) in patients with CDKN2 deletion and WT, respectively (refer to Table 2).

<table>
<thead>
<tr>
<th></th>
<th>CDKN2 DEL (n=57)</th>
<th>CDKN2 WT (n=184)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CR</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR1</td>
<td>39 (68.4%)</td>
<td>145 (77.8%)</td>
<td>0.015</td>
</tr>
<tr>
<td>CR2</td>
<td>5 (8.8%)</td>
<td>20 (10.9%)</td>
<td></td>
</tr>
<tr>
<td>NR</td>
<td>13 (22.8%)</td>
<td>19 (10.3%)</td>
<td></td>
</tr>
<tr>
<td>Relapsed</td>
<td>14 (31.8%)</td>
<td>31 (18.8%)</td>
<td></td>
</tr>
<tr>
<td><strong>After 1 chemo MRD</strong></td>
<td></td>
<td></td>
<td>0.57</td>
</tr>
<tr>
<td>Negative</td>
<td>26 (48.1%)</td>
<td>77 (43.8%)</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>28 (51.9%)</td>
<td>99 (56.3%)</td>
<td></td>
</tr>
<tr>
<td>MRD-negative before HSCT</td>
<td>19 (67.9%)</td>
<td>91 (70.5%)</td>
<td>0.779</td>
</tr>
<tr>
<td>MRD1-negative Relapsed</td>
<td>8 (30.8%)</td>
<td>8 (10.4%)</td>
<td>0.013</td>
</tr>
</tbody>
</table>

In total, 165 patients underwent allogeneic hematopoietic stem cell transplantation (allo-HSCT), consisting of 31 patients with CDKN2 deletion and 134 patients with CDKN2 WT (Table 1). Among these, 110 (70.1%) were MRD-negative before allo-HSCT, 19 had CDKN2 deletions, and 91 had wild-type CDKN2 deletions.
Additionally, 14 patients who did not achieve remission underwent allo-HSCT, with 5 having CDKN2 deletion and 9 with CDKN2 WT. Among these patients, eight succumbed during follow-up (four with CDKN2 deletion and four with CDKN2 WT). Furthermore, 76 patients continued consolidation and maintenance chemotherapy (including 26 with CDKN2 deletion and 50 with CDKN2 WT), 18 patients who did not achieve remission after two cycles of chemotherapy opted for salvage chemotherapy (involving 8 with CDKN2 deletion and 10 with CDKN2 WT), and 17 patients died during the follow-up period (comprising 8 with CDKN2 deletion and 9 with CDKN2 WT) (refer to Fig. 1).

In total, 110 patients underwent adult-type chemotherapy (26 with CDKN2 deletion and 84 with wild-type CDKN2). Among these, 80 patients (72.7%) achieved CR after one cycle of chemotherapy (including 18 with CDKN2 deletion and 62 with CDKN2 WT). Additionally, 41 patients (41.4%) attained MRD negativity after one cycle of chemotherapy (comprising 10 with CDKN2 deletion and 31 with CDKN2 WT). Of the 84 patients who received adult-type chemotherapy, 76.4% (19 with CDKN2 deletion and 65 with CDKN2 WT) proceeded to undergo allo-HSCT. Among them, 47 patients (61.8%) were MRD-negative prior to allo-HSCT (involving nine with CDKN2 deletion and 38 with CDKN2 WT), and 27 patients (29.7%) experienced relapse after achieving CR (comprising nine with CDKN2 deletion and 18 with CDKN2 WT).

The remaining 131 patients were treated with pediatric-type chemotherapy regimens (including 31 patients with CDKN2 deletion and 100 with wild-type CDKN2). Of these patients, 104 (79.4%) achieved CR after one cycle of chemotherapy (comprising 21 with CDKN2 deletion and 83 with CDKN2 WT). Moreover, 62 patients (47.3%) achieved MRD negativity after one cycle of chemotherapy (16 with CDKN2 deletion and 46 with CDKN2 WT). A total of 81 patients from this cohort underwent allo-HSCT (including 12 with CDKN2 deletion and 69 with CDKN2 WT). Among these, 77.8% (comprising 10 with CDKN2 deletion and 53 with CDKN2 WT) were MRD-negative before allo-HSCT and 18 patients (15.3%) experienced relapse after achieving CR (including 5 with CDKN2
deletion and 13 with CDKN2 WT (refer to Table 3).

### Table 3 Comparison of Chemotherapy Regimens’ Efficacy

<table>
<thead>
<tr>
<th></th>
<th>CDKN2 DEL</th>
<th></th>
<th>CDKN2 WT</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Pediatric-chemo</td>
<td>Adult-type chemo</td>
<td>P</td>
<td>Pediatric-chemo</td>
</tr>
<tr>
<td>CR1*</td>
<td>21(67.7%)</td>
<td>18(69.2%)</td>
<td>0.708</td>
<td>83(83%)</td>
</tr>
<tr>
<td>CR2*</td>
<td>23(74.2%)</td>
<td>21(80.8%)</td>
<td>0.556</td>
<td>95(95%)</td>
</tr>
<tr>
<td>Relapse</td>
<td>5(21.7%)</td>
<td>9(42.9%)</td>
<td>0.133</td>
<td>11(13.3%)</td>
</tr>
<tr>
<td>MRD1-**</td>
<td>16(51.6%)</td>
<td>10(43.5%)</td>
<td>0.554</td>
<td>46(55.4%)</td>
</tr>
<tr>
<td>MRD-before HSCT</td>
<td>10(83.3%)</td>
<td>9(56.3%)</td>
<td>0.129</td>
<td>53(76.8%)</td>
</tr>
</tbody>
</table>

CR1 CR after 1 cycle, CR2 CR after 2 cycle, MRD1 minimal residual disease at the end of 1 cycle induction

### 3.3 Relapse and survival

The median follow-up duration was 69.9 months, ranging from 14.7 to 152.5 months. The 5-year cumulative relapse rates post-CR were 30.9% (95% CI 17.5-45.3) and 17.5% (95% CI 11.2-25.1) (P = 0.004), the 5-year DFS rates were 39.7% (95% CI 25.6-53.4) and 53.8% (95% CI 45.1-61.7) (P = 0.002), and the 5-year OS rates were 36.8% (95% CI 23.2-50.5) and 58.2% (95% CI 49.1-66.2) (P < 0.001) for the CDKN2 deletion and WT groups, respectively (refer to Fig. 2 A,D,G).

When performing relapse and survival analyses based on treatment modalities, the 5-year relapse rates were 32.6% (95% CI 19.5-46.4) and 16.1% (95% CI 9.9-23.6) (P = 0.001), respectively, the 5-year DFS rates were 43.1% (95% CI 30.5-55.1%) and 54.3% (95% CI, 45.3-62.5%) (P < 0.001), and the 5-year OS rates were 40.4% (95% CI 27.6-52.7%) and 59.3% (95% CI 50-67.5%) (P < 0.001) for the non-HSCT and allo-HSCT groups, respectively (refer to Fig. 2 C,F,I). Moreover, the 5-year relapse rates were 27.7% (95% CI 18.1-38) and 14.3% (95% CI 7.5-23.3) (P = 0.03), the 5-year DFS rates were 35.9% (95% CI 26.2-45.6%) and 64% (95% CI 53.1-73%) (P < 0.001), and the 5-year OS rates were 39.9% (95% CI 29.7-53.8%) and 67.5% (95% CI 56.9-76%) (P = 0.004) for the adult-type and pediatric-type chemotherapy groups, respectively (refer to Fig. 2 B, E, H).

An analysis of the results for four different treatment combinations for adult
T-ALL patients, namely pediatric chemotherapy followed by allo-HSCT, adult chemotherapy followed by allo-HSCT, pediatric chemotherapy followed by consolidation chemotherapy (non-HSCT), and adult chemotherapy followed by consolidation chemotherapy (non-HSCT), revealed that pediatric chemotherapy followed by allo-HSCT was significantly associated with higher OS in all adult T-ALL patients (Supplemental Fig. 1). In the CDKN2 deletion subgroup, pediatric chemotherapy followed by allo-HSCT was also associated with higher OS.

Multivariate Cox regression analysis demonstrated that CDKN2 deletion was significantly associated with a higher relapse rate (HR 2.79 (95% CI 1.3-6), P = 0.009), shorter OS (HR 1.91 (95% CI 1.19-3.07), P = 0.008), and shorter DFS (HR 1.76 (95% CI 1.1-2.79), P = 0.018). Furthermore, MRD1 positivity was significantly associated with higher relapse (HR 4.24 (95% CI 1.96-9.17), P < 0.001), shorter OS (HR 2.01 (95% CI 1.28-3.17), P = 0.003), and shorter DFS (HR 2.51 (95% CI 1.6-3.93), P < 0.001). Notably, pediatric chemotherapy and allo-HSCT were associated with longer OS (HR 0.39, (95% CI 0.25-0.61), P < 0.001; HR 0.33, (95% CI 0.21-0.52), P < 0.001, respectively), longer DFS (HR 0.36,(95% CI 0.23-0.54), P < 0.001; HR 0.42,(95% CI 0.27-0.65), P< 0.001, respectively), and a lower relapse rate (HR 0.27, (95% CI 0.13-0.58), P < 0.001; HR 0.3, (95% CI 0.15-0.59), P < 0.001) (refer to Table 4).
<table>
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<tr>
<th></th>
<th>OS Univariate P value</th>
<th>OS Multivariate P value (HR 95%CI)</th>
<th>DFS Univariate P value</th>
<th>DFS Multivariate P value (HR 95%CI)</th>
<th>Relapse Univariate P value</th>
<th>Relapse Multivariate P value (HR 95%CI)</th>
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<td>&lt;0.001</td>
<td>&lt;0.001 (0.42, 0.27-0.65)</td>
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<td>&lt;0.001</td>
<td>&lt;0.001 (0.36, 0.23-0.54)</td>
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<td>0.688</td>
<td>0.91 (1.06, 0.38-2.94)</td>
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3.4 Effect of therapies on outcomes of patients with CDKN2 deletion

A total of 57 patients presented with CDKN2 deletion, with a median age of 22 years (range: 14-49). Among them, 26 (45.6%) patients received adult-type chemotherapy, whereas 31 (54.4%) received pediatric-type chemotherapy regimens. The CR1 rates were 69.2% and 67.7% (P = 0.708) and the MRD1-negative rates were 62.5% and 76.2% (P = 0.367) in patients who underwent adult and pediatric-type chemotherapy, respectively. Fourteen (31.8%) patients who achieved CR later experienced relapse, with relapse rates of 42.9% and 21.7% (P = 0.133) among patients who received adult and pediatric-type chemotherapy, respectively. Of the 57 patients with CDKN2 deletion, 31 (54.4%) underwent allo-HSCT and 19 patients were MRD-negative pre-transplant. A total of 56.3% and 83.3% (P = 0.129) of the patients who received adult and pediatric-type chemotherapy, respectively, were MRD-negative before allo-HSCT (refer to Table 3). The 5-year OS rates were 53.9% (95% CI 26.3-75.1) and 15.8% (95% CI 4.8-32.6) (P = 0.005), respectively, the 5-year OS rates were 17.4% (95% CI 4.8-36.5%) and 51.2% (95% CI 30.4-68.7%) (P < 0.001), and the 5-year DFS rates were 21.1% (95% CI 7.2-39.8%) and 51.8% (95% CI 30.9-69.1%) (P < 0.001) among patients who did not receive HSCT and those who underwent allo-HSCT, respectively (refer to Fig. 3 B, D, F). In addition, the 5-year relapse rates were 22% (95% CI 7.7-40.9) and 40.8% (95% CI 18.8-61.8) (P = 0.228), 5-year OS rates were 45.5% (95% CI 26.8-62.4%) and 30.5% (95% CI 13.2-49.9%) (P = 0.957), and 5-year DFS rates were 52.4% (95% CI 32.9-68.7%) and 33.9% (95% CI 16.1-52.8%) (P = 0.266) for patients who received pediatric and adult-type chemotherapy, respectively (refer to Fig. 3 A, C, E)).

Multivariate Cox regression analysis revealed that allo-HSCT was associated with a lower relapse rate (HR 0.25, (95% CI 0.08-0.83), P = 0.024), longer DFS (HR 0.26, (95% CI 0.11-0.62), P = 0.002), and longer OS (HR 0.32, (95% CI 0.15-0.68), P = 0.003) (refer to Supplemental Table 4).
## Supplemental Table 3: Univariate and Multivariate Analysis of CDKN2 Patients' OS, DFS, and Relapse

<table>
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Discussion

Our study underscores the adverse prognostic impact of CDKN2 deletion in adult T-ALL, and suggests that allo-HSCT may mitigate the negative effects associated with CDKN2 deletion.

The prevalence of CDKN2 deletion in our cohort of adult T-ALL patients was 23.7%, a rate similar to that reported in another Chinese center\textsuperscript{[19]}. In contrast, the E2993 ECOG clinical trial reported a higher incidence, with CDKN2 deletion observed in 41.5% of adult T-ALL patients\textsuperscript{[3]}. Likewise, the Spanish PETHEMA group trial identified CDKN2 deletions in 55% of adult T-ALL cases\textsuperscript{[18]}. These disparities in CDKN2 deletion frequencies in adult patients with T-ALL may be attributed to racial differences. Our study further revealed that CDKN2 deletion was more common among non-ETP patients, constituting 80.5% of CDKN2 deletion cases. This finding aligns with the observations of Genesca et al.\textsuperscript{[31]}, who reported a frequency of 73% in non-ETP patients without ETP in the CDKN2 deletion group. Several studies have suggested a connection between CDKN2 deletion and elevated white blood cell (WBC) counts in patients, and our results corroborate this association\textsuperscript{[14, 19, 30]}. Deletion of CDKN2-related cell cycle regulators can lead to uncontrolled tumor cell proliferation\textsuperscript{[32]}, which may explain the co-occurrence of CDKN2 deletion and elevated WBC counts. Furthermore, our study revealed an increased prevalence of MYC translocation, MLL rearrangement, and E2A/PBX1 abnormalities in T-ALL cases characterized by CDKN2 deletions. The interplay between and implications of these genetic aberrations remain unclear and require further investigation.

In B-ALL patients, the presence of CDKN2 deletion is associated with poorer survival and a higher likelihood of relapse than in those with wild-type CDKN2\textsuperscript{[9, 15, 16, 33]}. It has been suggested that allo-HSCT may mitigate the adverse prognostic impact of CDKN2 deletion. However, the prognostic value of CDKN2 deletion in adult T-ALL remains debatable \textsuperscript{[3, 11, 18, 19]}. For instance, the Spanish PETHEMA Group reported that among 35 adult T-ALL patients with CDKN2A/ARF/2B and CDKN2A/ARF deletions, those with the deletion had a
deeper MRD response than the other patients (90% vs. 68%, P = 0.04). However, this improved MRD response did not translate into survival benefit. Additionally, they observed that patients with CDKN2B deletion had a more favorable 3-year OS prognosis (63% vs. 37%, P = 0.045)[18]. Conversely, Wang et al.[19] reported poor outcomes in a cohort of 23 adult T-ALL patients with CDKN2 deletion out of 101 patients. In this study, the CDKN2 deletion group exhibited comparable CR rates but lower 2-year OS (18.6% vs. 47.4%, P=0.032) than the wild-type patients. These differences in survival outcomes may be attributed to several factors, including limitations in the sample size of patients with CDKN2 deletions, potential racial disparities, and heterogeneity in treatment regimens. In line with previous findings [15, 17, 19, 34], our study, which included a larger cohort, revealed similar rates of CR1 and MRD negativity after one round of induction chemotherapy in both CDKN2 deletion and wild-type groups. However, a more in-depth analysis demonstrated that patients with CDKN2 deletions were more prone to relapse after achieving MRD1 negativity than patients with CDKN2 wild-type. This reaffirms the status of CDKN2 deletion as an independent unfavorable prognostic factor for survival and relapse in adult patients with T-ALL, which is consistent with the findings reported by Wang et al.

Chemotherapy and allo-HSCT are effective treatments for adult patients with ALL. Scientific research has established that adult T-ALL patients can benefit from allo-HSCT, particularly those at high risk, those with a poor response to chemotherapy, and those with MRD-positive results after initial treatment [10, 35-37]. In the UKALLXII/ECOG2993 trial, patients with T-ALL who underwent allo-HSCT exhibited a better 5-year OS rate (61% vs. 46%) and a lower relapse rate (25% vs. 51%) [10]. Similarly, our analysis indicates that T-ALL patients undergoing allo-HSCT achieve extended 5-year OS and DFS, along with reduced 5-year relapse rates, compared to those receiving chemotherapy alone. Recent studies have demonstrated that combining polyethylene glycol-asparaginase (PEG-ASP) with multiagent induction chemotherapy for adult T-ALL significantly enhances OS outcomes and yields a high CR rate [38, 39]. The GRAALL study revealed that adult T-ALL patients subjected to pediatric-intensive therapy achieved 3-year OS rates of 58% and 92%
CR1 rate. Our findings align with these data, suggesting that patients treated with pediatric-style regimens containing PEG-ASP experience improved 5-year OS and DFS, as well as reduced 5-year relapse rates, compared with those treated with adult-style chemotherapy. Multivariate analysis identified both allo-HSCT and pediatric-style chemotherapy as independent protective factors in adult patients with T-ALL. Wang et al. reported that among six patients with CDKN2 deletion who underwent allo-HSCT, four survived, suggesting a potential for allo-HSCT to improve prognosis, although the study included a small number of transplant recipients, and further exploration of allo-HSCT in patients with CDKN2 deletion was deemed necessary. In our study, 31 patients with CDKN2 deletion underwent allo-HSCT, and the CDKN2 deletion subgroup showed improved 5-year OS, DFS, and relapse rates compared with those who received chemotherapy alone. However, we did not observe significant differences in the 5-year OS, DFS, or relapse rates between patients receiving pediatric and adult chemotherapy regimens. Multivariate analysis identified allo-HSCT as an independent protective prognostic factor for CDKN2 deletion subgroup patients. Although there was no statistically significant difference among CDKN2 deletion patients, those treated with pediatric chemotherapy exhibited higher MRD1 and pre-transplantation MRD negativity rates and lower relapse rates than those treated with adult chemotherapy regimens. These results suggest potential benefits associated with pediatric chemotherapy regimens, which should be further validated using a larger dataset of CDKN2 deletion patients. Furthermore, our previous study indicated the potential advantages of a pediatric chemotherapy regimen for adult T-ALL patients undergoing transplantation. Expanding on this discovery, we compared the combination of pediatric chemotherapy followed by allo-HSCT with other treatment approaches, and the findings indicated a trend toward improved overall survival in both the entire T-ALL sample and CDKN2 deletion subgroup. Hence, patients with CDKN2 deletions may benefit from allo-HSCT following pediatric chemotherapy. This study is the first attempt to directly compare the survival outcomes of patients with T-ALL with CDKN2 deletions treated with different regimens. Further research with a larger sample size is required to ascertain
the effectiveness of the combined approach.

This study has several limitations. First, this was a retrospective, single-center analysis with a relatively small sample size, particularly within the CDKN2 subgroup. Second, we did not analyze the prognosis of CDKN2 deletion in conjunction with different genetic abnormalities or the impact of various treatment modalities on the prognosis of this combined set of abnormalities.

Overall, CDKN2 deletion is an adverse independent prognostic factor for adult T-ALL; however, allo-HSCT may offer a means to mitigate this negative impact.

Authors’ contributions
XSH wrote the initial manuscript, ZXW designed tables and figures and YTQ performed the MRD analysis. QFL and SJY designed the initial outline, contributed to the writing, and finalized the manuscript. All authors have read and approved the final manuscript.

Xiaoshan Hu: Conceptualization, Methodology, Formal analysis, Writing-original draft. Zhixiang Wang: Methodology and Formal Analysis. Yuting Qin: Formal analysis. Jun Xu, Na Xu, Qiang Wang, Ren Lin, Ke Zhao, Hongsheng Zhou, Li Xuan: Resources, Data Curation. Sijian Yu and Qifa Liu: Conceptualization, writing–review and editing, visualization, supervision, and funding acquisition.

ACKNOWLEDGEMENTS
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Declaration of competing interest
The authors declare no conflict of interest.

References


Figure and Table Legends

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Table 3: Comparison of Chemotherapy Regimens' Efficacy
Table 4: Univariate and Multivariate Analysis of T-ALL OS, DFS, and Relapse
Supplemental Table 1: PDT-ALL-LBL Treatment Protocol
Supplemental Table 2: CDKN2 Association with Other FISH Abnormalities
Supplemental Table 3: Univariate and Multivariate Analysis of CDKN2 Patients' OS, DFS, and Relapse

Figure:
Figure 1: Study Population Flow Diagram
Figure 2: Outcomes for CDKN2 Deletion vs. CDKN2 Wild-type: (A) 5-Year OS; (D) 5-Year DFS; (G) 5-Year Relapse. Outcomes for Paediatric-type vs. Adult-type Chemotherapy: (B) 5-Year OS; (E) 5-Year DFS; (H) 5-Year Relapse. Outcomes for Allo-HSCT vs. Non-HSCT: (C) 5-Year OS; (F) 5-Year DFS; (I) 5-Year Relapse
Figure 3: CDKN2 Deletion Subgroup Outcomes with Adult-type vs. Paediatric-type: (A) 5-Year OS; (C) 5-Year DFS; (E) 5-Year Relapse. CDKN2 Deletion Subgroup Outcomes with Non-HSCT vs. Allo-HSCT: (B) 5-Year OS; (D) 5-Year DFS; (F) 5-Year Relapse
Supplemental Figure 1: OS for Various Treatment Combinations among All Subjects
Supplemental Figure 2: OS for Various Treatment Combinations among CDKN2 Deletion Patients
T-ALL after data searching for eligible age (n=272)

eligible T-ALL patients (n=241)

reason of exclusion:
- 6 no cytogenetic data
- 7 mixed leukemia
- 6 loss of follow-up
- 12 <2 cycle of chemotherapy

CDKN2 deletion (n=57)
- CR (n=44)
  - 18 chemotherapy alone
  - 26 allo-HSCT
- NR (n=13)
  - 8 chemotherapy alone
  - 5 allo-HSCT

CDKN2 wild type (n=184)
- CR (n=165)
  - 40 chemotherapy alone
  - 125 allo-HSCT
- NR (n=19)
  - 10 chemotherapy alone
  - 9 allo-HSCT
Fig 3

A

OS

$\begin{align*}
\text{Percentage of survival} \\
0 & \quad 20 & \quad 40 & \quad 60 & \quad 80 & \quad 100 & \quad 120 \\
\text{Months} \\
\end{align*}$

$p = 0.957$

B

OS

$\begin{align*}
\text{Percentage of survival} \\
0 & \quad 20 & \quad 40 & \quad 60 & \quad 80 & \quad 100 & \quad 120 \\
\text{Months} \\
\end{align*}$

$p < 0.001$

C

DFS

$\begin{align*}
\text{Percentage of survival} \\
0 & \quad 20 & \quad 40 & \quad 60 & \quad 80 & \quad 100 & \quad 120 \\
\text{Months} \\
\end{align*}$

$p = 0.266$

D

DFS

$\begin{align*}
\text{Percentage of survival} \\
0 & \quad 20 & \quad 40 & \quad 60 & \quad 80 & \quad 100 & \quad 120 \\
\text{Months} \\
\end{align*}$

$p < 0.001$

E

Relapse

$\begin{align*}
\text{Cumulative Incidence of relapse} \\
0 & \quad 0.2 & \quad 0.4 & \quad 0.6 & \quad 0.8 & \quad 1.0 \\
\text{Months} \\
\end{align*}$

$p = 0.228$

F

Relapse

$\begin{align*}
\text{Cumulative Incidence of relapse} \\
0 & \quad 0.2 & \quad 0.4 & \quad 0.6 & \quad 0.8 & \quad 1.0 \\
\text{Months} \\
\end{align*}$

$p = 0.005$
Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementalFigure1.pdf
- SupplementalFigure2.pdf
- tableSupplemental13.pdf