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Stereotyped BCR Subset #8 in Chinese CLL: Molecular Genetics, Clinical Behavior, and Prognosis

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OBJECTIVES

- To analyze the molecular genetic characteristics, clinical features, and survival outcomes of Chinese CLL patients belonging to stereotyped B-cell receptor (BCR) subset#8.
- To further explore the clinical utility of identifying subset #8 patients in evaluating disease prognosis and guiding treatment decisions.

CONCLUSIONS

- Subset #8 patients exhibit distinct molecular genetic features and clinical manifestations.
- Subset #8 is characterized by a high frequency of molecular genetic abnormalities indicative of poor prognosis, demonstrates an aggressive clinical course requiring early treatment after diagnosis.
- For subset #8 patients, first-line therapy containing BTKi may improve clinical outcome. Early IGHV sequencing and identification of subset #8 in clinical practice facilitates prognostic assessment and aids in selecting treatment strategies.

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INTRODUCTION

- The mutational status of the immunoglobulin heavy variable region (IGHV) genes plays an important role in predicting the outcomes of CLL patients and in guiding therapeutic decisions.
- As research advances, studies have revealed a biased usage of the IGHV gene repertoire, leading to the discovery that subsets of CLL harbor stereotyped heavy variable complementarity-determining region 3 (VH CDR3) sequences. Patients belonging to the same subset exhibit consistent clinical behavior and molecular genetics characteristics.
- Emerging evidence indicates a geographic differences in the usage of IGHV genes, which may be related to the differences in disease incidence rates and causes of disease.

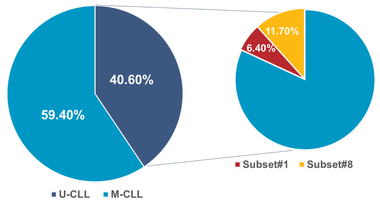
METHODS

- This study included CLL patients with IGHV gene sequencing data from two centers. Patients belonging to subset #8, subset #1 subset #4 were identified.
- Clinical and molecular genetic data were retrospectively collected and analyzed, including β2-MG, LDH, fluorescence in situ hybridization (FISH) results, karyotype.
- Statistical and survival analyses were conducted to summarize the distinct molecular genetic features and clinical characteristics of subset #8 patients.

RESULTS

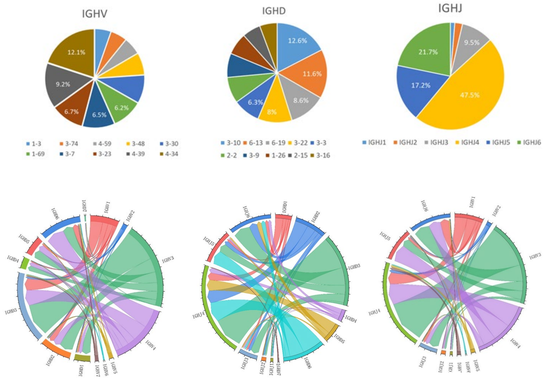
- This retrospective study included 1,824 CLL patients from two centers, with a median follow-up of 53 months. 1,083 patients (59.4%) were categorized as mutated CLL(M-CLL) A total of 87 patients (4.8%) belonged to subset #8, representing a significantly higher proportion than previously reported in Western studies (4.8% vs. 2.9%, P < 0.001).
- The most frequently used IGHV gene was IGHV4-34 (12.1%). IGHV3-21, which is the most commonly used gene in subset #2 accounted for only 2.8%. The most commonly used IGHD gene was IGHD3-10 (12.6%). The IGHJ4 family shows the highest usage frequency (47.5%) among IGHJ gene.
- Patients of subset #8 exhibited higher levels of β2-MG and LDH. Genetically, subset #8 showed a higher incidence of del(11q) , +12 and complex karyotype, but a lower incidence of del(13q).
- Clinically, subset #8 patients demonstrated a significantly higher proportion of patients requiring treatment indications (95.0% vs. 70.8%, P < 0.001). Both the median time to first treatment (TTFT) (14.4 months vs. 37.9 months, P < 0.001), and median overall survival (OS) (120.8 months vs. 173.2 months, P < 0.001) were significantly shorter compared to non-subset #8 patients. These findings indicate that subset #8 patients generally follow an aggressive disease course with inferior overall survival requiring early therapeutic intervention. Patients belonging to subset #8, subset #1 and subset #4 were stratified based on whether Bruton's tyrosine kinase inhibitor (BTKi) were included in their first-line treatment. BTKi-containing regimens improved survival and prolonged time to next treatment (TTNT) in subset #8, but not in subset #1.

Figure #1. Somatic Hypermutation Status and the frequency of subset #8.



Figure#1:Chinese CLL patients in this study exhibit a higher frequency of mutated IGHV and demonstrate a higher proportion of subset #8 compared to Western cohorts.

Figure #2. Distribution of the IGHV, IGHD, IGHJ gene usage and the partnership of IGHV-IGHD-IGHJ gene recombination.



Figure#2:In terms of gene combinations, IGHV3 subgroup genes were most commonly rearranged with IGHD3 genes. IGHD3 genes were most commonly rearranged with IGHJ4 genes.

Table#1. Clinical characteristics and results of FISH of cohort of subset #8 and non-subset #8.

	Subset #8 （n= 87）	Non-subset #8 （n=1719）	P-value
Male	50（65.3%）	1124（65.3%）	0.504
Rai staging system			<0.001
0	3（4.3%）	223（13.8%）	
1	18（25.7%）	418（25.9%）	
2	16（22.9%）	337（20.9%）	
3	22（31.4%）	224（13.9%）	
4	11（15.7%）	409（25.4%）	
Binet staging systm			0.038
1	9（15.0%）	395（28.6%）	
2	29（48.3%）	487（35.3%）	
3	22（36.7%）	499（36.1%）	
Treatment indications	76（95.0%）	1186（70.8%）	<0.001
Complex karyotype	36（52.9%）	503（36.5%）	0.006
β2-MG>3.5mg/L	38（62.3%）	559（43.3%）	0.003
LDH>248U/L	44（67.7%）	385（26.1%）	<0.001
del(17p)（FISH）	13（17.3%）	173（11.8%）	0.150
del（11q）（FISH）	20（27.8%）	188（12.7%）	<0.001
del(13q)（FISH）	4（7.4%）	412（30.6%）	<0.001
+12（FISH）	30（48.4%）	212（18.2%）	<0.001

Figure #3. K–M curves for OS of U-CLL patients versus M-CLL patients.

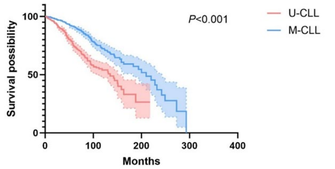


Figure #3: U-CLL patients exhibited a shorter OS compared to M-CLL patients (135 months versus 220 months (P < 0.001).

Figure #4. K-M curves for OS and TTFT of subset #8 patients versus non-subset #8 patients.

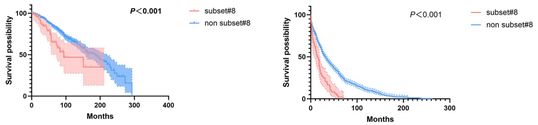


Figure #4: Subset #8 patients exhibited a shorter OS compared to non-subset #8 (94 months versus 183 months, *P* < 0.001). Subset #8 patients have a significantly shorter TTFT, only 8 months.

Figure #5. K-M curves for OS and TTFT of subset #8 patients versus U-CLL non-subset #8 patients.

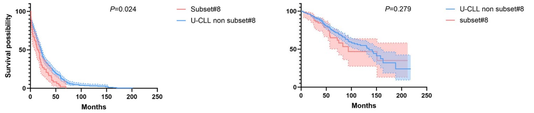


Figure #5:Subset #8 patients have a shorter TTFT even compared to U-CLL patients belonging to non-subset #8. The median OS after treatment was 90 months for subset #8 patients and 130 months for non-subset # 8 patients, which shows no statistically significant difference between these two groups (*P*=0.279).

Figure #6. TTNT of subset #8, subset #1 and subset #4 patients stratified based on whether BTKi were included in their first-line treatment.

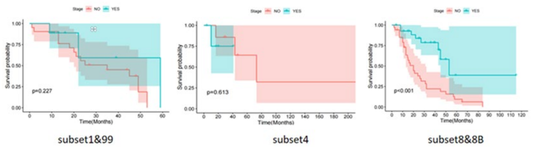


Figure #6：BTKi-containing therapy improved survival and prolonged TTNT in subset #8, but not in subset #1 or subset #4.

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