LETTER TO THE EDITOR

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BCL11B Mutations Are Associated with Higher CD8+ T-Cell Percentage and Favorable Clinical Outcomes in Patients with T-Cell Acute Lymphoblastic Leukemia

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T-cell acute lymphoblastic leukemia (T-ALL) is a highly aggressive leukemia with poor prognosis, and currently, there is no effective or targeted therapy.[1] Although intensive chemotherapy or hematopoietic stem cell transplantation is used for patients with T-ALL, the 5-year overall survival (OS) is less than 50%, especially for relapsed patients.[2] The pathogenesis of T-ALL is relatively complex, mainly caused by abnormal gene rearrangement and amplification, differentiation retardation, and apoptosis disorders during T-cell development and differentiation.[3,4] Notably, genetic alterations exert an important role in abnormal gene rearrangement and amplification, as well as risk stratification in precision therapy in T-ALL.[3] Our previous studies have explored the prognostic value of genetic alterations in patients with T-ALL.[5] However, high heterogeneity has led to difficulty in accurately stratifying all patients with T-ALL. Therefore, further exploration of novel biomarkers related to gene mutations is needed to improve the risk stratification for patients with T-ALL.

B-cell leukemia/lymphoma 11B (*BCL11B*) belongs to the Kruppel-like C2H2-type zinc finger transcription factor family and plays an important role in regulating the T-cell activation and differentiation, as well as patient outcomes.[3,6] Our previous reports suggested that lower expression of *BCL11B* results in T-cell dysfunction and is a reason for T-cell deficiency in myelodysplastic syndrome (MDS), and then is associated with poor clinical outcomes.[7] Moreover, *BCL11B* is upregulated in T-ALL and inhibition of *BCL11B* induces downregulation of *PTK7* and results in growth retardation and apoptosis in T-ALL.[8] Crucially, most T-ALL subtypes have *BCL11B* haploid deficiency.[3] Functional loss of *BCL11B* mutations leads to lymph node enlargement in mice and the development of T-ALL in humans.[3] Our previous study has demonstrated that *BCL11B* mutation is associated with favorable clinical outcomes in patients with T-cell lymphoma (TCL).[9] Although both T-ALL and TCL belong to T-cell malignancies, there are significant differences between them on the origin of malignant T cells, genetic background, mutation landscape, and treatment options. Therefore, the prognostic value in this study was similar to the published articles on different types of diseases.[9] Moreover, a previous report found that *BCL11B* mutations predict better OS and event-free survival for patients with adult and pediatric T-ALL and may be a potential biomarker for risk stratification in T-ALL[10]; the relationship between *BCL11B* mutations and T cells in T-ALL, and the prognostic importance, still remains unclear.

In this study, 3 data sets (PNAS, PRJCA002270, and COSMIC) were aggregated as larger data, including 741 patients with T-ALL, for exploring the mutation patterns of *BCL11B* (Table S1). The mutation rate of *BCL11B* was 14.4% (107/741) in adult and pediatric T-ALL (Figure 1A and Table S1), which was consistent with a previous study (18%).[10] The hotspot mutation site of *BCL11B* was zf-H2C2-2 (Figure 1A). The types of mutations included missense, frameshift insertion, non-frameshift insertion, nonsense, frameshift deletion, non-frameshift deletion, and splice site mutation. Among them, the most frequent mutations were missense (Figure S1A). In addition, hotspot amino acid alteration was T > M (6 p.T379M and 3 p.T450M) in single-nucleotide polymorphism (Table S1 and Figure S1B-C). The correlation between *BCL11B* mutations and clinical outcomes for patients with T-ALL was further investigated. Due to the lack of complete OS or progression-free survival (PFS) information in publicly available data sets, we analyzed the importance of *BCL11B* mutations in predicting complete remission (CR) and minimal residual disease (MRD) in the PRJCA002270 data set that was the only data set containing prognostic information. Interestingly, there was a clear trend suggesting that patients with T-ALL harboring a *BCL11B* mutation had a higher percentage of CR ($P = .068$) and negative MRD ($P = .050$), although the data were not yet statistically significant at this point (Figure 1B). These results were consistent with a previous report.[10] However, patients with T-ALL harboring a missense mutation of *BCL11B* which was the most common type of mutation had a lower percentage of CR (42.9% vs 88.2%, $P < .001$) and negative MRD (38.5% vs 58.3%, $P = .173$) (Figure S2). Therefore, CR or MRD was not associated with the most common type of mutation, but rather positively correlated with the overall *BCL11B* mutation. Furthermore, *BCL11B* haplo-insufficiency may induce differentiation arrest at diverse stages of thymocyte development and occur in the

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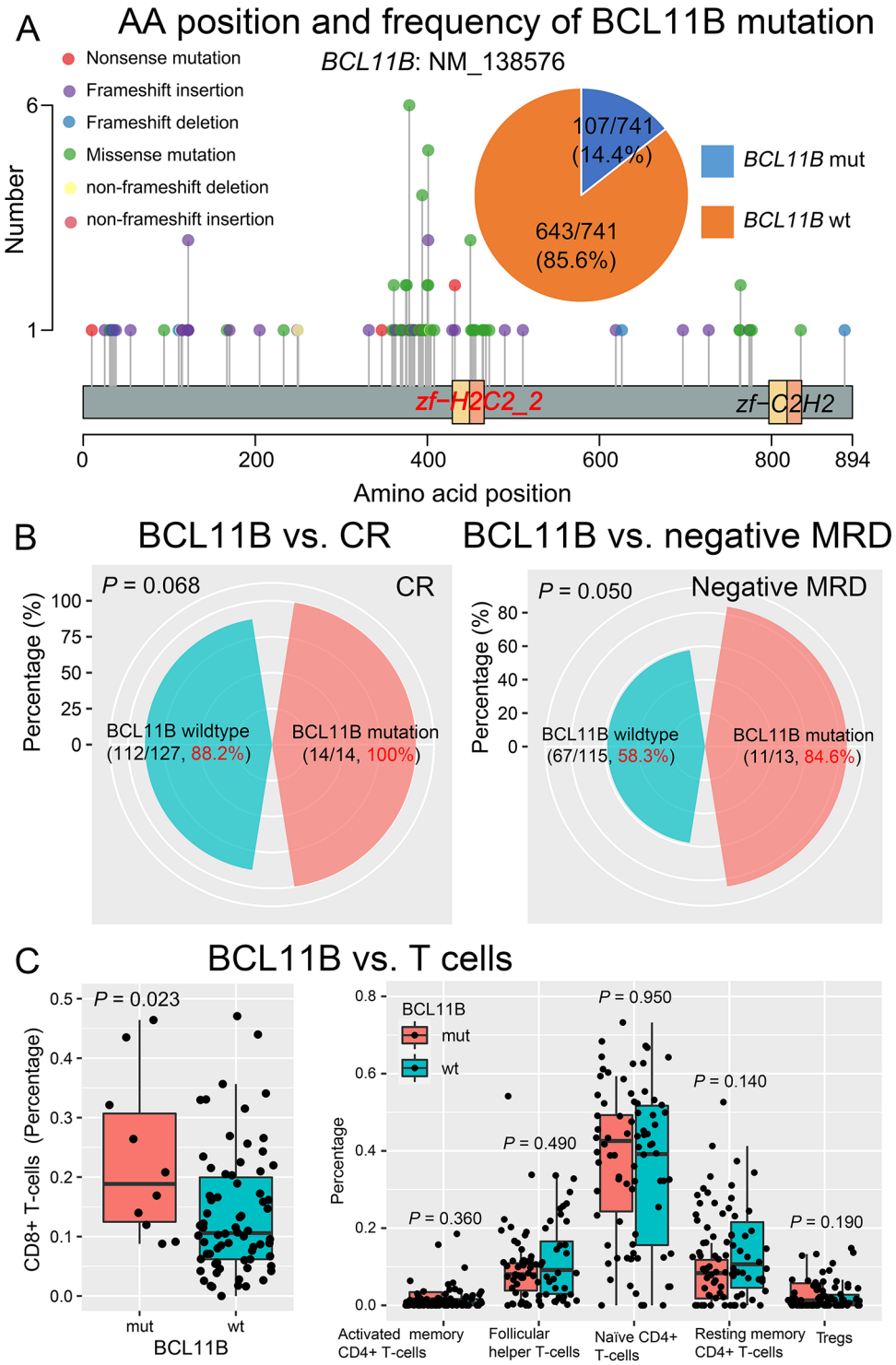

Figure 1. *BCL11B* mutation was associated with favorable clinical outcomes and higher CD8+ T-cell percentage in patients with T-ALL. (A) The amino acid positions and percentage of *BCL11B* mutation in the PRJCA002270, PNAS, and COSMIC data sets. (B) The proportion of CR (left panel), and negative minimal residual disease (MRD) (right panel) in patients with or without *BCL11B* mutation in the PRJCA002270 data set. (C) Differences of CD8+ T cells (left panel) and CD4+ T-cell subpopulation (right panel) in patients with and without *BCL11B* mutation. AA indicates amino acid; CR, complete remission; MRD, minimal residual disease; T-ALL, T-cell acute lymphoblastic leukemia.

major T-ALL molecular subtypes.[3] Altogether, *BCL11B* mutations were associated with favorable clinical outcomes in patients with T-ALL. However, more T-ALL samples will need to be collected for exome or Sanger sequencing to verify the importance of *BCL11B* mutations for predicting the clinical outcomes of patients in the future.

Our previous reports demonstrated that *BCL11B* is required for normal T-cell development and decreased *BCL11B*

expression in T cells predicts poor OS for patients with MDS.[3,7] Because only the PRJCA002270 data set has both exome and transcriptome sequencing data, it is used to analyze the relationship between *BCL11B* mutations and T-cell subsets. The results indicated that *BCL11B* mutations were positively correlated with CD8+ T cells ($P = .023$) other than all types of CD4+ T cells ($P > .05$) in patients with T-ALL (Figure 1C and S3). Then, the mechanisms of *BCL11B* mutation in T-ALL were explored. Patients with T-ALL were divided into 2 subgroups, including *BCL11B*-mut and *BCL11B*-wt, and the differential genes were selected for pathway analysis. As shown in Figures S4 and S5A-C, a total of 277 upregulated and 187 downregulated genes were used for KEGG and GSEA pathway analysis. Interestingly, in patients with *BCL11B* mutations, the antigen processing and presentation, and PI3K-Akt signaling pathways were significantly higher expressed (Figure S5D).

However, there are limitations in this study: first, due to the low mutation rate of *BCL11B* in T-ALL, there may be statistical biases in analyzing its correlation with clinical outcomes. Second, unfortunately, the publicly available databases are unable to provide complete clinical data to be used to confirm the relationship between *BCL11B* mutations and OS, PFS, and relapsed-free survival, or other factors in the risk stratification of T-ALL. Finally, there is a lack of additional T-ALL samples from our clinical center or multiple centers for exonome or Sanger sequencing to further validate our findings.

In conclusion, we made an observation that *BCL11B* mutations were associated with favorable clinical outcomes in patients with T-ALL, which might complement current prognostic stratification for T-ALL.

Author Contributions

CC interpreted the data and wrote the manuscript. YZ and XZ helped to interpret the data. YL and GKP and CZ contributed to the concept development, study design, and editing of the manuscript. All authors read and approved the final manuscript.

Availability of Data and Materials

The data sets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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SUPPLEMENTAL MATERIAL

Supplemental material for this article is available online.

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