A pediatric-inspired regimen for adolescent and adult patients with Philadelphia chromosome-negative acute lymphoblastic leukemia: a prospective study from China

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Abstract

Several international centers have used and reported on pediatric-inspired regimens to treat adolescent and adult patients with Philadelphia chromosome-negative acute lymphoblastic leukemia (Ph⁻ ALL). However, there is a lack of prospective data from the Chinese population. We performed a prospective study with a pediatric-inspired regimen (IH-2014 regimen) to treat adolescent and adult Ph⁻ ALL patients in our center. From 2014 to 2021, a total of 415 patients aged between 14 and 65 years (median age, 27 years) were included in this study. After a median follow-up of 40.8 months, the 5-year overall survival, disease-free survival, and event-free survival rates were 53.8%, 51.1% and 45.0%, respectively. The regimen was generally well tolerated and safe, and the overall chemotherapy-related mortality was 3.6%. Age ≥40 years and persistent detectable minimal residual disease (MRD) after induction were independent prognostic factors. Traditional risk factors for adult patients combined with post-induction MRD had predictive significance for survival and relapse, which is helpful in the selection of subsequent treatment. Patients with high-risk factors who can achieve a deep MRD response after induction do not derive benefit from allogeneic hematopoietic stem cell transplantation.

Introduction

Using multidrug combination chemotherapy to treat pediatric Philadelphia chromosome-negative acute lymphoblastic leukemia (Ph⁻ ALL) is one of modern oncology's great successes, with the 5-year overall survival (OS) rate now exceeding 80%.[1] In contrast to children, the clinical outcomes of adult patients with Ph⁻ ALL, treated with adult chemotherapy regimens, are dismal, since more than 50% of patients will experience a relapse.[2-4] Drawing on experience in children, several retrospective studies found that adolescents and young adult patients with Ph⁻ ALL derive greater survival benefits from pediatric-inspired regimens,[5-7] and these findings have been further confirmed by large prospective studies.[8] The development of treatment for adolescents and adults with ALL in the Chinese mainland lags behind that of developed countries. Moreover, there is a lack of prospective data on the efficacy and safety of pediatric-inspired regimens in adolescents and adults with Ph⁻ ALL in China.[9,10] Herein, we present our single-center prospective data on a pediatric-inspired regimen (IH-2014 regimen) for the treatment of patients aged 14-65 years with Ph⁻ ALL. The primary objective of the study was to assess the efficacy and safety of the pediatric-inspired regimen and to explore the prognostic significance of minimal residual disease (MRD) combined with traditional risk factors.

Methods

Patients

In total, 415 consecutive patients (aged ≥14 years and ≤65 years) with newly diagnosed Ph⁻ ALL were enrolled and treated from April 2014 to December 2021. A full description of genetic and molecular diagnostic methods is available in the *Online Supplementary Material*. The list of fusion genes and Ph-like related genes are listed in *Online*

Supplementary Tables S1 and *S2*. Before sample collection and treatment, every patient signed a consent form. This study was approved by the institutional ethics committee of the Blood Diseases Hospital and was registered at the Chinese Clinical Trial Registry website with registration number ChiCTR-OOC- 15006328.

Treatments

Patients were treated according to a revised edition of the Children's Oncology Group protocol (CCG-1961).[11] *Online Supplementary Tables S3* and *S4* show the specific details of the protocol for patients aged ≤55 and >55 years, respectively. Additional details about the treatments can be

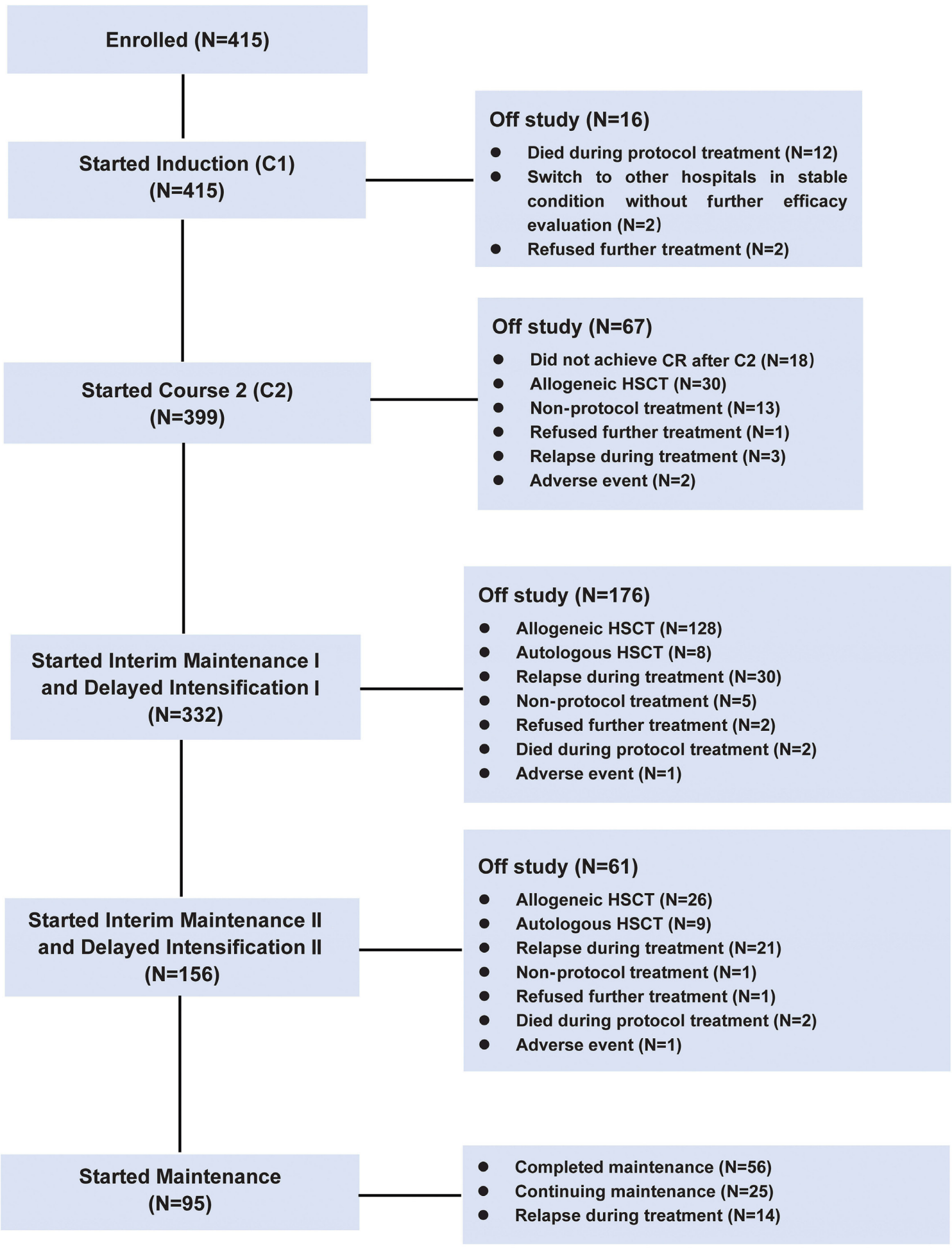


Figure 1. Flowchart of patients' disposition in the study. CR: complete remission; HSCT: hematopoietic stem cell transplantation.

found in the *Online Supplementary Material*.

Risk stratification

Patients with Ph⁻ ALL who presented with one or more of the following conditions were categorized as high risk (HR): age ≥40 years, white blood cell count ≥30×10⁹/L for B-cell ALL or ≥100×10⁹/L for T-cell ALL, hypodiploid ALL, mature T-ALL or early T-ALL, ALL with t(v;11q23) or *MLL* rearrangements/*KMT2A* rearrangements, and ALL with t(1;19)/*TCF3-PBX1* or with a complex karyotype (≥5 unrelated clonal abnormalities). Patients without these HR factors were stratified into the standard-risk (SR) group.[12]

Hematopoietic stem cell transplantation

Allogeneic hematopoietic stem cell transplantation (HSCT) was recommended to HR patients with a donor (related or unrelated) or SR patients with persistent MRD at the end of induction (EOI). Autologous HSCT was recommended to SR patients unable to tolerate multiple courses of intensive chemotherapy who had achieved MRD negativity early and to HR patients who had achieved MRD negativity early but did not have a suitable allogeneic donor. The transplantation procedures were not completely uniform because they were performed in different transplant centers in China.

Response evaluation and minimal residual disease definitions

The response evaluation and MRD assessment are shown in the *Online Supplementary Material*. MRD was measured using bone marrow aspirates with eight-color multiparametric flow cytometry on day 14 of induction, at the EOI (days 29-42), after the first consolidation (post-C1), and throughout the treatment period. MRD levels of <0.01% and ≥0.01% were considered as negative and positive, respectively.[13] Patients in complete remission (CR) who were MRD-positive were further stratified into three groups according to MRD level: MRD low positive (MRD-lp), ≥0.01% to <0.1%; MRD high positive (MRD-hp), ≥0.1% to <1%; and MRD very high positive (MRD-vhp), ≥1%.

Statistical analysis

The primary endpoints of the study were OS and event-free survival (EFS). The analysis of the data was conducted using GraphPad Prism 8 software and R statistical software (version 3.0). The survival rates were calculated using the Kaplan-Meier method and survival curves. To compare patients who received an allogeneic HSCT with those who did not, a separate landmark analysis was performed at 6 months (median time to allogeneic HSCT) after enrollment. The multivariate Cox proportional hazards regression model analysis included variables from the univariate analysis that had *P* values of ≤0.2. The cumulative incidence of relapse and treatment-related mortality were calculated via a competing risk analysis with the Gray test.

Results

In total, 415 patients were registered, and Figure 1 shows the patients' disposition in the study. The participants' median age was 27 years (range, 14-65), and males accounted for 59.3% of all participants. Of the 415 patients, 312 presented with B-precursor ALL and 103 with T-cell ALL. The patients' demographic and baseline clinical characteristics

Table 1. Baseline characteristics of the 415 patients studied.

Characteristic	N (%)
Sex	
Male	244 (58.8)
Female	171 (41.2)
Age at diagnosis in years	
Median (range)	27 (14-65)
Distribution	
<20	120 (28.9)
20-29	105 (25.3)
30-39	81 (19.5)
40-49	62 (14.9)
50-59	37 (8.9)
≥60	10 (2.4)
Immunophenotype	
B-ALL	N=312 (75.2% of all patients)
Pro-B	36 (11.5)
Common B	205 (65.7)
Pre-B	71 (22.8)
T-ALL	N=103 (24.8% of all patients)
Pro-T	42 (40.8)
Pre-T	33 (32.0)
Cortical T	12 (11.7)
Medullary T	16 (15.5)
WBC×10⁹/L	
Median (range)	13.2 (0.59-504.00)
Distribution	
B-ALL with WBC ≥30×10⁹/L	87 (27.9)
B-ALL with WBC <30×10⁹/L	225 (72.1)
T-ALL with WBC ≥100×10⁹/L	21 (20.4)
T-ALL with WBC <100×10⁹/L	82 (79.6)
Cytogenetics	
Normal	216 (52.0)
t(v;11q23) or *KMT2A* rearrangements	23 (5.5)
t(1;19)/*TCF3-PBX1*	13 (3.1)
Hypodiploidy (<44 chromosomes)	2 (0.5)
Hyperdiploidy (51-65 chromosomes)	12 (2.9)
Complex karyotype (≥5 chromosomal abnormalities)	20 (4.8)
Other abnormalities	101 (24.3)
No metaphases	25 (6.0)
Not done	3 (0.7)
Ph-like screening since 2017	N=194
Positive	24 (12.4)
Negative	170 (87.6)
Risk stratification	
Standard risk	148 (35.7)
High risk	267 (64.3)

ALL: acute lymphocytic leukemia; WBC: white blood cells; Ph: Philadelphia chromosome.

are displayed in Table 1. Multiple molecular methods were available to screen for Ph-like ALL since 2017 and a total of 24 patients were identified with a confirmed diagnosis of Ph-like ALL. The genomic alterations in patients with Ph-like ALL are listed in *Online Supplementary Table S5*.

Remission induction

All registered patients received induction therapy. In total, 12 patients died during induction therapy, and the induction-related mortality was 2.89%. Two patients were discharged after induction therapy in a stable condition without further efficacy evaluations at our center. Among 401 efficacy-evaluable patients, 355 (85.5%) achieved CR after induction chemotherapy. Of 47 patients with induction failure, 29 (61.7%) achieved CR after the first salvage chemotherapy. The overall CR rate after two courses of chemotherapy was 92.5%.

Overall, event-free, and disease-free survival

Patients who survived were followed up until September 30, 2022. With a median follow-up time of 40.8 months, the median OS of the cohort has not yet been reached. The median EFS of all patients and the disease-free survival (DFS) of patients who achieved CR within two courses of chemotherapy were 25.6 months and not reached, respectively. The 5-year OS, EFS, and DFS rates were 53.8% (95% confidence interval [95% CI]: 48.1%-59.5%), 45.0% (95% CI: 31.3%-50.3%), and 51.1% (95% CI: 45.4%-56.8%), respectively (Figure 2A). Table 2 shows the EFS and OS of the overall cohort and subgroups.

Hematopoietic stem cell transplantation

During the study period, a total of 241 patients underwent HSCT. Most of the patients (92.9%, n=224) underwent allogeneic HSCT (184 in first CR [CR1], 40 in second CR [CR2] or beyond), and 17 (7.1%) patients underwent autologous HSCT in CR1. Among the 224 patients who underwent allogeneic HSCT, 75 were in the SR group and 149 were in the HR group. Among the 17 patients who underwent autologous HSCT, eight were in the SR group and nine were in the HR group. The 5-year OS rates of patients receiving allogeneic HSCT and autologous HSCT were 63.8% (95% CI: 52.9%-70.1%) and 70.1% (95% CI: 41.3%-98.9%), respectively (P=0.322) (Figure 2B). It should be noted that the characteristics of the patients in the two groups were not comparable.

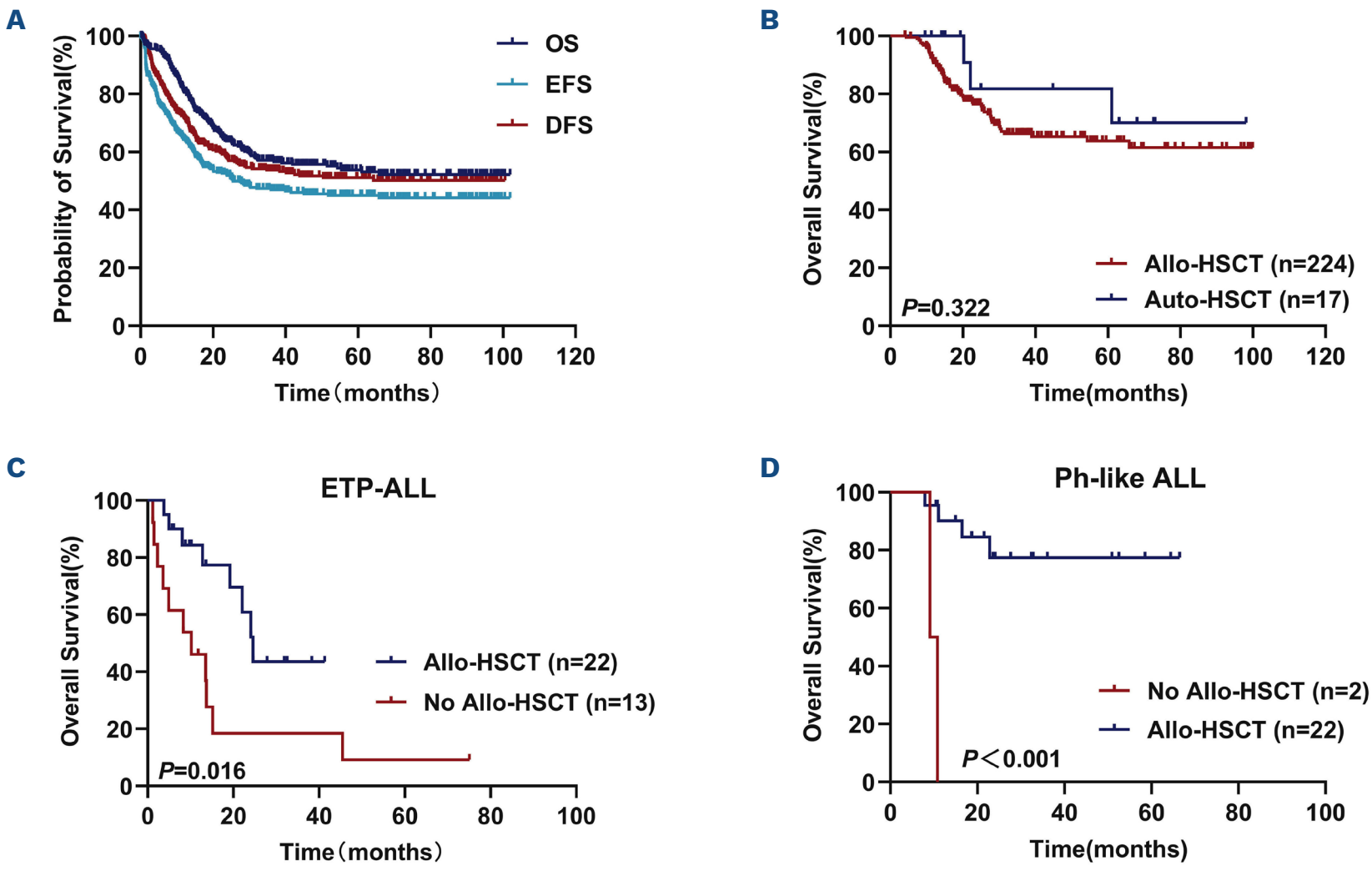


Figure 2. Survival outcomes. (A) Overall survival (OS), event-free survival and disease-free survival curves for the cohort. (B) OS curves according to type of hematopoietic stem cell transplantation (allogeneic *vs.* autologous). (C) OS curves for patients with early T-cell precursor acute lymphocytic leukemia according to transplantation status; survival curves originate at a landmark of 6 months (median time from enrollment to allogeneic hematopoietic stem cell transplantation) to adjust for bias related to early events. (D) OS curves for patients with Philadelphia chromosome-like acute lymphocytic leukemia according to transplantation status. EFS: event-free survival; DFS: disease-free survival; allo: allogeneic; auto: autologous; HSCT: hematopoietic stem cell transplantation; ETP-ALL: early T-cell precursor acute lymphocytic leukemia; Ph-like ALL: Philadelphia chromosome-like acute lymphocytic leukemia.

Of the 42 patients diagnosed with early T-cell precursor-ALL, 22 underwent allogeneic HSCT in CR1, the remaining 20 patients did not undergo allogeneic HSCT. In a landmark analysis including only patients alive at 6 months (the median time to allogeneic HSCT), the 5-year OS rates of patients with early T-cell precursor-ALL who received an allogeneic transplant (n=22) and those who did not (n=13) were 43.5% (95% CI: 16.1%-70.9%) and 6% (95% CI: 0%-26.3%), respectively (P=0.016) (Figure 2C). Of the 24 patients diagnosed with Ph-like ALL, 20 and two patients underwent allogeneic HSCT in CR1 and CR2, respectively, and the remaining two patients did not undergo allogeneic HSCT. A much higher 5-year OS was seen in patients with Ph-like ALL who received an allogeneic HSCT compared with those who did not (77.5% *vs*. 0%, P<0.001) (Figure 2D).

Prognostic value of minimal residual disease

There were 386, 389, and 346 bone marrow samples available for MRD evaluation on day 14 of induction, at EOI, and post-C1, respectively. Figure 3A presents the distribution of MRD status over time. Figure 3B depicts the compositions of MRD levels at EOI stratified according to disease types. Notably, Ph-like ALL and early T-cell precursor-ALL were associated with extremely lower achievements of MRD negativity at EOI compared with other types.

The 5-year OS rates of patients with MRD negativity (n=193), MRD-lp (n=52), MRD-hp (n=55), and MRD-vhp (n=89) at EOI were 68.0% (95% CI: 60.2%-75.8%), 44.8% (95% CI: 28.9%-60.7%), 52.4% (95% CI: 34.2%-70.6%), and 36.7% (95% CI: 24.2%-49.2%), respectively (P<0.001) (Figure 4A). If patients were censored at the time of HSCT, the 5-year OS rates of these patients were 74.9% (95% CI: 65.1%-84.7%), 39.7% (95% CI: 18.7%-60.7%), 42.3% (95% CI: 11.7%-72.9%) and 0%, respectively (P<0.001) (Figure 4B). Patients with a negative MRD status at EOI had a more favorable OS than those who were MRD-positive at EOI. There was no statistically significant difference in terms of survival time between patients with MRD-lp and MRD-hp. Patients with MRD-vhp had the worst survival.

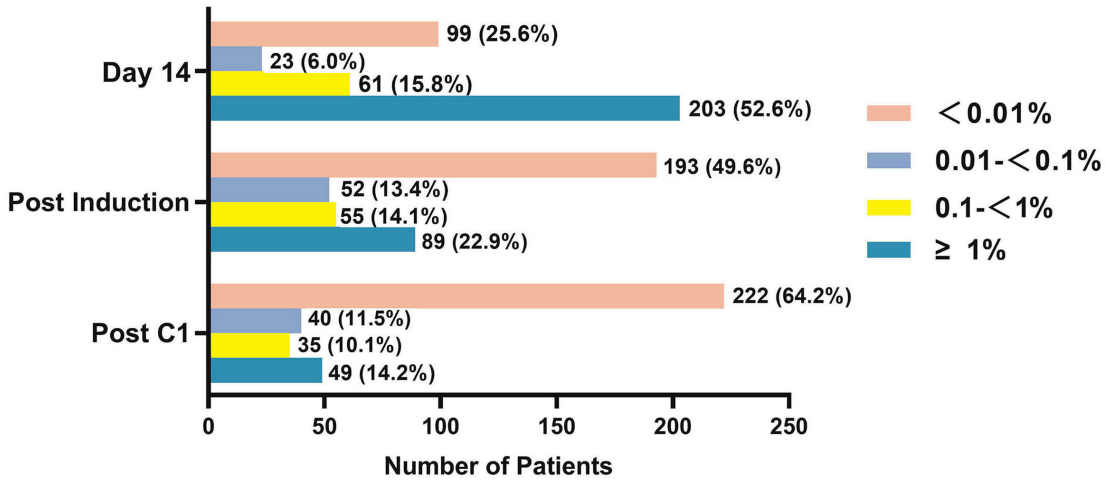
The relapse probabilities had a similar pattern. Patients with MRD negativity at EOI had a lower 5-year cumulative incidence of relapse than those with MRD positivity at any levels (31.9% *vs*. 47.4%, 43.8%, and 49.1%). Compared to MRD-lp and MRD-hp patients, patients with MRD-vhp experienced a significantly higher rate of early relapse. However, with a longer follow-up, the 5-year cumulative incidence of relapse did not differ significantly among patients who were MRD-positive in any of the three groups, with rates of

Table 2. Five-year event-free and overall survival rates of the whole cohort and subgroups.

Types of patients	N	5-year EFS		5-year OS	
		%	95% CI	%	95% CI
Overall	415	45.0	31.3-50.3	53.8	48.1-59.5
B-ALL	312	47.0	40.9-53.1	57.5	51.0-64.0
Ph-like B-ALL*	24	49.7	27.6-71.8	70.7	50.5-90.9
T-ALL	103	39.4	29.4-49.4	42.1	30.5-53.7
ETP T-ALL	42	24.0	9.3-38.7	13.8	0-34.6
Non-ETP T-ALL	61	49.7	36.6-62.8	56.2	42.3-70.1
MRD negative at EOI	193	60.5	52.7-68.3	68.0	60.2-75.8
MRD-lp at EOI	52	44.5	29.2-59.8	44.8	28.9-60.7
MRD-hp at EOI	55	43.2	27.3-59.1	52.4	34.1-70.6
MRD-vhp at EOI	89	19.3	10.9-27.7	36.7	24.2-49.2
Standard risk	148	57.6	48.6-66.6	70.9	62.7-79.1
High risk	267	38.0	31.5-44.5	44.0	36.7-51.3
Standard-risk B-ALL	143	57.8	48.8-66.8	71.5	63.3-79.7
High-risk B-ALL	169	37.6	29.4-45.8	44.9	35.7-54.1
Standard-risk T-ALL	5	60.0	17.1-100.0	53.3	4.7-100.0
High-risk T-ALL	98	38.6	28.4-48.8	42.0	30.2-53.8
Age <40 years	306	49.8	43.5-56.1	59.2	52.7-65.7
Age ≥40 years	109	31.5	21.9-41.1	38.3	27.5-49.1

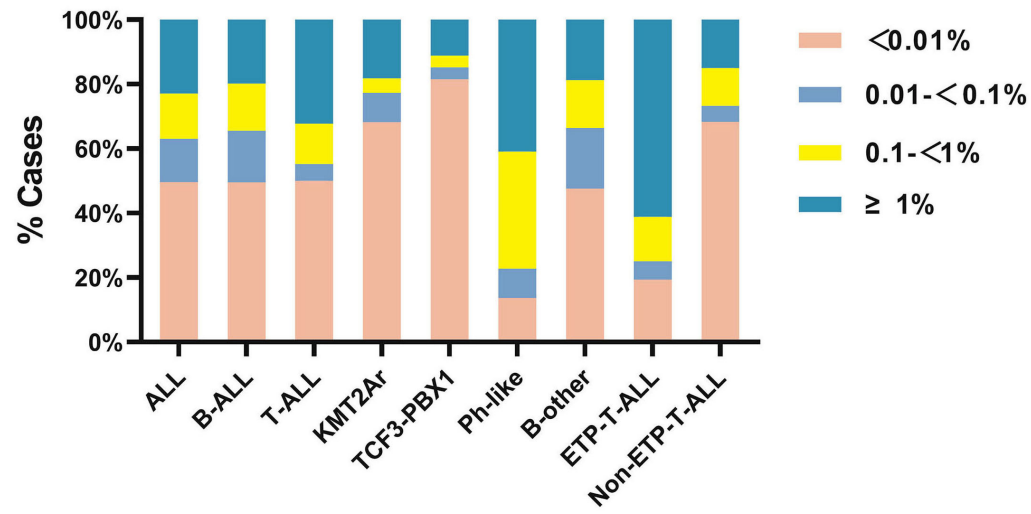
*The screening of Ph-like ALL started in 2017. EFS: event-free survival; OS: overall survival; ALL: acute lymphocytic leukemia; Ph: Philadelphia chromosome; ETP: early T-cell precursor; MRD: minimal residual disease; EOI: end of induction; lp: low positive; hp: high positive; vhp: very high positive.

A



Time points	Number of CR patients with different MRD levels (%)			
	＜0.01%	0.01-＜0.1%	0.1-＜1%	≥1%
Day 14 of induction	99 (25.6%)	23 (6%)	61 (15.8%)	203 (52.6%)
Post induction	193 (49.6%)	52 (13.4%)	55 (14.1%)	89 (22.9%)
Post-C1	222 (64.2%)	40 (11.5%)	35 (10.1%)	49 (14.2%)

B



Types of patients	Number of CR patients with different MRD levels at end of induction (%)			
	＜0.01%	0.01-＜0.1%	0.1-＜1%	≥1%
Overall	193 (49.6%)	52 (13.4%)	55 (14.1%)	89 (22.9%)
B-ALL	145 (49.5%)	47 (16.0%)	43 (14.7%)	58 (19.8%)
T-ALL	48 (50.0%)	5 (5.2%)	12 (12.5%)	31 (32.3%)
KMT2A-r	15 (68.2%)	2 (9.1%)	1 (4.5%)	4 (18.2%)
TCF3-PBX1	22 (81.5%)	1 (3.7%)	1 (3.7%)	3 (11.1%)
Ph-like	3 (13.6%)	2 (9.1%)	8 (36.4%)	9 (40.9%)
B-other	106 (47.6%)	42 (18.8%)	33 (14.8%)	42 (18.8%)
ETP-T-ALL	7 (19.4%)	2 (5.6%)	5 (13.9%)	22 (61.1%)
Non-ETP-T-ALL	41 (68.3%)	3 (5.0%)	7 (11.7%)	9 (15.0%)

Figure 3. Schematic graphs of minimal residual disease levels. (A) Minimal residual disease (MRD) status at three time points: day 14 of induction, after induction, and after the first consolidation (post-C1). (B) MRD levels at the end of induction stratified by disease types. The numbers and proportions of patients for each group are shown in tables below the figures. Post-C1: after the first consolidation; ALL: acute lymphocytic leukemia; KMT2Ar: *KMT2A* rearrangement; Ph-like: Philadelphia chromosome-like; ETP: early T-cell precursor; CR: complete remission; MRD: minimal residual disease.

47.4%, 43.8%, and 49.1% in patients with MRD-lp, MRD-hp, and MRD-vhp, respectively (Figure 4C).

To explore the prognostic value of dynamic MRD measurements during treatment, four groups were defined according to the MRD levels at EOI and post-C1: EOI negative/post-C1 negative (n=173, 50%), EOI positive/post-C1 negative (n=48, 13.9%), EOI negative/post-C1 positive (n=5, 1.4%), and EOI positive/post-C1 positive (n=120, 34.7%). The OS of patients with an early and durable MRD response (EOI negative/post-C1 negative) was significantly superior to that of the other patients, with a 5-year OS rate of 72.4% (95% CI: 64.6%-80.24%). There was not a statistically significant difference in OS between patients who converted from MRD positivity at EOI to negativity post-C1 and those with persistent MRD from EOI to post-C1 (5-year OS rate: 46.7% *vs*. 46.0%, *P*=0.363). The number of patients who transitioned from MRD negativity at EOI to positivity post-C1 was very small (n=5), and patients with such changes also had extremely poor OS (median OS, 12.6 months) (Figure 4D).

Univariate and multivariate analyses of overall survival

Online Supplementary Table S6 shows the prognostic factors for OS based on univariate and multivariate analyses. Compared with adolescents and young adults, patients aged ≥40 years had a significantly worse survival (Figure 5A). Multivariate analysis showed that age ≥40 years and positive post-induction MRD were independent predictors for OS. *Online Supplementary Figure S1* presents a forest plot for multivariate Cox regression of prognostic variables for OS.

Integrating risk stratification and minimal residual disease status to define new clinically prognostic subgroups

Based on their MRD status at EOI (negativity *vs*. positivity) and risk stratification at diagnosis (SR *vs*. HR), patients were divided into four groups: SR patients who were MRD negative (SR-MRD^{neg}; n=73), SR patients who were MRD positive (SR-MRD^{pos}; n=69), HR patients who were MRD negative (HR-MRD^{neg}; n=120), and HR patients who were MRD positive (HR-MRD^{pos}; n=127). The 5-year OS rates of SR-MRD^{neg}, SR-MRD^{pos}, HR-MRD^{neg}, and HR-MRD^{neg} patients were 82.6% (95% CI: 73.2%-92.0%), 58.7% (95% CI: 45.4%-72.0%), 58.3% (95% CI: 47.3%-69.3%), and 36.1% (95% CI: 25.5%-46.7%), respectively (*P*<0.001) (Figure 5B). The 5-year cumulative incidences of relapse were 24.2%, 41.1%, 36.3%, and 50.1%, respectively (*P*<0.001) (Figure 5C).

The four groups of patients were further stratified according to their transplantation status to explore the impact of allogeneic HSCT on survival. The baseline characteristics of patients who did or did not undergo allogeneic HSCT in CR1 in the same group are shown in *Online Supplementary Table S7*. In a landmark analysis, the 5-year OS rates of SR-MRD^{neg}

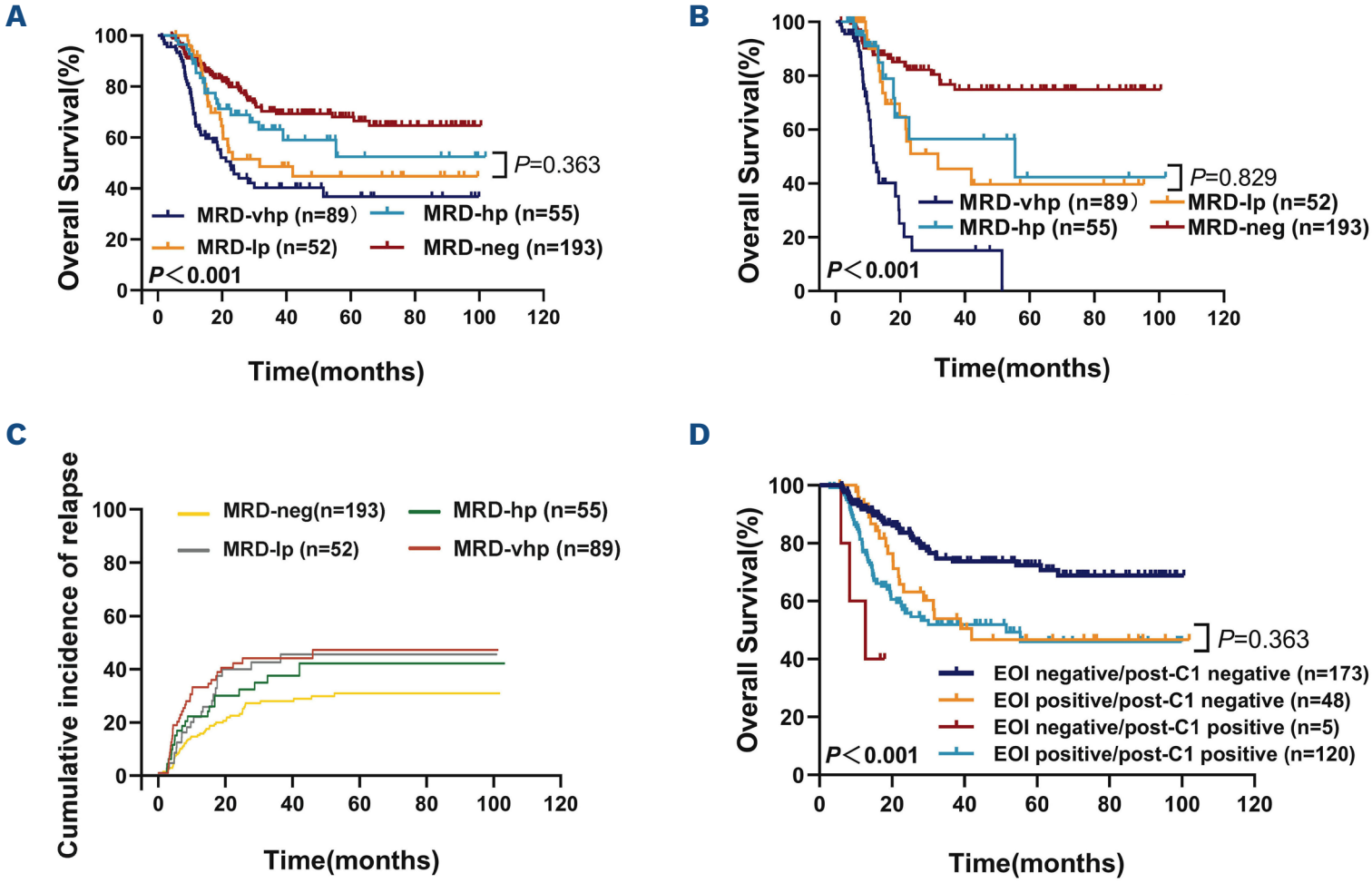


Figure 4. Survival outcomes. (A) Overall survival (OS) curves according to minimal residual disease (MRD) levels at the end of induction. (B) OS curves censored at the time of hematopoietic stem cell transplantation according to MRD levels at the end of induction. (C) Cumulative incidence of relapse curves according to MRD levels at the end of induction. (D) OS curves according to the combination of MRD levels at the end of induction and after the first consolidation (post-C1). MRD-neg: MRD-negative; MRD-lp: MRD-low positive; MRD-hp: MRD-high positive; MRD-vhp: MRD-very high positive; EOI: end of induction; post-C1: after first consolidation.

patients who underwent allogeneic HSCT in CR1 (n=28) and those who did not (n=37) were 44.5% (95% CI: 11.8%-77.2%) and 89.0% (95% CI: 78.8%-99.2%), respectively (*P*=0.044) (Figure 5D). The 5-year OS rates of HR-MRD^{neg} patients who received allogeneic HSCT in CR1 (n=67) and those who did not (n=41) were 64.8% (95% CI: 49.5%-80.1%) and 54.6% (95% CI: 36.8%-72.4%), respectively (*P*=0.150) (Figure 5E). Allogeneic HSCT in CR1 did not improve OS in patients in the same risk group who were MRD negative at EOI. However, in patients who were MRD positive at EOI, allogeneic HSCT in CR1 improved OS significantly both in the SR and HR groups. In the landmark analysis, the 5-year OS rates of SR-MRD^{pos} patients who received allogeneic HSCT in CR1 (n=38) and those who did not (n=22) were 59.3% (95% CI: 61.7%-90.3%) and 36.4% (95% CI: 15.2%-57.6%), respectively (*P*=0.016) (Figure 5F). The 5-year OS rates of HR-MRD^{pos} patients who received allogeneic HSCT in CR1 (n=67) and those who did not (n=41) were 59.3% (95% CI: 45.0%–73.6%) and 8.4% (95% CI: 0%–18.6%), respectively (*P*<0.001) (Figure 5G). Without considering the risk stratification, the 5-year OS rates of patients who were MRD-positive at EOI and who did (n=105) or did not (n=63) receive allogeneic HSCT in CR1 were 65.3% (95% CI: 54.5%-76.1%) and 18.0% (95% CI: 7.0%-29.0%), respectively, in the landmark analysis (*P*<0.001) (Figure 5H).

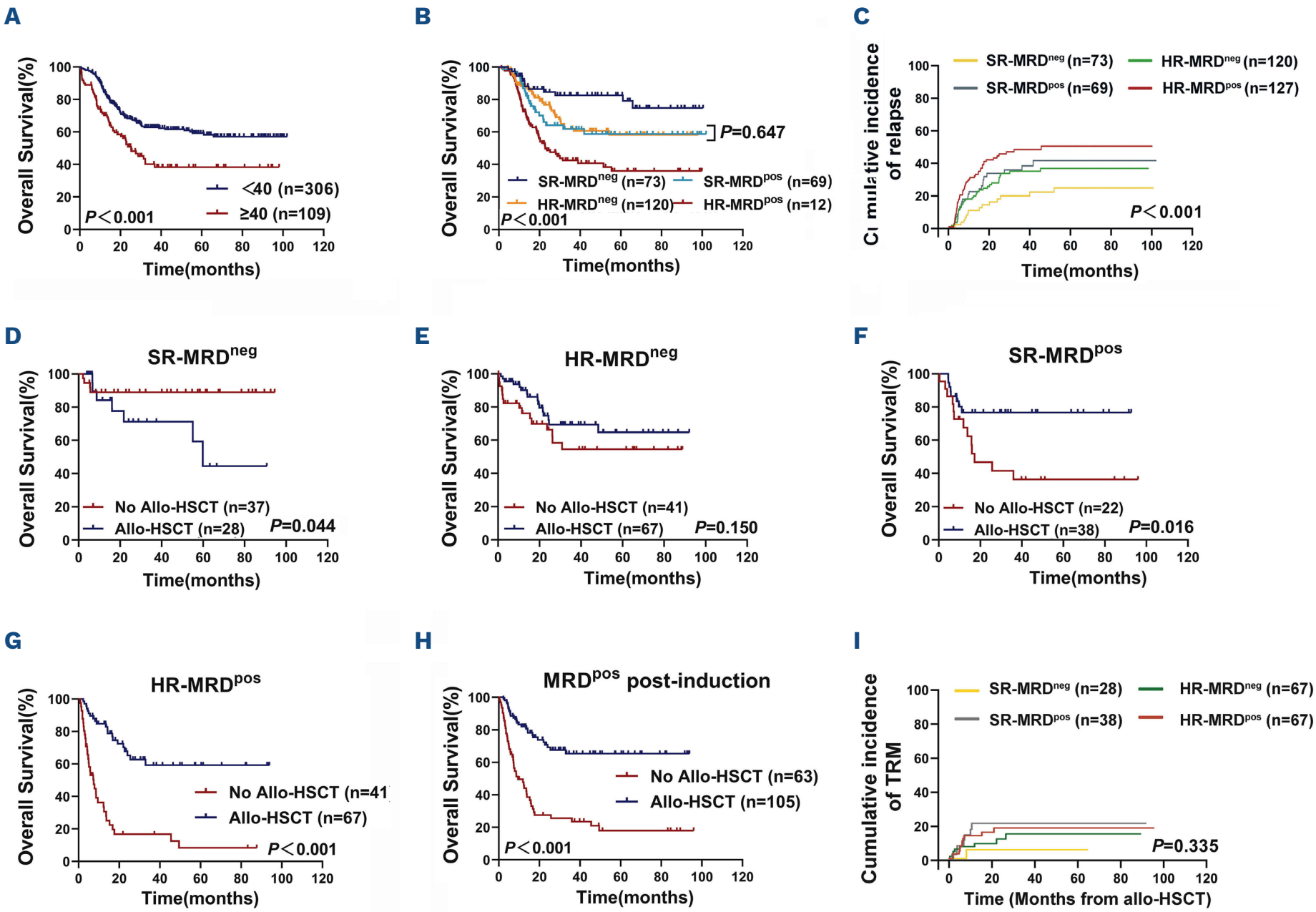


Figure 5. Survival outcomes. (A) Overall survival (OS) curves according to age (<40 *vs.* ≥40 years). (B) OS curves according to risk stratification combined with minimal residual disease (MRD) levels after induction. (C) Cumulative incidence of relapse curves according to risk stratification combined with post-induction MRD levels. (D) OS curves for standard-risk patients who were MRD-negative after induction according to allogeneic hematopoietic stem cell transplantation (allo-HSCT) status. (E) OS curves for high-risk patients who were MRD-negative after induction according to allo-HSCT status. (F) OS curves for standard-risk patients who were MRD-positive after induction according to allo-HSCT status. (G) OS curves for high-risk patients who were MRD-positive after induction according to allo-HSCT status. (H) OS curves for patients who were MRD-positive after induction according to allo-HSCT status. For (D) to (H), survival curves originate at a landmark of 6 months (the median time from enrollment to allo-HSCT) to adjust for bias related to early events. (I) Cumulative incidence of treatment-related mortality after allo-HSCT in first complete remission according to risk stratification combined with post-induction MRD levels. SR-MRD^{neg}: standard-risk patients who were negative for MRD following induction therapy; HR-MRD^{neg}: high-risk patients who were negative for MRD following induction therapy; SR-MRD^{pos}: standard-risk patients who were positive for MRD following induction therapy; HR-MRD^{pos}: high-risk patients who were positive for MRD following induction therapy; TRM: treatment-related mortality.

There were no statistically significant differences in cumulative incidence of treatment-related mortality among SR-MRD^{neg}, SR-MRD^{pos}, HR-MRD^{neg} and HR-MRD^{pos} patients who underwent allo-HSCT in CR1, with the 3-year treatment-related mortality rates of these patients being 5.55%, 22.22%, 15.56% and 19.24%, respectively (P=0.335) (Figure 5I).

Toxicities

In total, 12 (2.89%) patients with a median age of 47.5 years died during the induction phase. The primary causes of mortality were infection (75%) and intracranial hemorrhage (16.7%). There were four additional treatment-related deaths caused by infection during consolidation therapy. Therefore, the overall treatment-related mortality of the chemotherapy was 3.86%. Table 3 shows the grade 3-5 toxicities related to the induction and early consolidation cycles. As shown in the table, hematologic toxicity and infections (including bloodstream infection) were the most common toxicities, followed by liver toxicity. Asparaginase-related thromboembolic events were relatively infrequent.

Discussion

Novel immunotherapy has greatly changed the treatment paradigm for ALL, especially in the field of B-ALL;[14] nevertheless, the accessibility of novel immunotherapy is limited for the majority of Chinese patients in the frontline setting. Chemotherapy remains the cornerstone of treatment for newly diagnosed patients with Ph⁻ ALL, and combined with immunotherapy can further improve the survival of patients.[15] Compared with adult protocols, pediatric protocols have higher accumulated doses of non-myelosuppressive agents such as vincristine, glucocorticoids and asparaginase, and emphasize more intensive and prolonged central nervous system prophylaxis.[16] Due to significant survival benefits, pediatric-inspired regimens have been recommended as an international standard treatment for adolescents and young adults with Ph⁻ ALL.[12] However, the approach to treating adult patients is still a subject of controversy. Some studies have shown that the efficacy and tolerability of pediatric-inspired regimens are acceptable in adult patients aged up to 60 years. However, adult patients have a higher prevalence of treatment-related toxicities than adolescents and young adults.[17,18] Our study showed that the 5-year OS of adolescents and young adults (aged <40 years) and other adult patients (aged ≥40 years) were 59.2% and 38.3%, respectively. Patients who died during induction therapy were older (median age: 47.5 *vs*. 27 years for the cohort). In our study, the efficacy and tolerability of the pediatric-inspired regimens in adult patients was significantly lower than those in adolescents and young adults.

The incidence of asparaginase-induced toxicities in our study was lower than that reported in other studies,[8,20,21] which may be related to factors such as a lower median age of enrolled patients, using preventive treatment for hepatotoxicity, consuming a low-fat diet, and Chinese people being at a lower risk of thrombotic events.[22] Even so,

Table 3. Selected grade 3 to 5 adverse events in induction and early consolidation cycles.

Adverse event N (%)	Induction N=415			Consolidation I N=382			Consolidation II N=336			Interim maintenance I N=271		
	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5
Elevated ALT	31 (7.5)	2 (0.5)	-	17 (4.5)	4 (1.0)	-	22 (6.5)	1 (0.3)	-	-	-	-
Elevated AST	25 (6.0)	4 (1.0)	-	8 (2.1)	-	-	5 (1.5)	-	-	-	-	-
Hyperbilirubinemia	21 (5.1)	-	-	13 (3.4)	-	-	11 (3.3)	-	-	-	-	-
Hyperglycemia	11 (2.7)	3 (0.7)	-	3 (0.8)	-	-	-	-	-	-	-	-
Bloodstream infection	66 (15.9)	6 (1.4)	4 (1.0)	54 (14.1)	2 (0.5)	-	29 (8.6)	1 (0.3)	-	-	-	-
Infection (except BSI)	366 (88.2)	10 (2.4)	5 (1.2)	302 (79.1)	3 (0.8)	-	208 (61.9)	-	-	8 (3.0)	-	-
Intracranial hemorrhage	-	-	2 (0.5)	-	-	-	-	-	-	-	-	-
Gastrointestinal hemorrhage	-	1 (0.2)	-	3 (0.8)	-	-	-	-	-	-	-	-
Tumor lysis syndrome	4 (1.0)	2 (0.5)	-	-	-	-	-	-	-	-	-	-
Pancreatitis	3 (0.7)	1 (0.2)	-	2 (0.5)	-	-	1 (0.3)	-	-	-	-	-
Neutropenia	4 (1.0)	408 (98.3)	-	12 (3.1)	363 (95.0)	-	23 (6.8)	307 (91.4)	-	11 (4.1)	32 (11.8)	-
Thrombocytopenia	49 (11.8)	319 (76.9)	-	24 (6.3)	348 (91.1)	-	29 (8.6)	296 (88.1)	-	13 (4.8)	26 (9.6)	-
Intestinal obstruction	18 (4.3)	-	-	10 (2.6)	-	-	1 (0.3)	-	-	1 (0.4)	-	-
Thrombosis	3 (0.7)	-	1 (0.2)	-	-	-	-	-	-	-	-	-
Heart failure	3 (0.7)	-	-	2 (0.5)	-	-	-	-	-	-	-	-
Elevated serum creatinine	3 (0.7)	-	-	-	-	-	-	-	-	13 (4.8)	1 (0.4)	-

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BSI: bloodstream infection.

a small number of patients who were unable to tolerate toxicities of chemotherapy and achieve early MRD negativity underwent autologous HSCT as an alternative treatment option.[23] More consideration should be given to the patients who were intolerant to pediatric-inspired chemotherapy. Dose modification to chemotherapy regimens and the introduction of novel immunotherapies could be the future directions for decreasing toxicity and improving survival in adult patients, particularly those aged ≥40 years.[24,25]

The prognostic factors for ALL mainly include genetic and molecular factors as well as clinical factors.[26,27] The identification of genetic prognostic subgroups requires the combination of molecular diagnostic techniques including polymerase chain reaction, G-banding, fluorescence *in situ* hybridization, RNA sequencing, and targeted next-generation sequencing. However, the abovementioned tests are less likely to be available at diagnosis for Chinese patients. Indeed, the application of genetic and molecular prognostic classification is limited by the inaccessibility of molecular diagnostic techniques. Meanwhile, risk stratification based on traditional prognostic factors such as white blood cell count, age, and immunophenotype is still widely used in clinical practice due to its simplicity and lower requirements for testing techniques.[12,27,28] In addition to the abovementioned static prognostic indicators, MRD is currently considered the most powerful predictor in patients with ALL.[29] The timepoints and thresholds for MRD monitoring in pediatric ALL have been well established.[30] However, the surveillance strategy in adult ALL has not yet been standardized. Stock and colleagues[8] showed that adolescents and young adults with an MRD level of >0.01% at EOI had a significantly inferior DFS compared to those with an MRD of <0.01%. Bassan *et al*. found that MRD persistence at 10 weeks is an indication for allogeneic HSCT in adult patients after induction therapy.[31] Our study confirmed that MRD negativity at EOI is an independent prognostic factor for OS. Patients with MRD-lp and MRD-hp at EOI had a lower OS and a higher relapse incidence than those who were MRD-negative. In addition, only 13.9% of patients who were MRD-positive at EOI became MRD-negative post-C1, and their OS was not improved compared to that of patients with persistent MRD from EOI to post-C1. Therefore, early and deep MRD clearance is important, and even extremely low, but detectable, levels of MRD levels can predict poor prognosis.

Patients were further grouped based on both post-induction MRD levels and traditional risk factors. The 5-year OS rates of SR-MRD^{neg}, SR-MRD^{pos}, HR-MRD^{neg}, and HR-MRD^{pos} patients were 82.6%, 58.7%, 58.3%, and 36.1%, respectively. The survival rates did not differ significantly between HR-MRD^{neg} patients who received allogeneic HSCT in CR1 and those who did not. This finding is consistent with that of a multicenter prospective clinical study conducted by a Spanish collaborative group.[12] Allogeneic HSCT improves survival in post-induction MRD-positive patients, regardless of stratification at diagnosis. However, this conclusion was only based on the use of pediatric-inspired chemotherapy and/or allogeneic HSCT, not incorporating novel immunological agents in the frontline setting. Given the promising efficacy of blinatumomab in clearing MRD,[32] more clinical evidence is needed to confirm the timing of and necessity for allogeneic HSCT for CR1 patients with MRD response after blinatumomab treatment in the context of standard chemotherapy combined with immunotherapy.

The present study had some limitations. First, it was performed at a single center. Second, the protocol design of this study did not dynamically adjust the intensity of chemotherapy or introduce immunotherapy according to MRD levels. Third, the relatively high rate of allogeneic HSCT is not entirely consistent with the principles of apediatric regimen. In conclusion, adolescents and young adults are more likely to benefit from pediatric-inspired regimens compared with patients aged ≥40 years. The pediatric-inspired regimen was safe and well tolerated by patients. Age ≥40 years and persistent MRD detectable after induction were independent prognostic factors. Traditional risk factors combined with post-induction MRD status exhibit good predictive significance for survival and recurrence, which is helpful in guiding the selection of allogeneic HSCT.

Disclosures

No conflicts of interest to disclose.

Contributions

YM and JW contributed to the study design. X-YG wrote the initial draft of the manuscript. All authors analyzed data and approved the final version of the manuscript.

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Data-sharing statement

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

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