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Co-Mutational Patterns with *BCOR* Influences Biological Characteristics and Clinical Outcomes of Myeloid Neoplasms

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Introduction

BCL6 co-repressor (*BCOR*), a tumor suppressor gene located on chromosome X (locus Xp11.4) is involved in hematopoiesis via non-canonical polycomb repressive complex 1 (PRC1). The prevalence of *BCOR* mutation in myeloid neoplasms (MN) is approximately 5%, and it is also implicated in clonal hematopoiesis. In the 2022 ELN, WHO, and ICC classifications, *BCOR* is categorized as a myelodysplasia-related gene. Mutational patterns include frequent co-occurrence with *DNMT3A* and *RUNX1* in AML and mutual exclusivity with *NPM1* mutations. Although it has been theorized that *BCOR* ^{MT} may cooperate preferentially with certain groups of genes, the prognostic significance of the *BCOR* co-mutational landscape has yet to be fully studied.

Methods

The total cohort (n = 20149) consists of 624 MN patients (169 primary (p) AML, 136 secondary (s) AML, 84 MDS, 34 MDS/MPN, 66 MPN, and 135 with other MN) from Karmanos Cancer Institute, publicly available metanalytic cohort consisting of various sub-studies (Awada et al., 2021; Kewan et al., 2023), and cohorts from open-access cancer genomics resource cBioPortal and AACR GENIE (v13.1) (Cerami et al., 2012; Gao et al., 2013). Clinical and genomic characteristics were reviewed. Chi-square and T-tests were used for analysis of various parameters as described, and Kaplan-Meier and log-rank methods were used to estimate overall survival (OS). The prevalence of *BCOR* ^{MT}, co-occurring mutations, and their outcomes were analyzed based on co-mutational patterns.

Results

A total of 745 (3.7%) patients carried *BCOR* ^{MT}. Male: Female ratio was 1.48, with a median age of 68 ys.(IQR 59-75). *BCOR* ^{MT}showed a trend to be most frequent in pAML compared to other MN (54 vs 46%, p=0.33). *BCOR* ^{MT} was less associated with abnormal karyotype vs. *BCOR* ^{WT} [41 vs. 51%, p=0.0002]. Median variant allele frequency (VAF) was 45% (IQR 22-69), and most mutations were frameshift (41%) followed by nonsense (27%), and missense (22%). Median OS was not different between *BCOR* ^{WT} and *BCOR* ^{MT} patients [21.9 vs. 19.6 mo., p=0.089] in the entire cohort.

Oncoprint analysis centered around *BCOR* revealed frequent co-mutations with *RUNX1*, *DNMT3A*, *TET2* and *ASXL1*. As a result, the patients were divided into 10 groups (groups A-J), and the OS was analyzed between groups and compared with *BCOR* ^{WT}. Patients with *BCOR/TET2*, *BCOR/RUNX1/TET2*, and *BCOR/ASXL1* (groups G, B, and H resp.) had the lowest median OS with 14.5 mo., 16.7 mo., and 17.4 mo., resp. However, no significant differences in median OS were observed between the compared groups except those involving *BCOR/ASXL1* vs. *BCOR*/Others and *BCOR* ^{WT}. *BCOR/ASXL1* patients had significantly lower median OS compared to *BCOR*/Others [17.4 vs. 22.5 mo., p=0.022] and *BCOR* ^{WT} [17.4 vs. 21.9 mo., p=0.017].

Further *BCOR* ^{MT} and *ASXL1* ^{MT} comutational analysis irrespective of other co-occurring mutations, revealed that in those with *BCOR* ^{MT}, *ASXL1* co-mutation was seen in 143 (19.2%) patients. *BCOR* and *ASXL1* co-mutation were primarily enriched in primary AML (49%), followed by sAML (25%). Median *BCOR* VAF was higher than *ASXL1* [39 vs. 31%, p<0.0001]. The most

associated mutational categories in this subgroup were related to myeloid transcription factors (TF) (*RUNX1*, *CEBPA*; 62%), spliceosome (*SRSF2*, *U2AF1*, *SF3B1*, *ZRSR2*; 22%), and DNA methylation family (*DNMT3A*, *TET2*, *IDH1/2*; 8%). *BCOR* ^{MT}/ *ASXL1* ^{MT}/DNA Methylation mutations had poorer median OS compared to *BCOR* ^{MT}/ *ASXL1* ^{MT}/Spliceosome mutations [9.2 vs. 17.4 mo., p=0.044]. Whereas *BCOR* ^{MT}/ *ASXL1* ^{MT}/Myeloid TF and *BCOR* ^{MT}/ *ASXL1* ^{MT}/Spliceosome mutations had no significant survival difference compared to *BCOR* ^{WT}, patients with *BCOR* ^{MT}/ *ASXL1* ^{MT}/DNA Methylation had worse median OS [9.2 vs. 21.9 mo., p=0.007].

Conclusion

This large cohort study confirms common *BCOR* co-mutation patterns and reveals prognostic differences in patients with co-occurring *ASXL1* mutation. We demonstrated *BCOR* ^{MT} with *ASXL1* ^{MT} without concurrent *RUNX1* ^{MT}, *DNMT3A* ^{MT}, and *TET2* ^{MT} had poorer overall survival. Furthermore, patients with *BCOR* ^{MT}, *ASXL1* ^{MT}, and concomitant DNA methylation-related gene mutations had worse outcomes compared to those with concomitant spliceosome mutation and *BCOR* ^{WT}. Our findings suggest that co-mutational patterns of *BCOR* may further clarify diagnosis and classification schemes, highlighting potential synergies among subcategories of gene mutations and their prognostic value.

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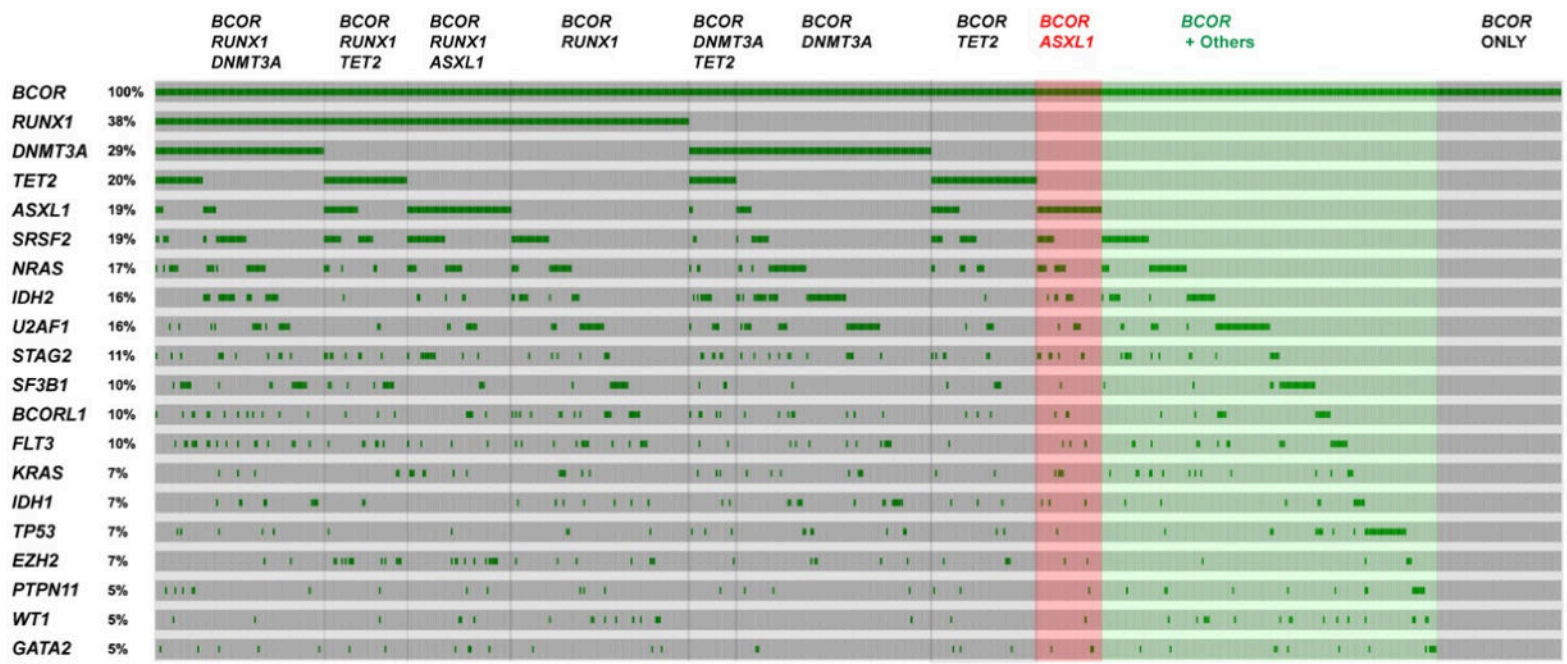
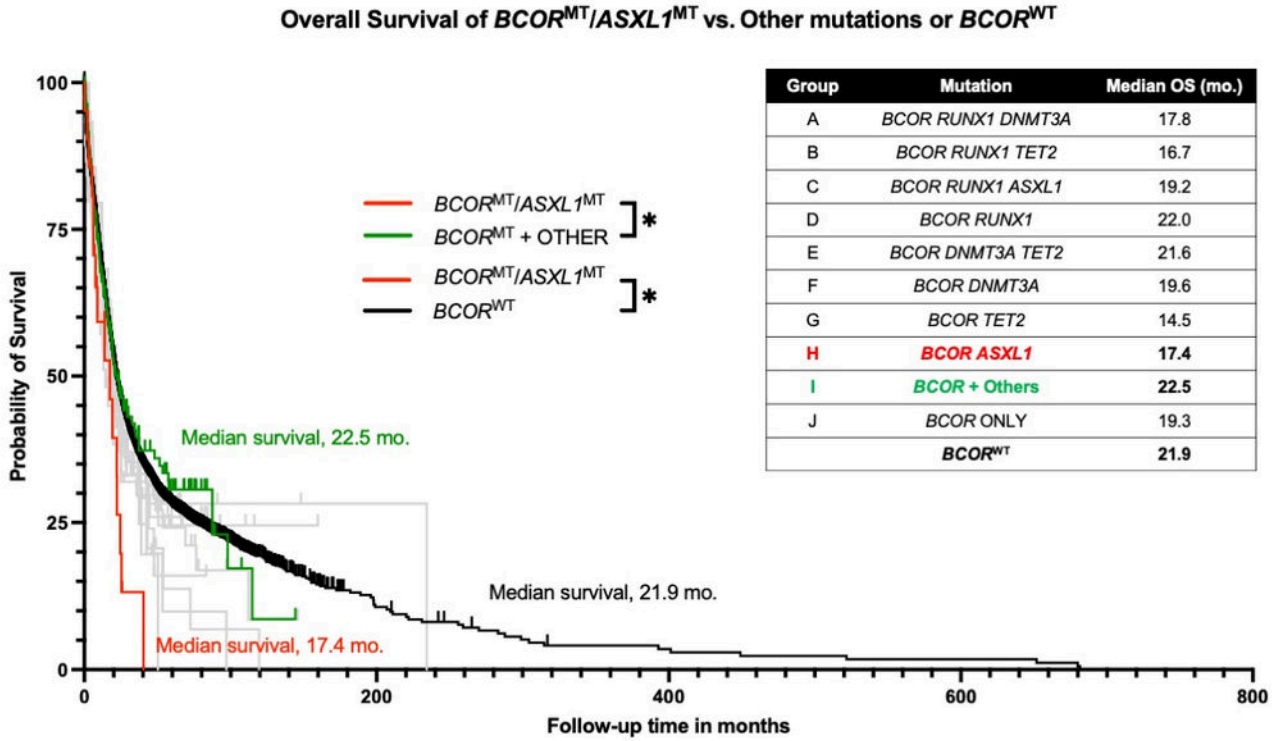


Panel 2. Kaplan-Meier survival curves for $BCOR^{MT}/ASXL1^{MT}$ vs. $BCOR^{MT}$ + Other mutation or $BCOR^{WT}$



Group	Mutation	Median OS (mo.)
A	*BCOR RUNX1 DNMT3A*	17.8
B	*BCOR RUNX1 TET2*	16.7
C	*BCOR RUNX1 ASXL1*	19.2
D	*BCOR RUNX1*	22.0
E	*BCOR DNMT3A TET2*	21.6
F	*BCOR DNMT3A*	19.6
G	*BCOR TET2*	14.5
H	***BCOR ASXL1***	**17.4**
I	***BCOR* + Others**	**22.5**
J	*BCOR* ONLY	19.3
	$BCOR^{WT}$	**21.9**

Figure 1