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Prognostic impact of *IL7R* mutations on acute myeloid leukemia

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Abstract

Background: Interleukin-7 receptor (*IL7R*) mutation has been demonstrated to be an adverse prognostic factor in acute lymphoblastic leukemia (ALL) patients. However, the effects of the *IL7R* mutation on acute myeloid leukemia (AML) have rarely been reported. Here, we investigated *IL7R* mutations and their effects on AML patients.

Methods: A total of 346 newly diagnosed AML patients from January 2017 to July 2020 at Nanfang Hospital were analyzed in this study. A genomic panel of 167 gene targets was detected by next-generation sequencing.

Results: Among 346 patients, 33 (9.5%) AML patients carried *IL7R* mutations. With a median follow-up of 50.7 months (95% confidence interval (CI) 17.3–62.2), the 5-year overall survival (OS) rates were 51.5% (95% CI 37.0%–71.0%) and 72.2% (95% CI 67.4%–77.3%; $p = 0.008$), the 5-year event-free survival (EFS) rates were 36.1% (95% CI 23.2%–57.1%) and 58.1% (95% CI 52.9%–63.8%; $p = 0.005$), the 5-year non-relapse mortality (NRM) were 21.4% (95% CI 8.5%–38.2%) and 6.2% (95% CI 3.7%–9.5%; $p = 0.004$) in the IL7R mutant ($IL7R^{MUT}$) group and non-IL7R mutant ($IL7R^{WT}$) group, respectively. There is no significant difference in the disease-free survival (75.1% vs 73.5%, $p = 0.885$) and cumulative incidence of relapse (25.7% vs 25.2%, $p = 0.933$) between $IL7R^{MUT}$ and $IL7R^{WT}$ group. Furthermore, patients who underwent hematopoietic stem cell transplantation (HSCT) still had more adverse outcomes in the $IL7R^{MUT}$ group than in the $IL7R^{WT}$ group (5-year OS: 61.9% vs 85.3%, $p = 0.003$). In the *TET2* ($p = 0.013$) and DNA methyltransferase 3A (*DNMT3A*; $p = 0.046$) mutation subgroups, the presence of *IL7R* mutations was associated with worse OS than in AML patients without *IL7R* mutations.

Conclusion: Our study demonstrated that the *IL7R* mutation is associated with an inferior prognosis for AML patients. Patients with *IL7R* mutations have higher NRM, shorter OS, and EFS than patients without *IL7R* mutations, even patients who have undergone HSCT. Future larger and multicentric prospective studies will be explored.

Plain language summary

The effects of IL7R mutation on AML patients

With the development of NGS, more and more cytogenetic and molecular markers have been found to be associated with prognosis of ALL. IL7R mutation is associated with an inferior prognosis for AML patients. Patients with IL7R mutation have higher NRM, shorter OS and EFS than patients without IL7R mutation, even patients who have undergone HSCT.

Keywords: acute myeloid leukemia, hematopoietic stem cell transplantation, IL7R mutation, next-generation sequencing, prognosis analysis

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Background

Acute myeloid leukemia (AML) is a clonal malignant proliferative disease of myeloid blasts in the hematopoietic system.[1–3] With the development of next-generation sequencing (NGS), an increasing number of cytogenetic and molecular markers have been found to be associated with the pathogenesis and prognosis of AML.[4–9] European Leukemia Net (ELN), a genetic risk stratification, has been widely used in the clinical and plays a pivotal role in guiding appropriate treatment.[6] However, several studies have suggested that the clinical outcomes are heterogenous within the ELN risk groups and may be affected by other co-existing genetic mutations.[10,11] Previous study demonstrated that patients with DNA methylation regulatory gene mutations (*DNMT3A*, *IDH1/2*, *TET2*, *SETBP1*) was shorter in overall survival (OS) rate than patients without DNA methylation regulatory gene mutations in ELN favorable group, particularly in those with NPM1 mutant.[12] In addition, the prognosis of patients with single mutations and patients with multiple mutations are different. "Patients with isolated nucleophosmin 1 (*NPM1*)" have higher complete remission (CR) rates, and better relapse-free survival (RFS) and OS.[13–15] However, patients with *NPM1* and *DNMT3A* co-mutation significantly have worse OS and leukemia-free survival compared to isolated *NPM1*-mutated patients.[16–18] It has been demonstrated that CEBPA mutations that are in-frame mutations affecting the basic leucine zipper region (bZIP) confer a favorable outcome, irrespective of their occurrence as biallelic ($CEBPA^{bi}$) or single mutation ($CEBPA^{sm}$). There is no definitive conclusion about the impact of co-mutations. Tarlock et al. found that the presence of a colony-stimulating factor 3 receptor (CSF3R) mutation in patients with CEBPA mutations is associated with a remarkably high relapse risk and poor event-free survival (EFS).[6,19–22] Therefore, more prognostic markers need to be urgently explored to guide optimal treatments.[10,11,20]

The interleukin-7 receptor (*IL7R*), a heterodimer consisting of the specific IL7Rα chain (also known as CD127) and the common γ-chain (also known as CD132), are mainly expressed in hematopoietic cells, including T-cells, B cells, NK cells, and innate lymphoid cells. *IL7R* are required for the normal T-cell development and homeostasis of mature T-cells. *IL7R* mutational activation is one of the drivers of acute lymphoblastic leukemia (ALL).[23–27] Gain-of-function mutations in *IL-7R* have been identified in 7%–10% of T-cell acute lymphoblastic leukemia (T-ALL) patients and approximately 2%–3% of B-cell acute lymphoblastic leukemia (B-ALL) patients.[28–30] Most *IL7R* mutations are located in exon 6 in T-ALL and B-ALL patients. In addition, *IL7R* exon 5 mutations have also been found in a few patients with B-ALL.[23,31] A correlation of *IL7R* mutations with prognosis in ALL has been sporadically reported. Alsadeq et al. demonstrated that the *IL7R* mutation was an adverse prognostic factor in pediatric B-cell precursor ALL with higher central nervous system infiltration and relapse. Besides, the *IL7R* mutation in the relapse of T-ALL was correlated with worse survival.[32,33] However, the effects of the *IL7R* mutation on AML have rarely been reported. In adult AML, Kim et al. reported that *IL7R* exon6 mutation was around 1% in AML.[31] A case report showed that an *IL7R* mutation was found in a secondary AML patient with a dismal clinical course.[34] Therefore, we conducted a large retrospective study to explore *IL7R* mutations and their effects on AML patients.

Methods

Patients and data collection

This study examined patients with newly diagnosed AML between January 2017 and July 2020 at Nanfang Hospital. The clinical data cutoff date was August 31, 2023. Patients who met the following criteria were analyzed: (1) aged between 14 and 80 years, (2) diagnosed with de novo AML or secondary AML, and (3) NGS data available at diagnosis.

Cytogenetic and molecular analyses

Cytogenetic analyses were performed with Giemsa and reverse banding techniques and fluorescence in-situ hybridization (FISH). Conventional cytogenetic karyotyping was processed by standard G-banding or R-banding cytogenetic methods. Karyotypes were classified according to the International System for Human Cytogenetic Nomenclature (ISCN 2020). A FISH analysis is performed according to the standard protocol, using the following probes: PML/RARA(15Q22;17Q21.1), aml1/

eto(8q22;21q22), MLL(11q23), and CBFβ (16q22). NGS was used for molecular analyses. A genomic panel of 167 gene targets was detected in bone marrow (BM) samples by NGS at the time of diagnosis (Supplemental Table S1). NGS was carried out on the Ion Torrent platform (in the target rate of 97%–99%, with an average depth of 1000×, the average is 94%–97%). The reference sequence was used in the human genome GRCh37.[35,36] Risk groups were assigned using the 2022 ELN risk stratification scheme.

Treatment protocol

Generally, patients receive "3 + 7" standard induction therapy, and patients who are unfit for standard induction chemotherapy receive lower-intensity induction therapy, including VA (venetoclax, azacitidine) and D-CAG (decitabine, cytarabine, aclarubicin, granulocyte colony-stimulating factor).[37–39] After achieving CR, patients received cytarabine-based consolidation chemotherapy and/or bridged to auto-SCT/allo-SCT (Stem Cell Transplantation) based on Minimal Residual Disease (MRD) status and donor availability.[40] Patients who did not achieve CR received salvage chemotherapy, including CAG (aclarubicin, cytarabine, granulocyte colony-stimulating factor), FLAG (fludarabine, cytarabine, granulocyte colony-stimulating factor), and VAH (venetoclax, azacitidine, homoharringtonine).[41–43]

Evaluation, definitions, and statistics

This study focused mainly on OS, EFS, disease-free survival (DFS), cumulative incidence of relapse (CIR), and non-relapse mortality (NRM). OS was measured from the date of diagnosis until death or censored at the last follow-up. EFS was defined as the time from the date of diagnosis until documented failure to achieve CRc, relapse after CRc, or death from any cause, whichever occurred first. CRc comprised CR and CRi (defined as all the criteria for CR, except for neutropenia or thrombocytopenia). Relapse was defined by morphologic evidence of the original hematologic disease in the peripheral blood, BM, or any extramedullary site. DFS was defined as the time from CR to relapse or death from any cause. NRM was defined as death from any cause not subsequent to relapse.[4,6,20,44,45]

Comparisons of continuous variables between groups were conducted using the Mann–Whitney *U* test, while comparisons of categorical variables between groups were performed using the Chi-square test or Fisher's exact test. OS, EFS, and DFS were compared using the Kaplan–Meier analysis with the log-rank test. Hazard ratios (HRs) and 95% confidence interval (95% CI) were calculated using the Cox proportional hazards models. The CIR and NRM were adjusted for the competing risk analysis. Competing events were defined as follows: for relapse, NRM; for NRM, relapse. The Cox proportional hazards model was used for the analysis of risk factors for time-to-event variables. Only variables with a *p*-value less than 0.05 were included in the multivariable analysis. The correlations among various mutations were analyzed by the "ggcorrplot" package. Mutation status and frequency of genetic abnormalities were analyzed by the "oncoplot" package. A forest plot with HR and 95% CI was a simple and intuitive description of relative risks between *IL7R* mutation and concomitant genetics. All the statistical tests were two-tailed with a significance level of 0.05. Statistical analyses were conducted using GraphPad Prism 7, SPSS version 24.0, and R statistical software (version 4.1.1).

Results

Patient baseline characteristics and IL7R *mutations*

Total of 346 newly diagnosed AML patients from Nanfang Hospital from January 2017 to July 2020 were analyzed in this study. There were 324 de novo AML and 22 secondary AML in the cohort, including 18 patients progressing from myelodysplastic syndrome. There were 186 men and 160 women, with a median age of 38 years (range: 14–77). *IL7R* mutations were observed in 33 patients (9.5%). The median age at diagnosis in the $IL7R^{MUT}$ group was older than that in the $IL7R^{WT}$ group ($p = 0.031$). Except for age, other baseline characteristics were similar between the two groups (Table 1). There were 21.2% for ELN favorable, 36.4% for intermediate-risk, and 42.4% for adverse-risk among patients with *IL7R* mutation. We further explore the correlation between *IL7R* mutations and other gene mutations with mutation rates more than 5%. We found co-occurrence of *IL7R* mutations with

Table 1. Baseline characteristics ($n = 346$).

Characteristics	*IL7R* mutated type ($n = 33$)	*IL7R* wild type ($n = 313$)	*p*
Age, median (range), years	44.0 (17–75)	38.0 (14–77)	0.031*
Gender, no (%)			0.407
Male	20 (60.6)	166 (53.0)	
Female	13 (39.4)	147 (47.0)	
EOCG score, no (%)			0.469
0–1	28 (84.8)	249 (79.6)	
⩾2	5 (15.2)	64 (20.4)	
Diagnosis, no (%)			0.351
De novo AML	30 (90.9)	294 (93.9)	
Secondary AML	3 (9.1)	19 (6.1)	
Peripheral blood cells			
WBC, median (range), $\times 10^9$/L	19.0 (1.1–185.2)	16.9 (0.5–425.3)	0.873
HGB, median (range), g/L	78.0 (27.0–124.0)	76.0 (20.0–157.0)	0.961
PLT, median (range), $\times 10^9$/L	40.0 (11.0–288.0)	48.0 (3.0–484.0)	0.744
BM blasts, median (range), %	57.3 (13.0–95.0)	55.5 (3.5–98.5)	0.874
Cytogenetics risk, no (%)			0.580
Favorable	3 (9.1)	42 (13.4)	
Intermediate	25 (75.8)	201 (64.2)	
Adverse	4 (12.1)	48 (15.3)	
Unknown	1 (3.0)	22 (7.0)	
ELN risk stratification, no (%)			0.576
Favorable	7 (21.2)	71 (22.7)	
Intermediate	12 (36.4)	87 (27.8)	
Adverse	14 (42.4)	155 (49.5)	
Treatment, no (%)			0.293
Intensive chemotherapy	29 (87.9)	291 (93.0)	
Low-intensity chemotherapy	4 (12.1)	22 (7.0)	
Transplantation, no (%)			0.362
Yes	21 (63.6)	223 (71.2)	
No	12 (36.4)	90 (28.8)	

(Continued)

Table 1. (Continued)

Characteristics	*IL7R* mutated type ($n = 33$)	*IL7R* wild type ($n = 313$)	*p*
Mutation, no (%)			
KIT	0 (0)	26 (8.3)	—
FLT3-ITD	6 (18.2)	65 (20.8)	0.727
NPM1	8 (24.2)	52 (16.6)	0.271
CEBPA	3 (9.1)	28 (8.9)	1.000
TP53	1 (3.0)	20 (6.4)	0.707
RUNX1	1 (3.0)	28 (8.9)	0.337
ASXL1	5 (15.2)	53 (16.9)	0.794
IDH1	2 (6.1)	15 (4.8)	0.671
IDH2	2 (6.1)	35 (11.2)	0.555
DNMT3A	5 (15.2)	33 (10.5)	0.386
TET2	11 (33.3)	153 (48.9)	0.089
EZH2	5 (15.2)	57 (18.2)	0.663
BCOR	4 (12.1)	26 (8.3)	0.510
DDX18	4 (12.1)	37 (11.8)	1.000
TET1	12 (36.4)	105 (33.5)	0.745
EP300	11 (33.3)	74 (23.6)	0.219
CD101	8 (24.2)	82 (26.2)	0.808
FAT1	5 (15.2)	66 (21.2)	0.422
FAM46C	4 (12.1)	31 (9.9)	0.759
DNMT1	8 (24.2)	25 (8.0)	0.007*
PDGFRB	3 (9.1)	33 (10.5)	1.000
TNFAIP3	2 (6.1)	27 (8.6)	1.000
GATA2	2 (6.1)	25 (8.0)	1.000
ETV6	3 (9.1)	22 (7.0)	0.720
KDM6A	3 (9.1)	19 (6.1)	0.740
CSF3R	5 (15.2)	18 (5.8)	0.039*
ACTR5	2 (6.1)	20 (6.4)	1.000
SH2B3	3 (9.1)	16 (5.1)	0.409
CD123	1 (3.0)	19 (6.1)	0.707

*Statistically significant difference ($p < 0.05$) was observed between two groups.
AML, acute myeloid leukemia; BM, bone marrow; *CSF3R*, colony-stimulating factor 3 receptor; *DNMT1*, DNA methyltransferase 1; *DNMT3A*, DNA methyltransferase 3A; ELN, European Leukemia Net; HGB, hemoglobin; *IL7R*, interleukin-7-receptor; *NPM1*, nucleophosmin 1; PLT, platelet; WBC, white blood cell.

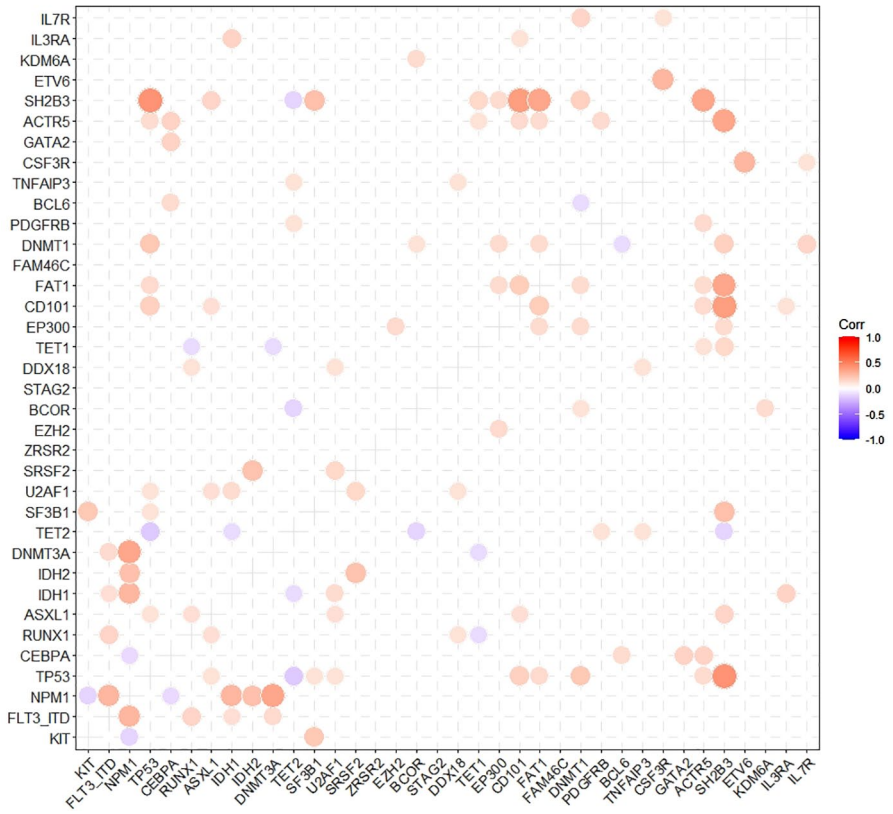

Figure 1. Correlation matrix for genetic mutations in AML patients (mutation frequency ⩾5%). Some co-occurrence mutations were negatively related, represented in blue, and others were positively related, represented in red. The darker the color, the higher the correlation was ($p < 0.05$).
AML, acute myeloid leukemia.

DNA methyltransferase 1 (*DNMT1;* $p = 0.007$) and *CSF3R* ($p = 0.039$), but no other genetic mutations in co-occurrence of *IL7R* mutations (Figure 1 and Supplemental Table S2).

Survival

With a median follow-up of 50.7 months (interquartile range (IQR) 17.3–62.2; 95% CI 46.5–54.3) the median OS was 24.9 months (IQR 7.9–62.0; 95% CI 9.0–60.5) in the $IL7R^{MUT}$ group and 50.6 months (IQR 21.8–64.1; 95% CI 46.9–54.0) in the $IL7R^{WT}$ group, corresponding to a 5-year OS of 51.5% (95% CI 37.0%–71.7%) for the $IL7R^{MUT}$ group versus 72.2% (95% CI 67.4%–77.3%) for the $IL7R^{WT}$ group (HR 2.0, 95% CI 1.2–3.5; $p = 0.008$, Figure 2a). The median EFS was 8.9 months (IQR 3.4–60.3; 95% CI 5.3–54.4) in the $IL7R^{MUT}$ group compared with 43.0 months (IQR 8.1–59.8; 95% CI 40.6–46.9) in the $IL7R^{WT}$ group, corresponding to a 5-year EFS of 36.1% (95% CI 23.2%–57.1%) for the $IL7R^{MUT}$ group versus 58.1% (95% CI 52.9%–63.8%) for the $IL7R^{WT}$ group (HR 1.9, 95% CI 1.2–3.1 $p = 0.005$, Figure 2b). The 5-year DFS was 75.1% (95% CI 59.6%–94.7%) in the $IL7R^{MUT}$ group and 73.5% (95% CI 68.3%–79.0%) in the $IL7R^{WT}$ group (HR 1.1, 95% CI 0.5–2.4 $p = 0.885$, Figure 2c). In the $IL7R^{MUT}$ and $IL7R^{WT}$ groups, the 5-year CIR was 25.7% (95% CI 10.8%–42.2%) and 25.3% (95% CI 20.2%–30.4%), respectively ($p = 0.933$, Figure 2d) and the 5-year NRM was 21.4% (95% CI 8.5%–38.2%) for the $IL7R^{MUT}$ group and 6.2% (95% CI 3.7%–9.5%) for the $IL7R^{WT}$ group ($p = 0.004$, Figure 2e). A multivariable analysis revealed that non-hematopoietic stem cell transplantation (HSCT), poorer prognostic stratification, and *IL7R* mutation were risk factors for OS and EFS. And poorer cytogenetic stratification, lower score of ECOG, and *IL7R* mutation were risk factors for NRM (Table 2).

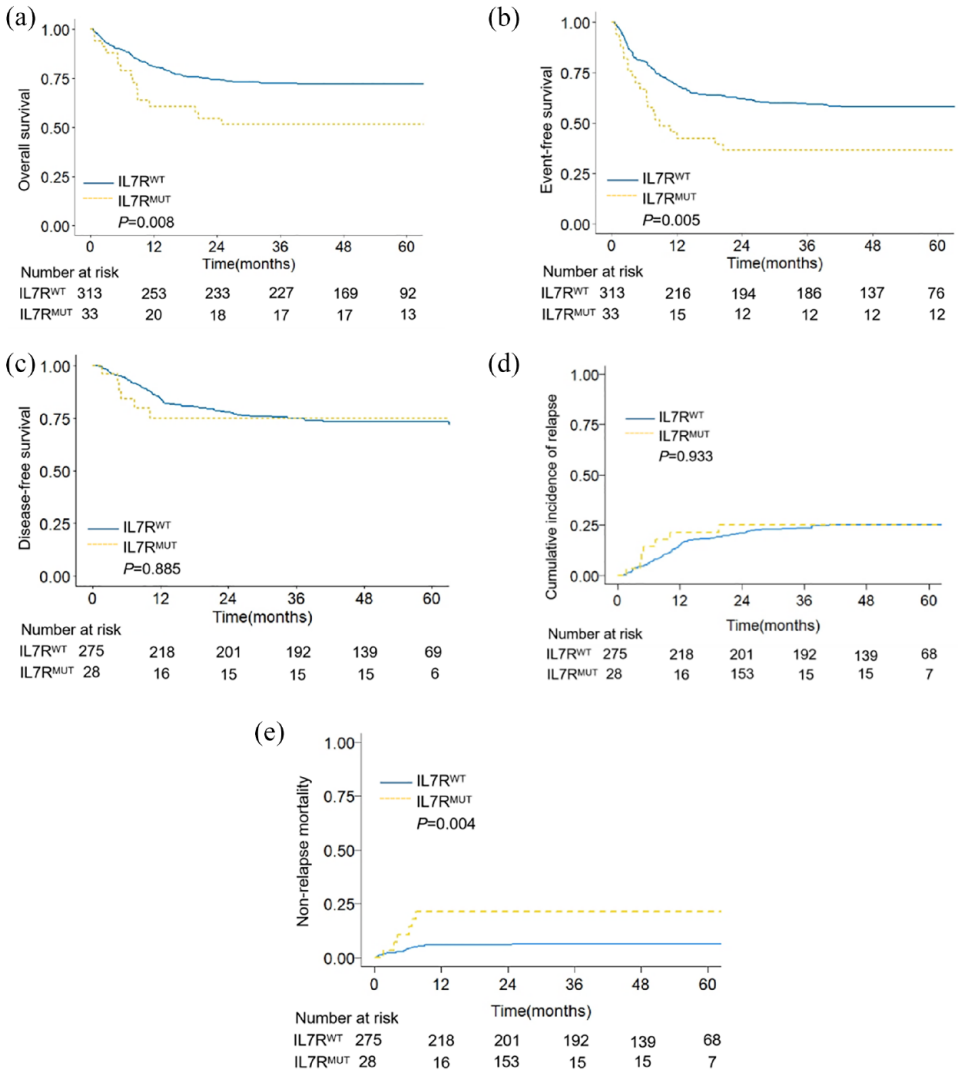

Figure 2. Survival between *IL7R*^{MUT} and *IL7R*^{WT} group among AML patients. (a) Overall survival, (b) event-free survival, (c) disease-free survival, (d) cumulative incidence of relapse, and (e) non-relapse mortality of the *IL7R*^{MUT} group and *IL7R*^{WT} group.
AML, acute myeloid leukemia; *IL7R*, interleukin-7-receptor.

To explore the impact of age and treatment intensity on outcome, we do further subgroup analysis. It demonstrated that patients with *IL7R* mutation had poorer prognosis 5-year OS and EFS in the subgroup of age<60 and intensive treatment. There is no significance in 5-year OS, EFS in the subgroup of age ⩾60 and low-dose treatment (Supplemental Table S3).

Among 346 AML patients, 103 (29.8%) patients died—16 in the *IL7R*^{MUT} group and 87 in the *IL7R*^{WT} group. In the IL7R^{MUT} group, the most common cause of death was infection (8 of 16 patients, 50.0%), which accounted for 37.5% for pneumonia cases and 43.8% for septicemia cases. In the *IL7R*^{WT} group, the incidence of infection was 26.4%, including 20.7% of pneumonia and 17.2% of septicemia. Infection-related mortality in patients with *IL7R* mutation was higher than non-*IL7R* mutation ($p = 0.003$, Table 3).

Effects of the IL7R *mutation in AML patients receiving HSCT*

Among 346 AML patients, 245 received HSCT. The baseline characteristics of the AML patients

Table 2. Uni- and multivariate analyses of overall survival, event-free survival, and non-relapse mortality in AML patients.

Variables	Overall survival				Event-free survival				Non-relapse morality			
	Univariable		Multivariable		Univariable		Multivariable		Univariable		Multivariable	
	HR (95% CI*)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Sex, male vs female	0.832 (0.563–1.30)	0.357	—	—	0.954 (0.694–1.311)	0.770	—	—	0.972 (0.429–2.202)	0.945	—	—
Age, <38 years vs ⩾38 years	2.183 (1.443–3.303)	<0.001*	—	—	1.328 (0.964–1.830)	0.083	—	—	2.438 (1.003–5.926)	0.049*	—	—
ECOG score, 0–1 vs ⩾2	2.194 (1.450–3.319)	<0.001*	—	—	1.577 (1.092–2.276)	0.015*	—	—	2.694 (1.142–6.355)	0.024*	3.288 (1.369–7.897)	0.008*
Treatment, low-dose vs intensive chemotherapy	0.529 (0.290–0.967)	0.039	—	—	0.655 (0.385–1.117)	0.120	—	—	0.686 (0.161–0.924)	0.610	—	—
WBC, $<17\times10^9$/L vs $\geqslant17\times10^9$/L	1.076 (0.728–1.590)	0.714	—	—	1.162 (0.841–1.605)	0.363	—	—	1.063 (0.469–2.410)	0.883	—	—
Transplantation, non-HSCT vs HSCT	0.170 (0.114–0.253)	<0.001*	0.138 (0.091–0.208)	<0.001*	0.353 (0.256–0.487)	<0.001*	0.297 (0.213 to −0.414)	<0.001*	0.396 (0.168–0.933)	0.034*	—	—
Cytogenetic stratification	1.561 (1.235–1.973)	<0.001*	1.575 (1.216–2.039)	0.001*	1.430 (1.178–1.736)	<0.001*	1.370 (1.109–1.693)	0.004	1.748 (1.084–2.817)	0.022*	1.857 (1.147–3.007)	0.012*
Favorable	Reference	—	Reference	—	Reference	—	Reference	—	Reference	—	Reference	—
Intermediate	2.788 (1.121–6.936)	0.027*	—	—	2.628 (1.327–5.203)	0.006*	2.100 (1.047–4.210)	0.037*	2.966 (0.388–22.672)	0.295	—	—
Adverse	6.343 (2.442–16.481)	<0.001*	4.550 (1.671–12.392)	0.003	5.320 (2.559–11.060)	<0.001*	3.903 (1.791–8.520)	0.001*	9.287 (1.142–75.544)	0.037*	10.588 (1.297–86.472)	0.028*
ELN risk stratification	1.458 (1.123–1.892)	0.005	1.710 (1.308–2.237)	<0.001*	1.469 (1.187–1.817)	<0.001*	1.581 (1.268–1.923)	<0.001*	1.366 (0.802–2.326)	0.252	—	—
Favorable	Reference	—	Reference	—	Reference	—	Reference	—	Reference	—	Reference	—
Intermediate	2.081 (1.089–3.978)	0.027	2.866 (1.476–5.565)	0.002*	1.879 (1.117–3.160)	0.017*	2.138 (1.251–3.654)	0.005*	4.462 (1.017–21.187)	0.048*	—	—
Adverse	2.434 (1.335–4.438)	0.004	3.535 (1.905–6.508)	<0.001*	2.358 (1.464–3.796)	<0.001*	2.791 (1.701–4.580)	<0.001*	3.174 (0.704–14.321)	0.133	—	—
Group, *IL7R*^{WT} vs *IL7R*^{MUT}	2.036 (1.194–3.471)	0.009	2.150 (1.248–3.703)	0.006	1.924 (1.213–3.052)	0.005*	1.900 (1.194–3.023)	0.007*	3.941 (1.522–10.008)	0.004*	5.179 (1.981–13.542)	0.001*

*Statistically significant difference ($p<0.05$) was observed between two groups.
AML, acute myeloid leukemia; CI, confidence interval; ELN, European Leukemia Net; HR, hazard ratio; HSCT, hematopoietic stem cell transplantation; *IL7R*, interleukin-7-receptor; WBC, white blood cell.

Table 3. Causes of death in AML patients ($n = 103$).

Events	*IL7R* mutated type ($n = 16$)	*IL7R* wild type ($n = 87$)	p
Infection, no (%)	8	23	0.005*
Pneumonia	6	18	0.018*
Viral infection	1	1	0.182
Bacterial infection	4	16	0.111
Fungal infection	2	9	0.283
Septicemia	7	15	0.002*
Viral infection	2	4	0.104
Bacterial infection	5	12	0.016*
Fungal infection	1	5	0.454
Primary disease, no (%)	6	52	0.807
Progressive primary disease	3	35	1.000
Relapse	3	17	0.422
Other reasons, no (%)	2	12	0.632
Intracerebral hemorrhage	1	4	0.396
System organ failure	1	4	0.396
GVHD	0	2	1.000
TMA	0	2	1.000

*Statistically significant difference ($p < 0.05$) was observed between two groups.
AML, acute myeloid leukemia; GVHD, graft-versus-host-disease; *IL7R*, interleukin-7-receptor; TMA, thrombotic microangiopathy.

who underwent HSCT were similar between the $IL7R^{MUT}$ and $IL7R^{WT}$ groups (Supplemental Table S4). Among AML patients receiving HSCT, patients with *IL7R* mutations still had poorer outcomes than patients in the $IL7R^{WT}$ group. With a median follow-up of 49.6 months (IQR 35.8–56.6; 95% CI 47.6–51.6) for patients who underwent HSCT, the 5-year OS was 61.9% (95% CI 44.3%–86.6%) for the $IL7R^{MUT}$ group versus 85.3% (95% CI 80.7%–90.0%) for the $IL7R^{WT}$ group (HR 3.1, 95% CI 1.4–6.6; $p = 0.003$, Figure 3a). The 5-year EFS was 57.1% (95% CI 39.5%–82.8%) for the $IL7R^{MUT}$ group versus 72.6% (95% CI 67.0%–78.7%) for the $IL7R^{WT}$ group (HR 1.8, 95% CI 0.9–3.7; $p = 0.083$, Figure 3b). The 5-year DFS was 82.6% (95% CI 66.6%–100.0%) in the $IL7R^{MUT}$ group and 77.2% (95% CI 71.8%–83.1%) in the $IL7R^{WT}$ group (HR 1.732, 95% CI 0.3–2.7 $p = 0.757$, Figure 3c). In the $IL7R^{MUT}$ and $IL7R^{WT}$ groups, the 5-year CIR was 19.0% (95% CI 5.6%–38.4%) and 21.5% (95% CI 16.4%–27.2%), respectively ($p = 0.790$, Figure 3d). The 5-year NRM was 23.8% (95% CI 8.3%–43.6%) for the $IL7R^{MUT}$ group versus 5.8% (95% CI 3.2%–9.4%) for the $IL7R^{WT}$ group ($p = 0.003$, Figure 3e). A multivariable analysis showed that poorer prognostic stratification and *IL7R* mutation were risk factors for OS and NRM among patients who underwent HSCT. Poorer prognostic stratification and non-CR before HSCT were risk factors for OS and EFS. Besides, age >34 years was a risk factor for NRM (Supplemental Table S5).

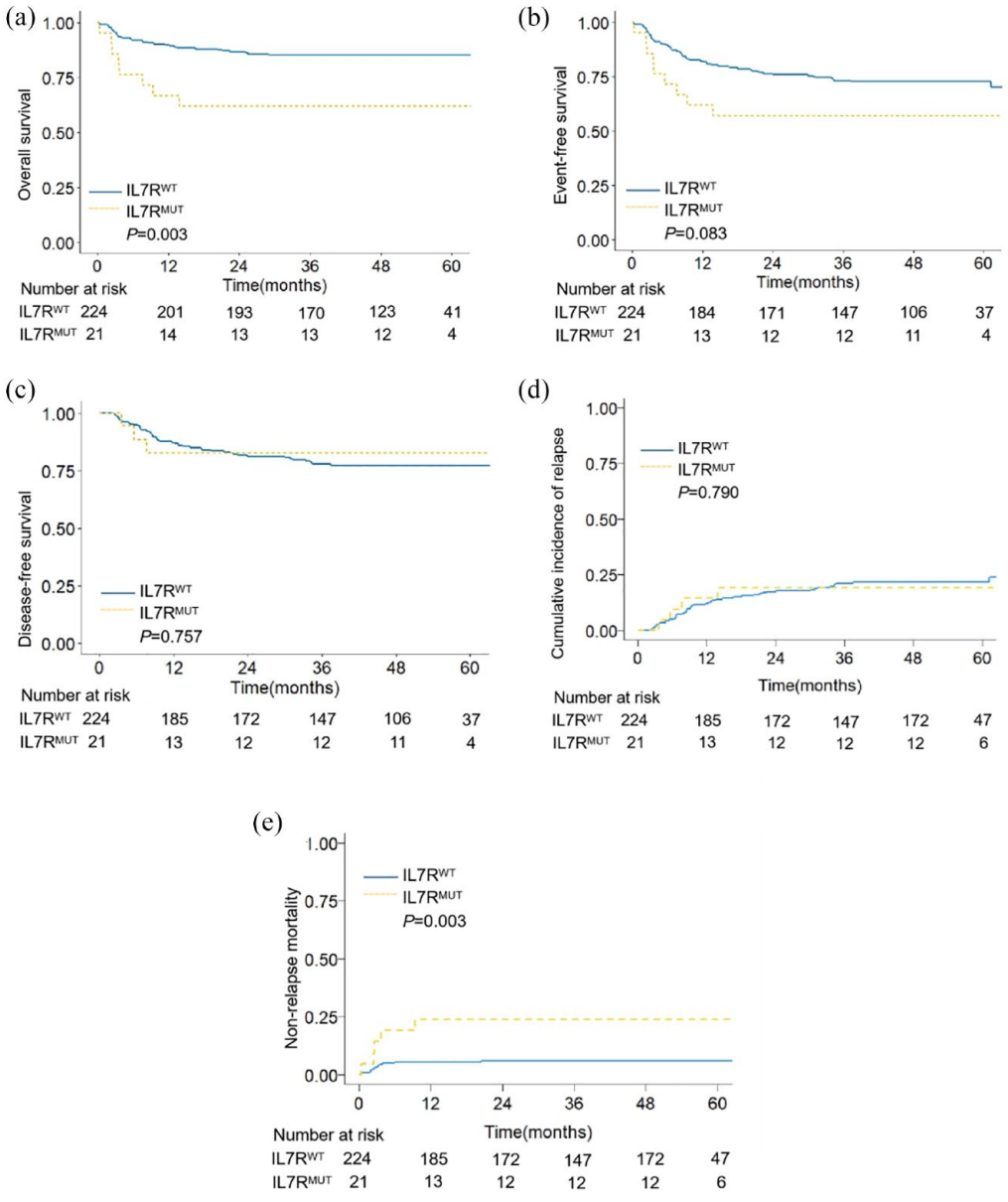

Figure 3. Survival between *IL7R*^{MUT} and *IL7R*^{WT} group among AML patients undergoing HSCT. (a) Overall survival, (b) event-free survival, (c) disease-free survival, (d) cumulative incidence of relapse, and (e) non-relapse mortality of the *IL7R*^{MUT} group and *IL7R*^{WT} group.
AML, acute myeloid leukemia; HSCT, hematopoietic stem cell transplantation; *IL7R*, interleukin-7-receptor.

Among the 244 AML patients who underwent HSCT, 41 patients died—8 in the *IL7R*^{MUT} group and 33 in the *IL7R*^{WT} group. In the *IL7R*^{MUT} group, the most common cause of death was infection (37.5%) compared with that in the *IL7R*^{WT} group (27.3%). Among patients receiving HSCT, there was also a trend of higher infection-related mortality in the *IL7R*^{MUT} group than in the *IL7R*^{WT} group ($p = 0.072$, Supplemental Table S6).

Among the 33 AML patients with *IL7R* mutations, 21 patients (21/33, 63.6%) received HSCT. Except for ages, other baseline characteristics were similar between the two groups (Supplemental Table S7). Among patients with

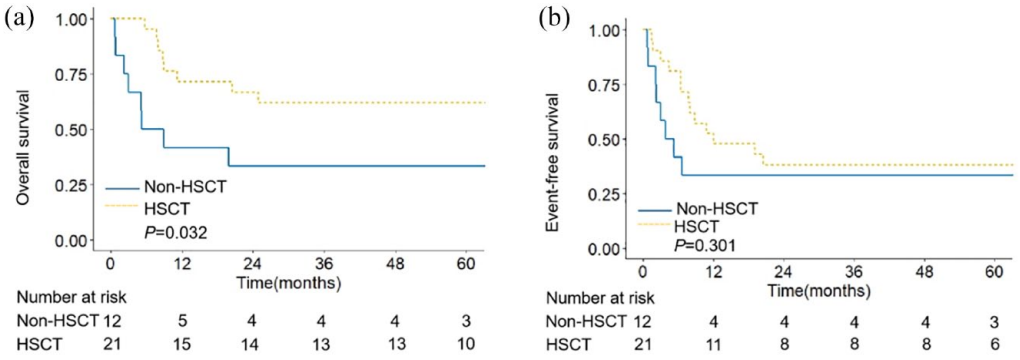

Figure 4. Survival between HSCT and non-HSCT group among AML patients with *IL7R* mutation. Overall survival (a) and event-free survival (b) analysis among 31 AML patients with *IL7R* mutation.
AML, acute myeloid leukemia; HSCT, hematopoietic stem cell transplantation; *IL7R*, interleukin-7-receptor.

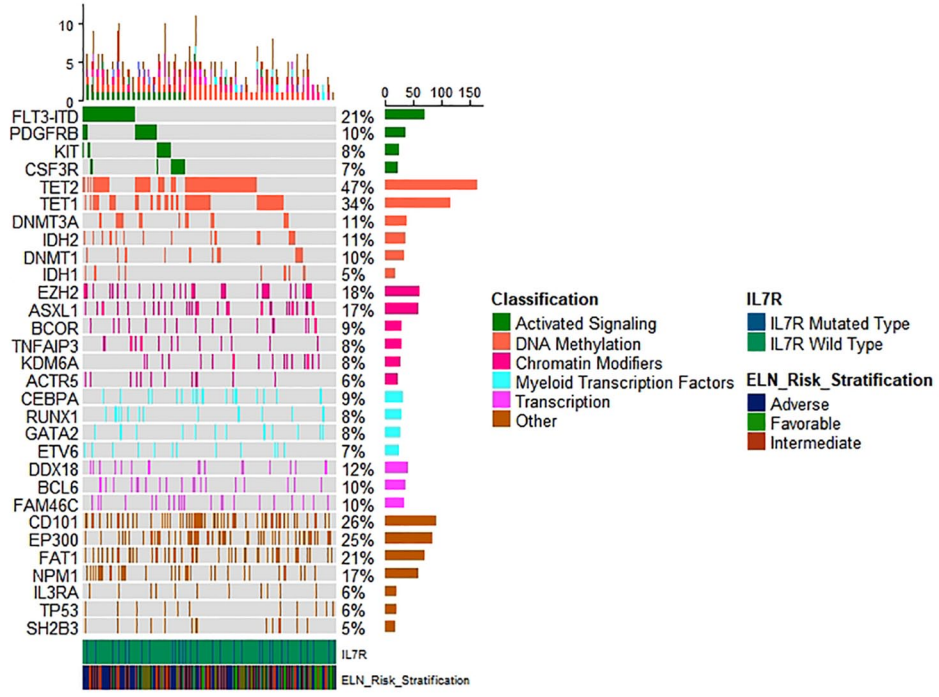

Figure 5. Mutation status and frequency of genetic abnormalities that detected in ⩾5% the patients.
Mutations are listed on the left and frequency is listed on the right, with the percent of patients for each type of genetic abnormality, including activated signaling (green), DNA methylation (orange), chromatin modifiers (pink), myeloid transcription factors (blue), transcription (purple), and other (brown).

IL7R mutations, 5-year OS rates were 61.9% (95% CI 44.3%–86.6%) for patients who underwent HSCT and 33.3% (95% CI 15.0%–74.2%) for patients who did not receive HSCT ($p = 0.032$), and the 5-year EFS rates were 38.1% (95% CI 22.1%–65.7%) and 33.3% (95% CI 15.0%–74.2%), respectively ($p = 0.301$, Figure 4 and Supplemental Table S7). HSCT might partially overcome the poor prognosis of patients with *IL7R* mutations.

Effects of the IL7R *mutation on concomitant genetics*

We identified a total of 167 gene targets by NGS at the time of diagnosis. The detailed molecular

Subgroup	No. of patients	IL7R mutant group n(%)	Non-IL7R mutant group n(%)	HR(95%CI)	P value
Overall	346	34	312	1.974(1.157-3.368)	0.013
ELN Risk Stratification					
Favorable	78	7(20.6)	71(22.8)	7.714(2.514-23.667)	<0.001
Intermediate	99	12(35.3)	87(27.9)	1.140(0.398-3.270)	0.807
Adverse	169	15(44.1)	154(49.4)	1.675(0.760-3.692)	0.201
Favorable genetic abnormalities					
NPM1	60	9(26.5)	51(16.3)	2.593(0.825-8.150)	0.103
CEBPA	31	3(8.8)	28(9.0)	1.952(0.217-17.579)	0.551
Adverse genetic abnormalities					
FLT3-ITD	71	6(17.6)	65(20.8)	1.630(0.485-5.482)	0.429
EZH2	62	6(17.6)	56(17.9)	0.845(0.111-6.436)	0.871
ASXL1	58	5(14.7)	53(17.0)	1.557(0.348-6.961)	0.562
DNMT3A	38	6(17.6)	32(10.3)	3.521(0.945-13.124)	0.043
BCOR	30	4(11.8)	26(8.3)	1.536(0.331-7.134)	0.584
Undefined genetic abnormalities					
TET2	164	12(35.3)	152(48.7)	2.625(1.180-5.842)	0.018
TET1	117	13(38.2)	104(33.3)	1.125(0.441-2.872)	0.805
CD101	90	8(23.5)	82(26.3)	1.305(0.392-4.351)	0.664
EP300	85	11(32.4)	74(23.7)	2.128(0.785-5.771)	0.138
FAT1	71	5(14.9)	66(21.2)	2.745(-.824-9.734)	0.107
DDX18	41	4(11.8)	37(11.9)	1.810(0.518-6.326)	0.353
PDGFRB	36	3(8.8)	33(10.6)	1.642(0.367-7.346)	0.517
FAM46C	35	4(11.8)	31(9.9)	0.041(0.001-708.887)	0.52
DNMT1	33	8(23.5)	25(8.0)	2.704(0.761-9.613)	0.124
GATA2	27	2(5.9)	25(8.0)	0.043(0.001-229.279)	0.691
KDM6A	28	3(8.8)	25(8.0)	4.615(0.415-51.327)	0.213
IDH2	37	2(5.9)	35(11.2)	2.989(0.348-25.689)	0.318
TNFAIP3	29	2(5.9)	27(8.7)	1.483(0.185-11.891)	0.71

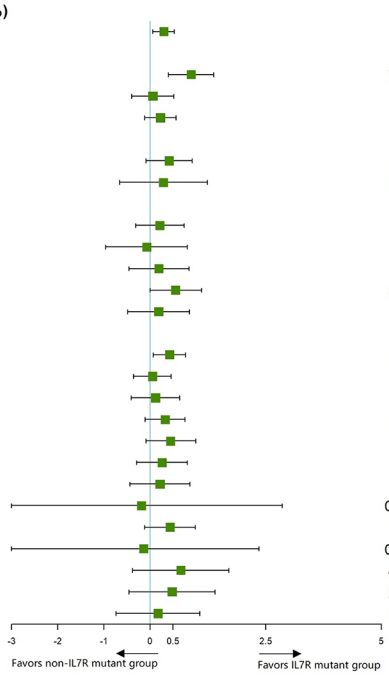

Figure 6. The effects of *IL7R* mutation in subgroups. Cox proportional hazard model for prognostic impact of *IL7R* mutation and concomitant genetics on overall survival in the cohort of 346 AML patients. The logarithm of HR is shown in the graph.
AML, acute myeloid leukemia; HR, hazard ratio; *IL7R*, interleukin-7-receptor.

mutation in which mutation rates were more than 5% is shown in Figure 5. For gene mutations, a total of 338 patients harbored at least one concomitant mutation. We further explored the effects of *IL7R* mutation on concomitant genetics in which the mutation rate was more than 8%. A forest plot showed that the *IL7R* mutation was a risk factor in patients with *TET2* ($p = 0.018$) and *DNMT3A* mutation ($p = 0.043$, Figure 6). In *TET2* and *DNMT3A* subgroups, the presence of *IL7R* mutation was associated with worse OS than in the $IL7R^{WT}$ patients ($p < 0.05$, Supplemental Figure 1). A tendency toward lower survival was observed in the $NPM1^{MUT}/IL7R^{MUT}$ group than in the $NPM1^{MUT}/IL7R^{WT}$ group ($p = 0.073$).

Discussion

Our study demonstrated that the *IL7R* mutation was an adverse prognostic factor for AML patients. Patients with *IL7R* mutations had significantly shorter OS and EFS and higher NRM than patients without *IL7R* mutations, even patients who underwent HSCT. The presence of *IL7R* co-mutation in the *TET2* and *DNMT3A* subgroups was associated with decreased survival.

Somatic gain-of-function mutations in *IL7R* have been shown to act as oncogenes in T- and B-ALL.[28,29] In our study, we analyzed 346 adult patients with newly diagnosed AML and identified mutations in *IL7R* in 9.5% (33/346). Approximately 10% of T-ALL patients are reported to have *IL7R* mutations, the poor prognosis might be due to the overactivation of the JAK/STAT and PI3K/AKT/mTOR pathways which are associated with glucocorticoid resistanc.[23,29,46] Activation of the JAK/STAT pathway and PI3K/Akt/mTOR pathway led to the down-regulation of $p27^{Kip1}$ and the up-regulation of Bcl2, which promoted the proliferation and survival of T-ALL cells. *IL7R* mutation related to poor prognosis of ALL, Xiao et al. and Fu et al. showed that the *IL7R* mutation was associated with poor clinical outcomes in adult ALL patients.[47–49] Richter-Pechańska et al. reported that pediatric T-ALL patients with IL7R mutations had lower EFS compared to *IL7R* wild-type patients. Li et al. showed that mutations in *IL7R* and its pathway-related genes such as JAK/RAS/

AKT have lower RFS, which are associated with steroid resistance in pediatric T-ALL.[32,46] However, the effect of *IL7R* mutation on AML pathogenesis and its related mechanisms have not been reported. In our study, we first demonstrated that *IL7R* mutation had a negative impact on survival among AML patients. The 5-year OS rate was 51.5% in the $IL7R^{MUT}$ group versus 72.2% in the $IL7R^{WT}$ group, corresponding to the 5-year EFS rate was 36.1% in the $IL7R^{MUT}$ group versus 58.1% in the $IL7R^{WT}$ group. The 5-year NRM for the $IL7R^{MUT}$ group was higher than $IL7R^{WT}$ group. The most common cause of death was infection. Infection-related mortality in patients with *IL7R* mutation was higher than in patients without *IL7R* mutation. The mechanism of *IL7R* mutation in infection remains unclear. Some polymorphisms of the *IL7Rα* were associated with immunodeficiency and inflammatory diseases.[50–52] Ampuero et al. further reported that single nucleotide polymorphisms of *IL7R* would be related to the severity of adults with community-acquired pneumonia (CAP).[53] It had been reported that polyglutamylation and deglutamylation of IL-7Rα tightly controlled the development and effector functions of ILC3s, which promoted lymphoid organogenesis and potentiated immune responses against bacterial infection.[54,55] Therefore, the mechanism of poor prognosis in *IL7R* mutation patients might be due to abnormal lymphocyte dysfunction and reduced anti-infection and anti-tumor immune function.

HSCT has been proven to be the most effective therapy for AML patients. However, among AML patients undergoing HSCT, patients with *IL7R* mutation still had poorer outcomes compared with patients in $IL7R^{WT}$ group. Our findings are in accordance with the previous study, showing that HSCT cannot improve OS in IL7-receptor pathway mutated ($IL7Rp^{MUT}$) T-ALL patients compared with IL7-receptor pathway non-mutated ($IL7Rp^{WT}$) T-ALL patients.[56] Patients with *IL7R* mutations who received HSCT had better OS than those who did not receive HSCT (4-year OS: 60.2% vs 31.2%, $p = 0.028$). We found that HSCT might partially overcome the poor prognosis of AML patients with *IL7R* mutation.

In our study, among $TET2^{MUT}$ and $DNMT3A^{MUT}$ AML patients, patients with *IL7R* mutations had shorter OS than patients in the $IL7R^{WT}$ group. DNA methylation regulatory gene mutations such as those in *DNMT3A*, *TET2*, *IDH1*, and *IDH2* have been shown to be associated with poor prognosis.[12,16,57] It is reported that *DNMT3A* was identified to negatively regulate the *SOCS5* expression levels and *SOCS5* downregulation potentiates the expression of *IL7R*, JAK-STAT signal transduction, and leukemia progression. In our study, patients with *TET2*/*IL7R* or *DNMT3A*/*IL7R* co-mutation have a poorer prognosis. The reason might be due to aberrant DNA methylation (hypermethylation) indirectly leads to hyperactivation of JAK/STAT signaling.[58–62]

There is strong therapeutical potential to target the *IL-7*/*IL-7R* pathway in T-ALL. For example, the use of downstream signaling elements JAK inhibitors, Bcl-2 drug inhibitors, and the reducing agent n-acetylcysteine (NAC) have been shown to be effective in the treatment of T-ALL.[63–65] These targeted drugs also might have the potential therapeutic value in AML, which will need to be further explored.

It has been reported that *IL7R* mutations are located in exon 5 and exon 6 in T-ALL and B-ALL. Limited by the depth and sensitivity of NGS technology in our study, we detected mutation sites of *IL7R* were only covered exon 5 and exon 6. In our study, all AML patients with *IL7R* mutations were located in exon 6 (c.731C>T; p.T244I). Besides, this is small sample size, monocentric, and retrospective study. Future large and multicenter prospective studies will be further explored.

Conclusion

Our study first demonstrates that the *IL7R* mutation is associated with an inferior prognosis for AML patients. Patients with *IL7R* mutations have poorer outcomes than those without *IL7R* mutation, even patients who have undergone HSCT. The presence of *IL7R* mutations was associated with higher NRM, shorter OS, and EFS than in AML patients without *IL7R* mutations.

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki Declaration and approved by the

Institutional Review Board of Nanfang Hospital. Informed consent was obtained from all individual participants included in the study.

Consent for publication

All authors have read and approved the manuscript for publication.

Author contributions

Qiqi Tao: Data curation; Formal analysis; Investigation; Methodology; Visualization; Writing – original draft.

Qiaoyuan Wu: Data curation; Formal analysis; Methodology; Software.

Yutong Xue: Data curation; Investigation; Software; Writing – original draft.

Changkun Chen: Data curation; Software; Writing – review & editing.

Ya Zhou: Conceptualization; Investigation; Visualization.

Ruoyang Shao: Conceptualization; Formal analysis; Software.

Haiyan Zhang: Conceptualization; Formal analysis; Methodology.

Hui Liu: Data curation; Resources.

Xiangzong Zeng: Data curation; Formal analysis; Software.

Lingling Zhou: Data curation; Resources.

Qifa Liu: Conceptualization; Project administration; Resources; Writing – review & editing.

Hua Jin: Conceptualization; Formal analysis; Funding acquisition; Resources; Supervision; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request. For the original data, please contact echohua1124@163.com.

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Supplemental material

Supplemental material for this article is available online.

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Appendix

Abbreviations

ALL	acute lymphoblastic leukemia
AML	acute myeloid leukemia
CAP	community-acquired pneumonia
CI	confidence interval
CIR	cumulative incidence of relapse
CR	complete remission
EFS	event-free survival
ELN	European Leukemia Net
GVHD	graft-versus-host-disease
HR	hazard ratio
HSCT	hematopoietic stem cell transplantation
IL7R	interleukin-7 receptor
IQR	interquartile range
MAC	myeloablative conditioning
MSD	matched sibling donor transplantation
MUD	matched unrelated donor
NGS	next-generation sequencing
NRM	non-relapse mortality
OS	overall survival
RIC	reducing intensity conditioning
TMA	thrombotic microangiopathy