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Prognostic significance and treatment strategies for *IKZF1* deletion in pediatric B-cell precursor acute lymphoblastic leukemia

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Abstract

Background The predictive importance of *IKZF1*^{del} in pediatric B-cell precursor acute lymphoblastic leukemia (BCP-ALL) has shown variability across different studies. Thus, the optimal treatment approach for children with *IKZF1*^{del} BCP-ALL remains contentious, with the ongoing debate surrounding the use of *IKZF1*^{del}-based high-risk stratification versus a minimal residual disease (MRD)-guided protocol.

Methods *IKZF1* status was reliably determined in 804 patients using multiplex ligation-dependent probe amplification (MLPA) data obtained from four hospitals in Fujian, a province of China. In the Chinese Children Leukemia Group (CCLG)-ALL 2008 cohort, *IKZF1* status was included in the risk assignment, with all *IKZF1*^{del} patients receiving a high-risk regimen. Conversely, in the Chinese Children's Cancer Group (CCCG)-ALL 2015 cohort, *IKZF1*^{del} was not incorporated into the risk assignment, and patients were treated based on an MRD-guided risk stratification protocol.

Results *IKZF1*^{del} was found in 86 patients (86/804, 10.7%) overall and in 30 (30/46, 65.2%) *BCR::ABL1*-positive patients. Overall, *IKZF1*^{del} was a poor prognostic predictor for patients, though the significance diminished upon age adjustment, white blood cell (WBC) count at diagnosis, treatment group, and MRD status. In the CCLG-ALL 2008 cohort, *IKZF1*^{del} conferred a notably lower 5-year overall survival (OS) and event-free survival (EFS) and a significantly higher 5-year cumulative incidence of relapse (CIR) than *IKZF1*^{wt}. In the CCLG-ALL 2015 cohort, *IKZF1*^{del} conferred a lower 5-year OS and EFS and a higher 5-year CIR than *IKZF1*^{wt}, but the differences were insignificant. The *IKZF1*^{del} patients treated with higher intensity chemotherapy (CCLG-ALL 2008 high-risk regimen) had a markedly lower 5-year OS and EFS compared with those treated with the MRD-guided protocol (CCCG-ALL 2015 protocol). Furthermore, patients treated with the CCLG-ALL 2008 high-risk regimen experienced a higher frequency of serious adverse events (SAEs), especially infection-related SAEs, compared with those treated with the CCCG-ALL 2015 MRD-guided protocol.

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Conclusions The prognostic effect of *IKZF1*^{del} may vary in different protocols. Compared with higher intensity chemotherapy, the MRD-guided protocol may be a more effective approach to treating BCP-ALL with *IKZF1*^{del} in children.

Keywords Pediatric B-cell precursor acute lymphoblastic leukemia, *IKZF1* deletion, Minimal residual disease-guided protocol

Background

The current cure rates of pediatric patients with B-cell precursor acute lymphoblastic leukemia (BCP-ALL) have dramatically improved to >80%, largely due to the combination of risk stratification and tailored treatment intensity guided by minimal residual disease (MRD) as an indicator of early therapeutic response [1–3]. Risk stratification in modern protocols for pediatric ALL is mainly based on cytogenetic abnormalities and fusion genes related to prognosis [4, 5]. For example, patients with high hyperdiploidy and the chromosomal translocation t(12;21)/*ETV6::RUNX1*, both linked to a positive prognosis, are typically classified as low-risk. Conversely, those with low hypodiploidy, t(9;22)/*BCR::ABL1*, and *KMT2A* rearrangements, which are correlated with an unfavorable prognosis, are generally classified as high-risk. In addition to classifying lesions that define the genetic groups of BCP-ALL, recent studies have identified copy number variations or mutations in genes implicated in the development of B-lymphocytes, such as *IKZF1*, *PAX5*, *EBF1*, *ETV6*, and *BTG1*, that may be associated with relapse in BCP-ALL [6, 7].

IKZF1 codes for the transcription factor IKAROS, which is essential in the development of all lymphoid lineages [8]. Deletions of the *IKZF1* gene (*IKZF1*^{del}) are present in approximately 15% of pediatric ALL cases [9]. This frequency is notably elevated in *BCR::ABL1*-positive (~70%) and *BCR::ABL1*-like (~40%) pediatric BCP-ALL [10]. The presence of *IKZF1*^{del} has been linked to specific risk features, including older age at diagnosis, higher initial white blood cell (WBC) counts, and elevated levels of MRD following induction and consolidation therapy [11].

Over the last 15 years, numerous studies have investigated the prognostic implications of *IKZF1*^{del} in pediatric ALL treated with different protocols. Several studies have demonstrated that *IKZF1*^{del} represents an independent risk factor, even after considering both risk stratification and MRD status [11–18]. Considering its adverse prognostic significance, *IKZF1*^{del} cases have been classified as high-risk and received higher intensity chemotherapy in several trials, including the European Organisation for Research and Treatment of Cancer (EORTC) Children's Leukemia Group study 58,951 [14], Berlin–Frankfurt–Münster (BFM) 95 protocol [19], Dutch Childhood Oncology Group (DCOG) ALL10 protocol [20], and Malaysia-Singapore ALL 2010 study [21]. However, some studies indicated that the prognostic impact of *IKZF1*^{del} alone was not sufficiently robust and that the best predictor of treatment failure in pediatric BCP-ALL is the combination of *IKZF1*^{del} and MRD status [22–26]. Consequently, employing *IKZF1*^{del} for high-risk treatment-stratification strategies could result in inappropriate over-treatment and unnecessary exposure to the toxic side effects of high-risk therapy for a substantial number of patients. Therefore, the two treatment strategies for children with *IKZF1*^{del} BCP-ALL, *IKZF1*^{del}-based high-risk stratification or the MRD-guided protocol, remain debatable. Here, we analyzed the data of 86 children with *IKZF1*^{del} BCP-ALL who underwent a high-risk treatment-stratification strategy based on *IKZF1* status or were treated with the MRD-guided protocol, irrespective of *IKZF1* status, to compare the efficacies of the *IKZF1*^{del} BCP-ALL treatment regimens.

Methods

Patients

From December 2015 to December 2020, 998 children aged<14 years were newly diagnosed with ALL at four hospitals in Fujian, China. All patients enrolled in this study had access to Morphology, Immunology, Cytogenetics, and Molecular Biology (MICM) analyses. Karyotyping was analyzed using chromosome banding methods, and translocations/oncogene fusion screening for rearrangements of common fusion transcripts t(12;21)/*ETV6::RUNX1*, t(1;19)/*TCF3::PBX1*, t(9;22)/*BCR::ABL1*, and 11q23/*KMT2A* were conducted using fluorescence in situ hybridization (FISH) and reverse transcription polymerase chain reaction (RT-PCR). The diagnosis of ALL was based on the 2016 revision of the World Health Organization classification of lymphoid neoplasms [27]. Among the 998 cases, 904 patients had BCP-ALL. Parents or legal guardians provided informed consent prior to enrolling in the study, following the principles outlined in the Declaration of Helsinki. The protocol received approval from the Ethics Committee of Fujian Medical University Union Hospital .

Multiplex ligation-dependent probe amplification (MLPA)

For the detection of deletions in the *IKZF1* gene, the multiplex ligation-dependent probe amplification (MLPA) assay was conducted using the SALSA kits P335 and P202 (MRC-Holland, Amsterdam, Netherlands). The P335 probe mixture is designed specifically to target the *IKZF1* gene and includes a distinct probe for

each of the eight exons within the gene: exon 1, exon 2, exon 3, exon 4, exon 5, exon 6, exon 7, and exon 8. Each probe in the P335 kit binds to a specific exon, allowing for precise detection of deletions across the entire *IKZF1* gene. Additionally, to ensure the accuracy of the deletion detection, deletions identified by any single probe in the P335 kit were further verified using the P202 kit. The P202 kit contains additional probes for the *IKZF1* gene, allowing for confirmation of the deletions detected by the P335 kit. This dual-kit verification process helps to minimize false positives and ensures robust detection of gene deletions.

Furthermore, the MLPA results were analyzed using Coffalyser. Net software (MRC-Holland, Amsterdam, Netherlands). The analysis was performed using the software's default settings, which include normalization of the probe signals to reference probes and comparison of normalized probe signals to a set of control samples. A specific threshold was set for detecting deletions, with a value of ≤0.7 indicating a deletion. Based on the MLPA analysis, the *IKZF1* gene status was classified into two categories: deleted (*IKZF1*^{del}), if any exon of the *IKZF1* gene was detected as deleted according to the set threshold, and wild type (*IKZF1*^{wt}), if no deletions were detected in any of the exons of the *IKZF1* gene. Among the 904 patients with BCP-ALL, reliable *IKZF1* status was determined for 804 patients (88.9%) with available MLPA data (Fig. 1). The presenting characteristics of patients with determined *IKZF1* status were comparable to those of all 904 patients with BCP-ALL (Supplementary Table S1). The distribution of enrolled patients across the four hospitals is detailed in Supplementary Table S2.

Treatment protocol

Patients newly diagnosed with ALL at Fujian Medical University Union Hospital between December 2015 and December 2018 and all patients from the First Affiliated Hospital of Xiamen University were treated in accordance with the Chinese Children Leukemia Group (CCLG)-ALL 2008 protocol. In this cohort, *IKZF1* status was incorporated into the risk assignment strategy. Patients harboring *IKZF1* deletions (*IKZF1*^{del}) were categorized into the high-risk group and received a high-risk regimen, whereas those with wild-type *IKZF1* (*IKZF1*^{wt}) were managed following the standard risk stratification in the protocol. The CCLG-ALL 2008 risk-stratification system, as previously described, relies on cytogenetic subtypes, the 7-day prednisone response, and the bone marrow response assessed on Day 15 (time point 1 [TP1]) and Day 33 (time point 2 [TP2]) [28]. Patients of Fujian Medical University Union Hospital newly diagnosed between January 2019 and December 2020 and all patients of Zhangzhou Affiliated Hospital of Fujian Medical University and Quanzhou First Hospital Affiliated to Fujian Medical University were treated following the Chinese Children's Cancer Group (CCCG)-ALL 2015 protocol. In this cohort, *IKZF1*^{del} was not incorporated into the risk assignment strategy; its risk stratification system was based on cytogenetic subtypes and Day 19 (TP1) and Day 46 (TP2) MRD, as previously described [3]. The comparison between the CCLG-ALL 2008 and CCCG-ALL 2015 regimens and risk stratification criteria are shown in Supplementary Tables S3 and S4. In summary, in induction chemotherapy, the CCCG-ALL 2015 regimen includes one to two doses of erythromycin, whereas the CCLG-ALL 2008 high-risk group regimen includes four doses of daunorubicin. In consolidation chemotherapy, the CCCG-ALL 2015 regimen includes high-dose methotrexate (3–5 g/m^2). In contrast, the CCLG-ALL 2008 regimen is a strong block regimen, which includes not only high-dose methotrexate (5 g/m^2) but also dexamethasone, vincristine, cyclophosphamide, arabinose, and asparaginase. In addition, *BCR::ABL1*-positive patients treated with the CCLG-ALL 2008 regimen began to receive imatinib (300–360 mg/m^2 per day) at a median of 18.0 days (interquartile range [IQR], 15.0–22.0 days. In contrast, patients treated with the CCCG-ALL 2015 regimen began to receive dasatinib (80 mg/m^2 per day) at a median of 10.0 days (IQR, 6.0–15.0 days) after the initiation of dexamethasone therapy and continued taking the medication until the end of therapy.

Statistical analyses

All statistical computations were performed using SPSS software, version 25.0 (SPSS Inc., Chicago, IL, USA). GraphPad Prism software, version 7 (GraphPad Software, San Diego, CA, USA), was used to generate charts. Overall survival (OS) was defined as the duration from diagnosis to time of death from any cause or censoring on March 31, 2024.

An event was characterized as the occurrence of one of the following: failure to attain complete remission (CR) post-induction, relapse, or death from any cause. Event-free survival (EFS) was defined as the duration from diagnosis to the first event occurrence or censoring on March 31, 2024.

CR was characterized by the bone marrow having < 5% leukemic cells with evidence of normal hematopoietic cell regeneration [29].

Kaplan–Meier curves were employed to illustrate the OS and EFS. The likelihoods of OS and EFS were calculated using the Kaplan–Meier technique, and the disparities in the survival curves were analyzed using the log-rank test. The cumulative incidence of relapse (CIR) and cumulative incidence of treatment-related mortality (CID_{TRM}) were estimated and compared using Gray's test. Mortality attributed to treatment-related complications was classified as a competing risk for CIR, whereas

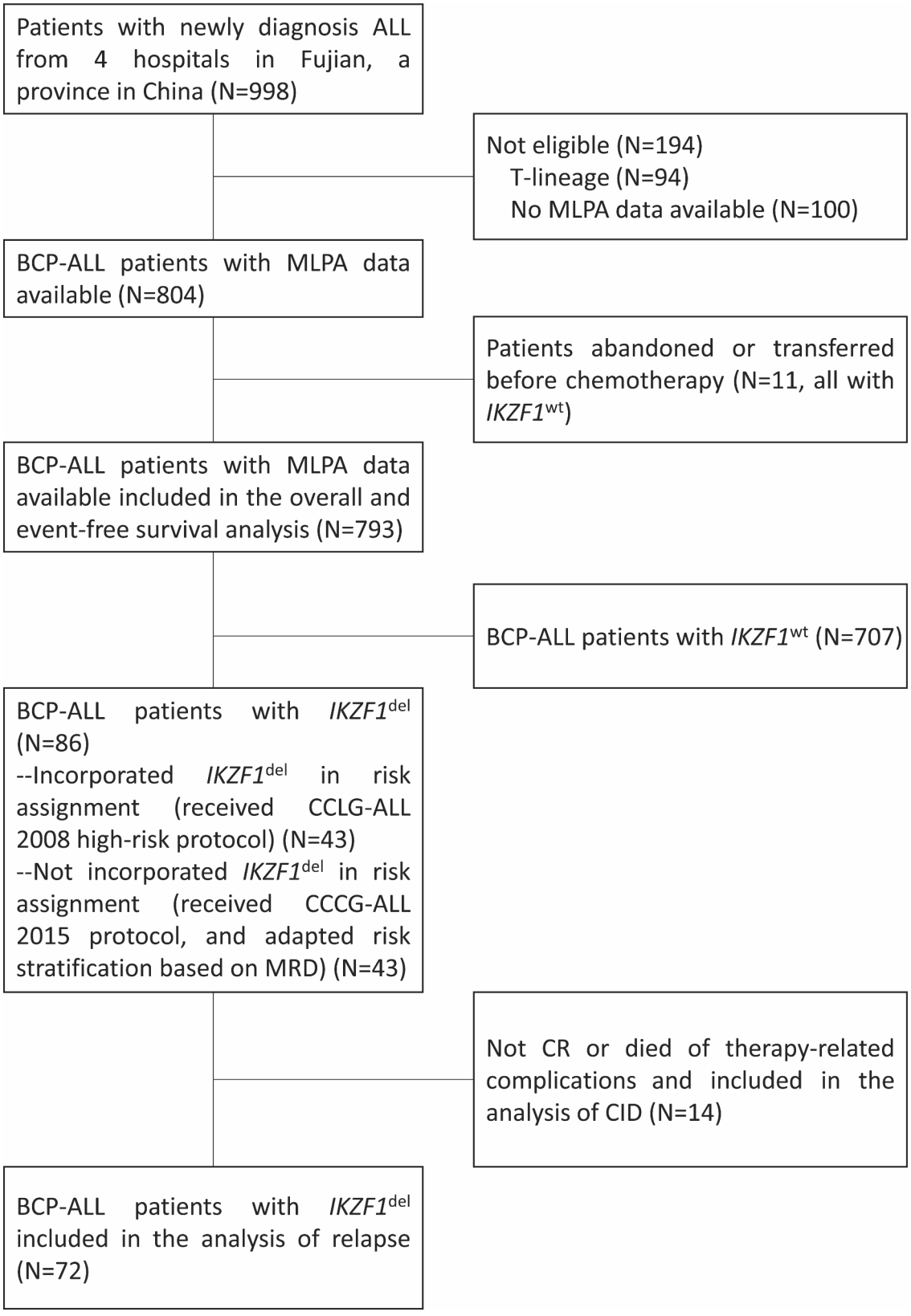

Fig. 1 Outline of patient enrollment in this study. ALL, acute lymphoblastic leukemia; BCP-ALL, B-cell precursor acute lymphoblastic leukemia; MLPA, multiplex ligation-dependent probe amplification; CCLG, Chinese Children Leukemia Group; CCCG, Chinese Children's Cancer Group; CR, complete remission

the occurrence of relapse was deemed a competing risk for CID_{TRM}.

Categorical data were assessed for differences using Pearson's chi-square test, and when data were sparse, Fisher's exact test was applied. The unadjusted Cox model was employed for univariate analyses to calculate hazard ratios (HRs). Variables that showed statistical significance in univariate analyses were selected for inclusion in the subsequent multivariate analyses. Both univariate and multivariate analyses were performed using the Cox proportional hazards model to assess whether the *IKZF1*^{del} had a distinct and significant effect on OS and/or EFS. The threshold for statistical significance for two-tailed P-values was established at <0.05.

Results

Frequencies and types of *IKZF1*^{del}

Of the 804 patients with BCP-ALL with MLPA data available, *IKZF1*^{del} was found in 86 patients (86/804, 10.7%) overall and in 30 (30/46, 65.2%) *BCR::ABL1*-positive patients. All deletions were hemizygous. Deletions affecting exons 4–7 (34 cases, 39.5%) and the whole gene (i.e., exons 1–8, 28 cases, 32.6%) were most frequent, whereas deletions affecting other exons (i.e., exons 2–7, exons 2–3, exons 2–8, and exons 4–8) were observed in lower frequencies. Results of the MLPA analysis of *IKZF1*^{del} in 804 patients with BCP-ALL are shown in Supplementary Table S5.

Clinical characteristics and early response to treatment of patients with *IKZF1*^{del}

Comparing clinical and biological features of patients with *IKZF1*^{del} and *IKZF1*^{wt}, no statistically significant disparities were observed concerning sex or the presence of a *TCF3::PBX1* fusion, *KMT2A*-rearrangement, or hypodiploid (Table 1). *IKZF1*^{del} exhibited a positive correlation with older age ($P=0.000$), elevated WBC count at diagnosis ($P=0.000$), presence of a *BCR::ABL1* fusion ($P=0.000$), and unfavorable early treatment response ($P=0.000$). Conversely, *IKZF1*^{del} was inversely associated with *ETV6::RUNX1* fusion ($P=0.000$) and high hyperdiploidy ($P=0.001$).

Prognostic significance of *IKZF1*^{del} in patients treated with the CCLG-ALL 2008 protocol

In the CCLG-ALL 2008 cohort, *IKZF1*^{del} was considered to be a high-risk stratification factor. For patients overall, *IKZF1*^{del} conferred a lower 5-year OS and EFS and a higher 5-year CIR than *IKZF1*^{wt} (OS: 66.9% ± 7.3% vs. 87.8% ± 1.6%, $P<0.001$; EFS: 57.5% ± 7.6% vs. 80.7%

Table 1 Patient characteristics and response to treatment according to *IKZF1* deletion status in 804 patients with BCP-ALL with MLPA data available

Characteristics	IKZF1^{del}, *n* (%)	IKZF1^{wt}, *n* (%)	*P*
Number of patients	86 (100)	718 (100)	
Sex			0.496
Male	53 (61.6%)	415 (58.2)	
Female	33 (38.4%)	303 (41.8)	
Age at diagnosis			0.000
<10 years	58 (67.4%)	663 (89.7)	
≥10 years	28 (32.6%)	55 (10.3)	
WBC ≥ 50×10^9/L at diagnosis	32 (37.2%)	112 (17.9)	0.000
Cytogenetic			
ETV6::RUNX1	4 (4.7%)	155 (19.8)	0.000
TCF3::PBX1	1 (1.2%)	47 (6.0)	0.051
BCR::ABL1	30 (34.9%)	16 (5.7)	0.000
KMT2A-rearrangement	2 (2.3%)	24 (3.2)	1.000
[a]High hyperdiploidy	3 (3.5%)	122 (15.5)	0.001
[b]Hypodiploidy	1 (1.1%)	16 (2.1)	1.000
[c]MRD risk groups			0.000
MRD-LR	38 (45.8)	458 (67.5)	
MRD-IR	39 (47.0)	209 (30.8)	
MRD-HR	6 (7.2)	12 (1.8)	
MRD-missing	3 (3.5)	25 (3.5)	1.000

BCP-ALL, B-cell precursor acute lymphoblastic leukemia; WBC, white blood cell; MRD, minimal residual disease

[a]High hyperdiploidy was defined as >50 chromosomes

[b]Hypodiploidy was defined as <44 chromosomes

[c]We excluded 11 patients who abandoned treatment or transferred before chemotherapy

Criteria for the MRD-risk groups were as follows [3, 28]: MRD-low-risk (MRD-LR), TP1 < 1% and TP2 < 0.01%; MRD-high-risk (MRD-HR), TP2 ≥ 1%; and MRD-intermediate-risk (MRD-IR), exclude MRD-LR and MRD-HR

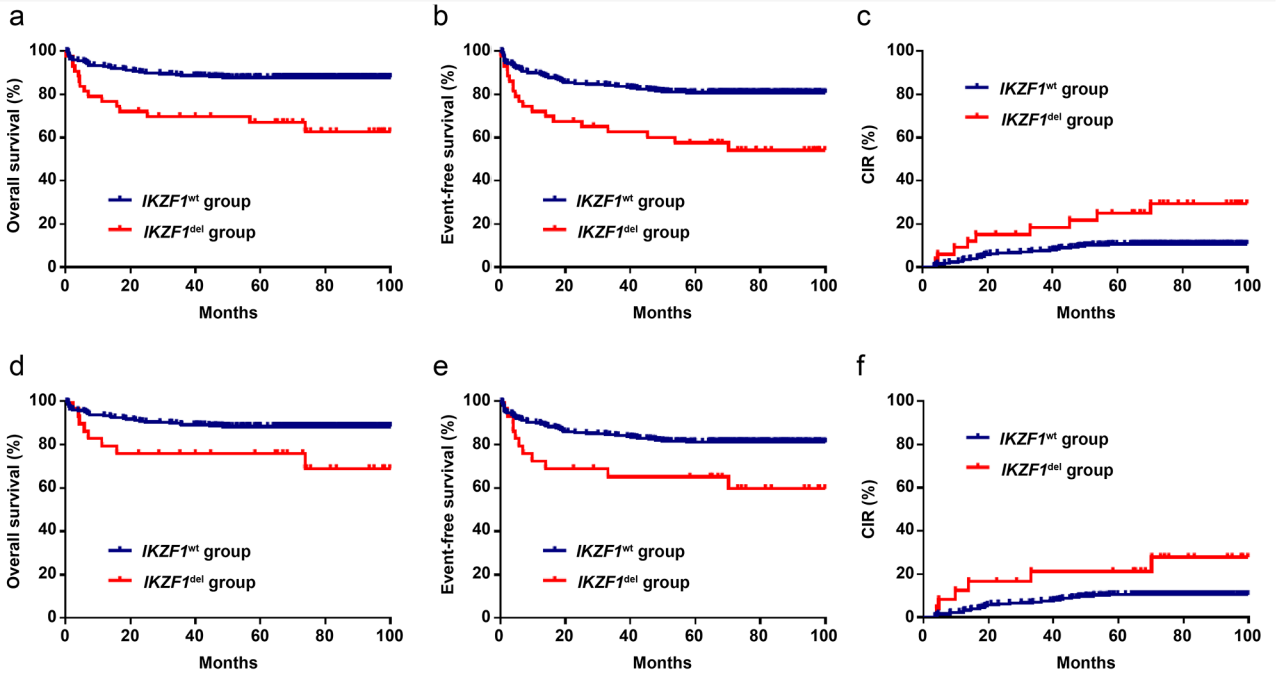

Fig. 2 Survival probability by *IKZF1* status for patients overall and those with *BCR::ABL1*-negative disease in the CCLG-ALL 2008 cohort. According to *IKZF1* status, patients were stratified into two groups: *IKZF1*^{del} and *IKZF1*^{wt}. EFS (**a**), OS (**b**), and CIR (**c**) according to *IKZF1* status for patients overall. EFS (**d**), OS (**e**), and CIR (**f**) according to *IKZF1* status for patients with *BCR::ABL1*-negative disease. EFS, event-free survival; OS, overall survival; CIR, cumulative incidence of relapse

Table 2 The contribution of *IKZF1*^{del} to the clinical outcomes of patients with BCP-ALL in the CCLG-ALL 2008 cohort, adjusting for known prognostic factors

Risk factor	Overall survival			Event-free survival		
	HR	95% *CI*	*P*-value	HR	95% *CI*	*P*-value
Age ≥ 10 years	1.239	0.581–2.641	0.579	1.373	0.741–2.545	0.314
WBC ≥ 50×10^9/L at diagnosis	1.880	1.096–3.225	0.022	1.367	0.853–2.189	0.194
IKZF1^{del}	1.644	0.872–3.098	0.124	1.527	2.101–4.667	0.136
Treatment risk (high-risk group)	2.131	1.174–3.867	0.013	1.834	1.136–2.960	0.013
[a]MRD-LR	0.364	0.194–0.683	0.002	0.413	0.256–0.668	0.000

BCP-ALL, B-cell precursor acute lymphoblastic leukemia; WBC, white blood cell; HR, hazard ratio; CI, confidence interval; MRD, minimal residual disease

[a]Criteria for MRD risk groups were as follows [3, 28]: MRD-low-risk (MRD-LR), TP1 < 1% and TP2 < 0.01%; MRD-high-risk (MRD-HR), TP2 ≥ 1%; MRD-intermediate-risk (MRD-IR), exclude MRD-LR and MRD-HR

± 2.0%, $P<0.001$; CIR: 24.9% ± 7.7% vs. 10.7% ± 1.6%, $P=0.005$) (Fig. 2a-c). In *BCR::ABL1*-negative patients, *IKZF1*^{del} was linked to a decreased 5-year OS and EFS and an elevated 5-year CIR, compared with *IKZF1*^{wt} (OS: 75.9% ± 7.9% vs. 88.4% ± 1.6%, $P=0.008$; EFS: 65.1% ± 8.9% vs. 81.2% ± 2.0%, $P=0.007$; CIR: 21.3% ± 8.5% vs. 10.6% ± 1.6%, $P=0.016$) (Fig. 2d-f). For *BCR::ABL1*-positive patients and CCLG-ALL 2008-high-risk patients, the prognostic significance of *IKZF1*^{del} was no longer statistically significant (Supplementary Figure S1).

In univariate analysis for patients overall and those with *BCR::ABL1*-negative disease, *IKZF1*^{del} was a poor prognostic predictor (Supplementary Tables S6 and S7). However, the statistical significance diminished after accounting for age, WBC at diagnosis, treatment group, and MRD status (Table 2, Supplementary Table S8).

Prognostic significance of *IKZF1*^{del} in patients treated with the CCCG-ALL 2015 protocol

In the CCLG-ALL 2015 cohort, *IKZF1*^{del} was not utilized as a criterion for determining patient risk stratification. For patients overall, *IKZF1*^{del} was associated with a reduced 5-year OS and EFS and an increased 5-year CIR, compared with those with *IKZF1*^{wt}, but the differences were not statistically significant (OS: 87.7% ± 5.2% vs. 93.6% ± 1.4%, $P=0.204$; EFS: 78.9% ± 6.9% vs. 90.4% ± 1.8%, $P=0.052$; CIR: 12.9% ± 6.3% vs. 6.5% ± 1.5%, $P=0.310$) (Fig. 3a-c). For patients with *BCR::ABL1*-negative disease, *IKZF1*^{del} did not confer significant

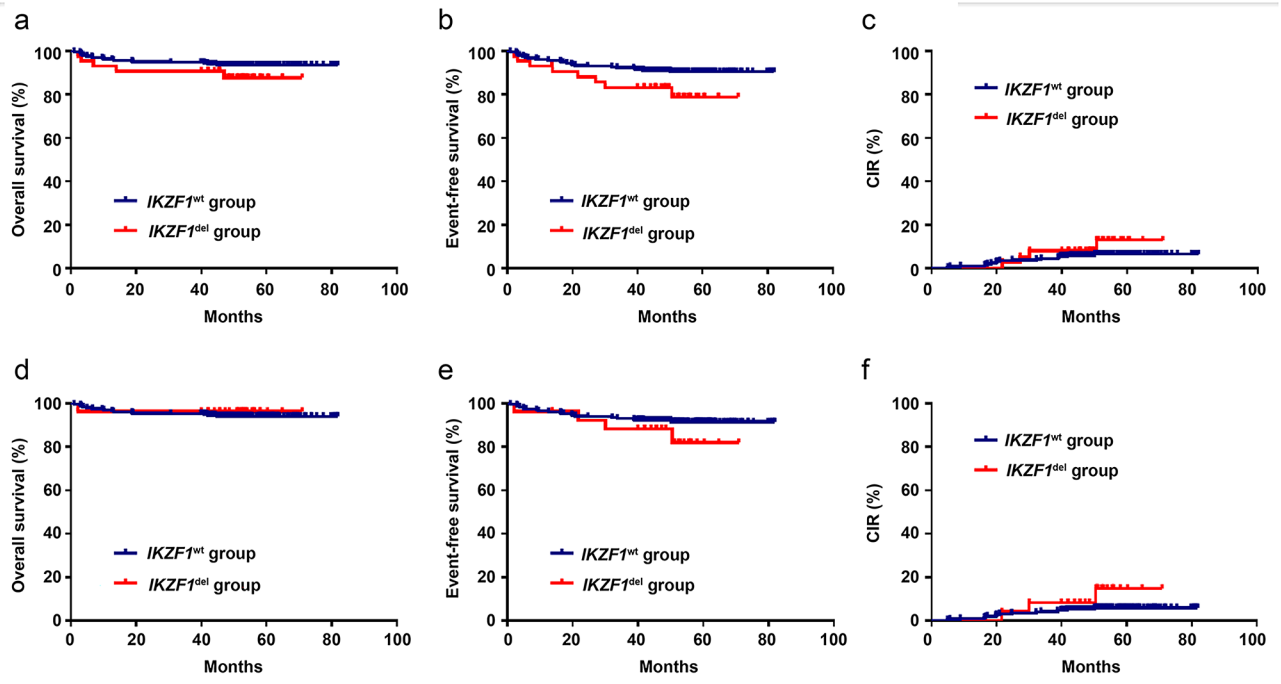

Fig. 3 Survival probability by *IKZF1* status for patients overall and those with *BCR::ABL1*-negative disease in the CCLG-ALL 2015 cohort. According to *IKZF1* status, patients were stratified into two groups: *IKZF1*^{del} and *IKZF1*^{wt}. EFS (**a**), OS (**b**), and CIR (**c**) according to *IKZF1* status for patients overall. EFS (**d**), OS (**e**), and CIR (**f**) according to *IKZF1* status for patients with *BCR::ABL1*-negative disease. EFS, event-free survival; OS, overall survival; CIR, cumulative incidence of relapse

differences in 5-year OS and EFS, with higher 5-year CIR (OS: 96.3% ± 3.6% vs. 94.5% ± 1.3%, P=0.193; EFS: 82.0% ± 8.5% vs. 91.5% ± 1.7%, P=0.229; CIR: 14.9% ± 8.0% vs. 6.0% ± 1.5%, P=0.201) (Fig. 3d-f).

In the CCCG-ALL 2015 cohort, only five patients, including two patients with *IKZF1*^{del}, were stratified into the high-risk group, so survival outcomes were not compared among patients in this group. For the CCCG-ALL 2015-low-risk and -intermediate-risk cohorts, *IKZF1*^{del} also did not result in any statistically significant differences in 5-year OS, EFS, and CIR (low-risk, OS: 100% vs. 100%, P=1.000; EFS: 100% vs. 97.7% ± 1.1%, P=0.709; CIR: 0% vs. 2.3% ± 1.1%, P=0.709) (intermediate-risk, OS: 84.9% ± 6.3% vs. 86.7% ± 3.1%, P=0.876; EFS: 79.2% ± 7.0% vs. 83.6% ± 3.4%, P=0.364; CIR: 10.3% ± 5.7% vs. 9.8% ± 2.8%, P=0.569) (Fig. 4a-f).

Comparing treatment outcomes of *IKZF1*^{del} patients treated with higher intensity chemotherapy (CCLG-ALL 2008 high-risk regimen) and MRD-guided protocol (CCCG-ALL 2015 protocol)

The rates and distributions of *IKZF1*^{del} between the CCLG-ALL 2008 and CCCG-ALL 2015 cohorts were similar (Table 3). The *IKZF1*^{del} patients treated with higher intensity chemotherapy (CCLG-ALL 2008 high-risk regimen) had notably lower 5-year OS and EFS than those treated with the MRD-guided protocol (CCCG-ALL 2015 protocol) (OS: 66.9% ± 7.3% vs. 87.7% ± 5.2%, P=0.028; EFS: 57.5% ± 7.6% vs. 78.9% ± 6.9%, P=0.023) (Fig. 5a, b). This difference was partly attributable to a lower 5-year CIR but mainly attributed to a significantly lower 5-year CID_{TRM} (CIR: 12.9% ± 6.3% vs. 24.9% ± 7.7%, P=0.168; CID_{TRM}: 10.4% ± 4.9% vs. 29.5% ± 7.8%, P=0.035) (Fig. 5c, d). Furthermore, patients treated with the CCLG-ALL 2008 high-risk regimen had a higher frequency of experiencing serious adverse events (SAEs) (51.2% vs. 30.2%, P=0.048). This was especially true for infection-related SAEs (41.9% vs. 20.9%, P=0.037), compared with those treated with the CCCG-ALL 2015 MRD-guided protocol (Supplementary Figure S2).

Subgroup comparisons were conducted based on whether patients exhibited conventional high-risk features, including *BCR::ABL1* positivity, *KMT2A* rearrangements, and MRD≥1% detected by multi-color flow cytometry (MFC) at TP2. These comparisons aimed to elucidate the impact of treatment intensification on patients harboring *IKZF1*^{del}. Patients without high-risk features treated with the CCLG-ALL 2008 high-risk regimen had a lower 5-year OS and EFS and a higher 5-year CIR and CID_{TRM} than patients without high-risk features treated with the MRD-guided protocol (CCCG-ALL 2015 non-high-risk regimen). These results were as follows: OS: 75.0% ± 8.2% vs. 95.8% ± 4.2%, P=0.046; EFS: 67.5% ± 8.9% vs. 78.8% ± 9.9%, P=0.194; CIR: 17.9% ± 8.1% vs. 17.7% ± 9.8%, P=0.168; CID_{TRM}: 21.7% ± 8.6% vs. 4.8% ± 4.7%, P=0.113 (Fig. 6a-f). These findings suggest

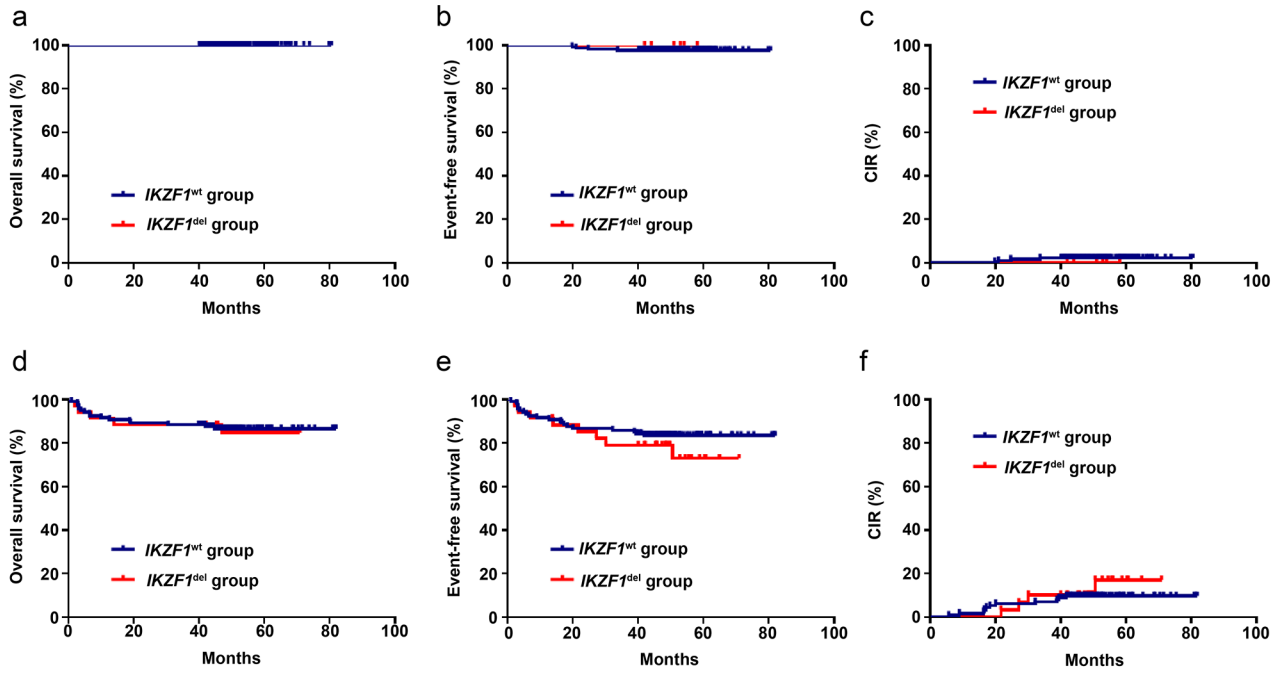

Fig. 4 Survival probability by *IKZF1* status for low-risk and intermediate-risk patients in the CCLG-ALL 2015 cohort. According to *IKZF1* status, patients were stratified into two groups: *IKZF1*^{del} and *IKZF1*^{wt}. EFS (**a**), OS (**b**), and CIR (**c**) according to *IKZF1* status for low-risk patients. EFS (**d**), OS (**e**), and CIR (**f**) according to *IKZF1* status for intermediate-risk patients. EFS, event-free survival; OS, overall survival; CIR, cumulative incidence of relapse

Table 3 Comparison of *IKZF1*^{del} frequencies in various groups of presenting characteristics and treatment responses in 793 patients with BCP-ALL

	No. of patients (IKZF1^{del}/Total) (%)			
Characteristics	Total	CCLG-ALL 2008 cohort	CCCG-ALL 2015 cohort	*P*
Number of patients	86/793 (10.8)	43/450 (9.6)	43/343 (12.5)	0.181
Sex				
Male	53/461 (11.5)	26/258 (10.1)	27/203 (12.3)	0.282
Female	33/332 (9.9)	17/192 (8.9)	16/140 (11.4)	0.439
Age at diagnosis				
<10 years	58/711 (8.2)	34/413 (8.2)	24/298 (8.1)	0.932
≥10 years	38/82 (46.3)	9/37 (24.3)	19/45 (42.2)	0.089
WBC ≥ 50×10^9/L at diagnosis	32/141 (22.7)	15/79 (19.0)	17/62 (27.4)	0.235
Cytogenetics				
ETV6::RUNX1	4/159 (2.5)	2/91 (2.2)	2/68 (2.9)	1.000
TCF3::PBX1	1/38 (2.6)	1/29 (3.4)	0/19 (0)	1.000
BCR::ABL1	30/44 (68.1)	14/20 (70.0)	16/24 (66.7)	0.813
KMT2A-rearrangement	2/24 (8.3)	1/16 (6.3)	1/8 (12.5)	1.000
[a]High hyperdiploidy	3/125 (2.4)	1/63 (1.6)	2/62 (3.2)	0.619
[b]Hypodiploidy	0/17 (0)	0/8 (0)	0/9 (0)	/
[c]MRD risk groups				
MRD-LR	38/496 (7.7)	13/225 (5.8)	25/271 (9.2)	0.151
MRD-IR	39/248 (15.7)	27/193 (12.4)	12/55 (27.3)	0.159
MRD-HR	6/18 (33.3)	4/13 (30.8)	2/5 (40.0)	1.000
MRD-missing	3/17 (17.6)	2/15 (13.3)	1/2 (50.0)	0.331

BCP-ALL, B-cell precursor acute lymphoblastic leukemia; WBC, white blood cell; MRD, minimal residual disease

[a]High hyperdiploidy was defined as >50 chromosomes

[b]Hypodiploidy was defined as <44 chromosomes

[c]We excluded 11 patients who abandoned treatment or transferred before chemotherapy

Criteria for the MRD-risk groups were as follows [3, 28]: MRD-low-risk (MRD-LR), TP1 < 1% and TP2 < 0.01%; MRD-high-risk (MRD-HR), TP2 ≥ 1%; and MRD-intermediate-risk (MRD-IR), exclude MRD-LR and MRD-HR

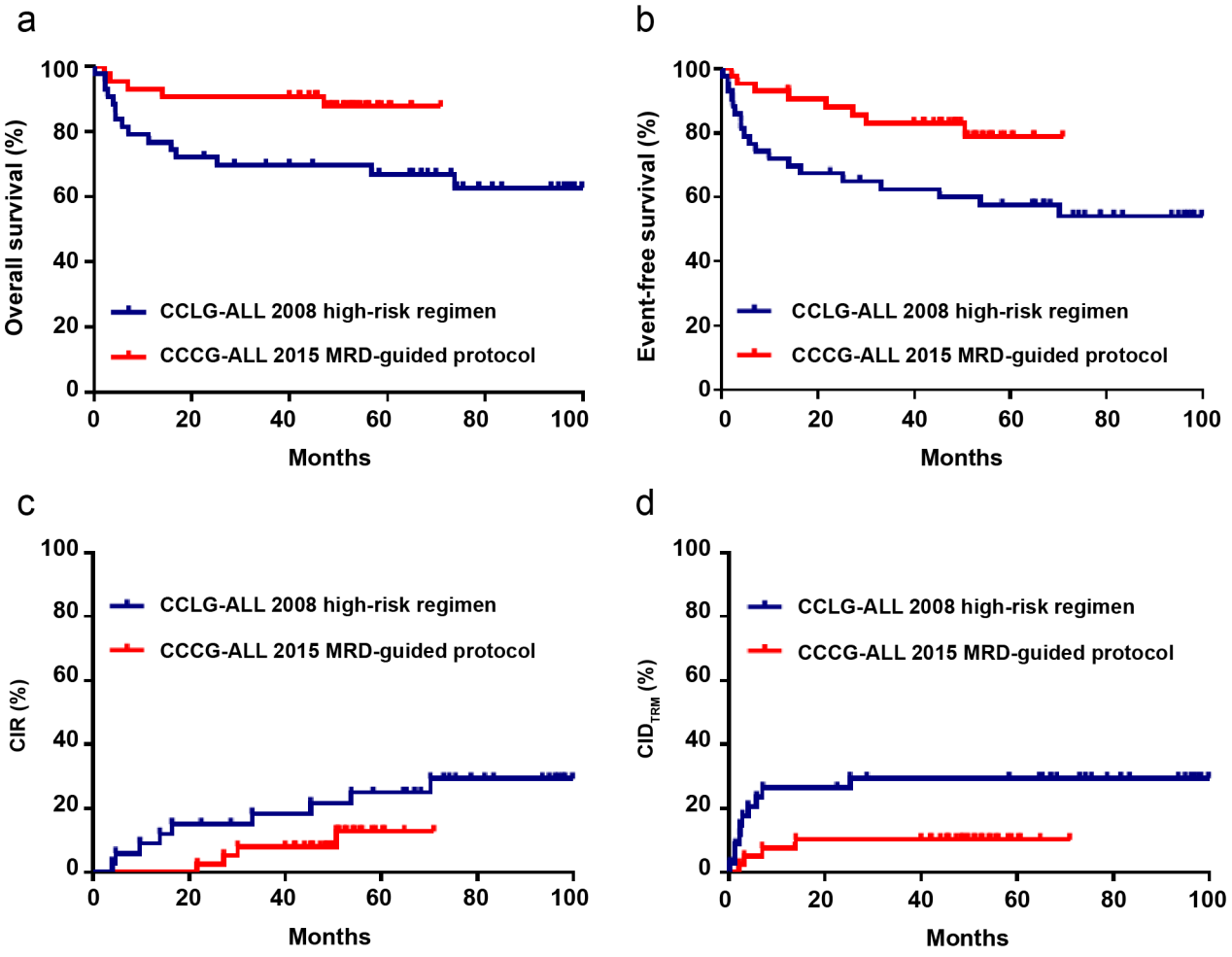

Fig. 5 Survival probability by treatment strategy in *IKZF1*^{del} patients. EFS (**a**), OS (**b**), CIR (**c**), and CID_{TRM} (**d**) according to treatment strategy. Patients were stratified into two groups: *IKZF1*^{del} patients treated with higher intensity chemotherapy (CCLG-ALL 2008 high-risk regimen) and those treated with the CCCG-ALL 2015 MRD-guided protocol. EFS, event-free survival; OS, overall survival; CIR, cumulative incidence of relapse; CID_{TRM}, cumulative incidence of treatment-related mortality

that upgrading risk groups for patients with *IKZF1*^{del} did not improve outcomes. Patients with high-risk features treated with the CCLG-ALL 2008 high-risk regimen also had a lower 5-year OS and EFS and a higher 5-year CIR and CID_{TRM} than patients with high-risk features treated with the MRD-guided protocol (CCCG-ALL 2015 non-high-risk regimen). The results were as follows: OS: 52.5% ± 13.1% vs. 74.9% ± 11.0%, P=0.226; EFS: 40.0% ± 12.6% vs. 78.9% ± 9.4%, P=0.028; CIR: 40.0% ± 15.5% vs. 6.3% ± 6.1%, P=0.067; CID_{TRM}: 45.5% ± 15.0% vs. 16.7% ± 8.8%, P=0.065 (Supplementary Figure S3). Comparison of the survival probability in the CCLG-ALL 2008 and CCCG-ALL 2015 group was summarized in Table 4.

Discussion

The present study demonstrated that *IKZF1*^{del} was significantly linked to a poorer prognosis among BCP-ALL patients, particularly in those who were *BCR::ABL1*-negative and were treated with the CCLG-ALL 2008 protocol. This finding aligns with those of previous studies [12–14, 18, 26, 30]. However, no association was found between *IKZF1*^{del} and survival outcomes in patients with BCP-ALL treated with the CCCG-ALL 2015 protocol. Furthermore, our results showed that intensification of chemotherapy did not improve outcomes and had a higher frequency of SAEs in *IKZF1*^{del} BCP-ALL patients, especially those without conventional high-risk features.

In the past decade, a multitude of studies have investigated the clinical significance of *IKZF1*^{del} in pediatric BCP-ALL across a spectrum of treatment protocols [10–22, 25, 26, 28–33]. As a common and significant characteristic observed in most prognostic studies of pediatric BCP-ALL, *IKZF1*^{del} has been correlated with unfavorable clinical outcomes in frontline treatment [11, 13–16, 30–32]. The prognostic relevance of this marker

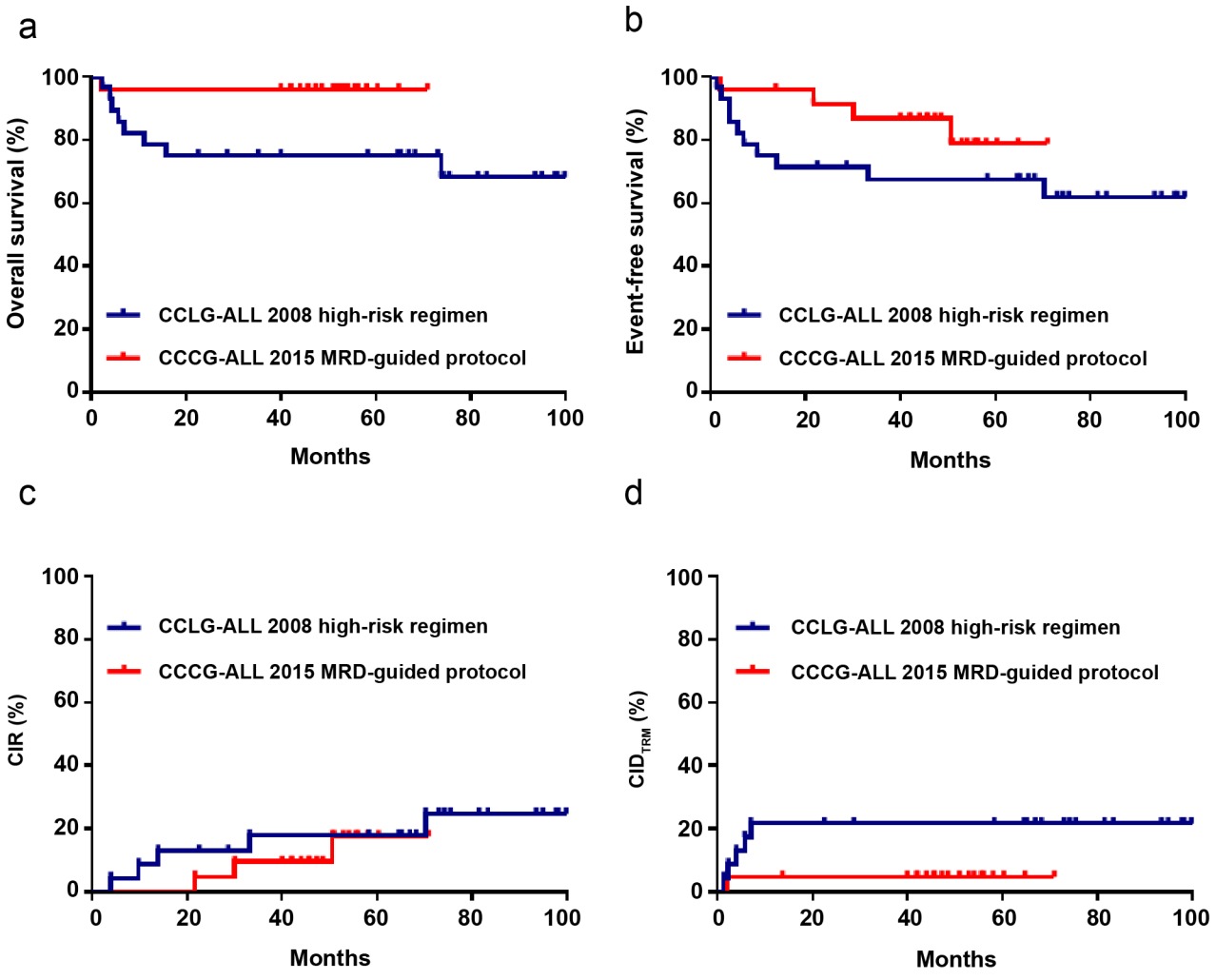

Fig. 6 Survival probability by treatment strategy in *IKZF1*^{del} patients without conventional high-risk features, including *BCR::ABL1*-positive, *KMT2A*-rearrangements, and MRD ≥ 1% detected by MFC at TP2. EFS (**a**), OS (**b**), CIR (**c**), and CID$_{TRM}$ (**d**) according to treatment strategy. Patients were stratified into two groups: *IKZF1*^{del} patients without conventional high-risk features treated with higher intensity chemotherapy (CCLG-ALL 2008 high-risk regimen) and those treated with the CCCG-ALL 2015 MRD-guided protocol. EFS, event-free survival; OS, overall survival; CIR, cumulative incidence of relapse; CID$_{TRM}$, cumulative incidence of treatment-related mortality

Table 4 Comparison of the survival probability in the CCLG-ALL 2008 and CCCG-ALL 2015 group

Survival probability	CCLG-ALL 2008 group	CCCG-ALL 2015 group	*P*
5-y OS for all patients	85.8%	92.8%	0.002
5-y EFS for all patients	78.5%	88.9%	< 0.001
Incidence rate of SAEs for all patients	36.1%	25.9%	0.021
5-y OS for patients with *IKZF1*^{del}	66.9%	87.7%	0.028
5-y EFS for patients with *IKZF1*^{del}	57.5%	78.9%	0.023
Incidence rate of SAEs for patients with *IKZF1*^{del}	51.2%	30.2%	0.048
5-y OS for patients with *BCR::ABL1* and *IKZF1*^{del}	50.0%	75.0%	0.220
5-y EFS for patients with *BCR::ABL1* and *IKZF1*^{del}	42.9%	73.1%	0.104
5-y OS for patients with *BCR::ABL1*-negative and *IKZF1*^{del}	75.9%	96.3%	0.035
5-y EFS for patients with *BCR::ABL1* -negative and *IKZF1*^{del}	65.1%	82.0%	0.083

is conspicuous in our cohort of patients with BCP-ALL treated with the CCLG-ALL 2008 protocol, especially those without *BCR::ABL1* fusion. Nevertheless, when adjusting for older age at the time of ALL diagnosis, high initial WBC, and elevated MRD level at the end of induction, the adverse prognostic impact of the *IKZF1* deletion diminished. The aforementioned factors often coincide with high-risk clinical characteristics commonly associated with *IKZF1*^{del}. Meanwhile, *IKZF1*^{del} has also been demonstrated to independently predict relapse in BCP-ALL, with a high CIR of 29–55% [16, 32–35]. In a Dutch study, the integrated utilization of MRD and *IKZF1*^{del} status enabled the prediction of 79% of relapses [22]. Additionally, recent research has provided compelling evidence suggesting that the high recurrence rate in *IKZF1* is not influenced by the deletion range, even in cases that were previously classified as non-recurrent *IKZF1* deletions [10, 36].

However, when shifting the focus from *IKZF1*^{del} as a risk factor to adjusting risk based on MRD, the prognostic value of *IKZF1*^{del} does not manifest. Based on MRD adjustments, patients with *IKZF1*^{del}, who were categorized as high-risk and experienced relapse, exhibited poor response to treatment, as evidenced by high MRD levels, and were thus deemed eligible for transplantation. In the intermediate-risk group, intensified therapeutic approaches showed promise for improving outcomes. As a result, the identification of *IKZF1*^{del} does not provide substantial value for enhanced risk stratification in this context, as reported in a previous study [24]. The BFM group also demonstrated that patients achieving MRD negativity at the end of induction showed no negative impact on treatment outcomes from the presence of *IKZF1*^{del}, while patients with detectable MRD encountered a tenfold higher risk of disease relapse [15]. Some studies also emphasize the detrimental impact of *IKZF1*^{del} on MRD status [20]. Therefore, for children with *IKZF1*^{del} BCP-ALL, the MRD-adjusted protocol is considered appropriate.

In accordance with MRD-guided risk stratification, most pediatric patients with *IKZF1*^{del} were classified into the MRD-intermediate-risk (MRD-IR) group. In our study, conducted according to the CCCG-ALL 2015 protocol, the MRD-IR group accounted for 27% of patients with *IKZF1*^{del}. Although the high-risk group represented 30% of the cohort, it comprised only six patients. Consistent with other recent studies, relapses were predominantly concentrated within the MRD-IR group and often occurred shortly after completing 2-year chemotherapy. This underscores the urgent requirement for more effective therapy for *IKZF1*^{del} [10, 20, 37, 38]. In the DCOG ALL11 protocol, the inclusion of patients with *IKZF1*^{del} ALL involved the addition of third-year maintenance therapy, consisting of MTX administered every 3 weeks and intermittent 6-mercaptopurine. The results demonstrated a significant improvement in outcomes compared with the DCOG ALL10 protocol. The 5-year CIR decreased from 23 to 11%, representing a 2.2-fold reduction, whereas EFS improved from 72 to 87% and OS improved from 83 to 93%. Notably, when milestone analysis was performed at the 2-year mark, the 5-year CIR rate further decreased 2.9-fold, from 26 to 9% [20]. In our study, the main difference between the CCLG-ALL 2008 and CCCG-ALL 2015 protocols was the increased frequency and dosage of anthracyclines and asparaginase during the induction and consolidation phases in the former protocol. However, a higher CID_{TRM} associated with the high-intensity chemotherapy regimen in the CCLG-ALL 2008 protocol led to lower 5-year OS and EFS rates when compared with those of patients treated with the CCCG-ALL 2015 protocol. Therefore, intensifying the chemotherapy regimen during early induction and consolidation therapy fails to improve the prognosis of patients with *IKZF1*^{del}. Instead, it may lead to a higher incidence of SAEs.

In the study by Stanulla et al., a subgroup termed "*IKZF1* plus" was defined by the presence of *IKZF1*^{del} with deletions in *CDKN2A*, *CDKN2B*, *PAX5*, or *PAR1*, excluding ERG deletion [17]. This subgroup was identified as a very poor prognostic group, dependent on MRD. In certain studies, *IKZF1* plus, rather than *IKZF1*^{del}, was found to be prognostic [10, 17, 39]. Boer JM et al. observed that almost all patients with deletions of exons 4–7 had the *IKZF1* plus genotype, which offers a reasonable explanation for the consistent association between this particular genetic alteration and significantly adverse clinical outcomes [10]. Unfortunately, owing to incomplete data, we were unable to assess whether differences in prognosis exist between *IKZF1* plus and *IKZF1*^{del}. This limitation is acknowledged as a shortcoming of our study.

Conclusions

In summary, our study demonstrated that *IKZF1*^{del} had a detrimental effect on both EFS and OS. After adjusting for MRD status, the impact of *IKZF1*^{del} on survival outcomes was significantly mitigated. These findings indicate that the MRD-guided protocol may be a more effective treatment strategy for pediatric patients with BCP-ALL and *IKZF1*^{del}. In addition, intensifying the chemotherapy regimen during early induction and consolidation therapy does not enhance the prognosis of patients with *IKZF1*^{del}. Instead, it may result in an increased occurrence of SAEs. Notably, this study employed a nonrandomized design and relied on a historical control group. Further investigations involving larger cohorts and randomized controlled trials are essential to comprehensively grasping the prognosis and therapeutic efficacy of *IKZF1*^{del}.

Abbreviations

BCP-ALL	B-cell precursor acute lymphoblastic leukemia
BFM	Berlin–Frankfurt–Münster
CCCG	Chinese Children's Cancer Group
CCLG	Chinese Children Leukemia Group
CID_{TRM}	Cumulative incidence of treatment-related mortality
CIR	Cumulative incidence of relapse
CR	Complete remission
DCOG	Dutch Childhood Oncology Group
EFS	Event-free survival
EORTC	European Organisation for Research and Treatment of Cancer
FISH	Fluorescence in situ hybridization
HR	Hazard ratio
IQR	Interquartile range
MFC	Multi-color flow cytometry
MICM	Morphology, Immunology, Cytogenetics, and Molecular Biology
MLPA	Multiplex ligation-dependent probe amplification
MRD-IR	Minimal residual disease-intermediate-risk
MRD	Minimal residual disease
OS	Overall survival
RT-PCR	Reverse transcription polymerase chain reaction
SAE	Serious adverse event
TP1	Time point 1
TP2	Time point 2
WBC	White blood cell

Supplementary Information

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Supplementary Material 1

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Author contributions

YZ and NL designed the study and reviewed the manuscript. LP and YC analyzed and interpreted patients' data, created the tables, plotted the figures, and wrote the paper. LP recorded and analyzed patients' data, created the tables, plotted the figures, and wrote the paper. KW, BG, SZ, SH, ZL, and XW were responsible for the investigation and resources. All authors read and approved the final manuscript.

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Data availability

The datasets supporting the conclusions of this article are not publicly available due to data protection for enrolled centers but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The protocol received approval from the Ethics Committee of Fujian Medical University Union Hospital. Parents or legal guardians of patients provided informed consent prior to enrolling in the study, following the principles outlined in the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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