Non-CLL-type MBL and CHIP are Associated Precursor Conditions: Insights from Mayo Clinic's MBL Screening Cohort

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INTRODUCTION

- Monoclonal B-cell lymphocytosis (MBL) is a common premalignant condition that can be classified into chronic lymphocytic leukemia (CLL)-type and non-CLL-type based on their immunophenotypes.
- CLL-type MBL is well characterized with increased risk of malignancies and serious infections; however, non-CLL-type MBL remains understudied. Current evidence indicates that, similarly to CHIP, non-CLL-type MBL is also associated with hematologic malignancies.
- However, the relationship between non-CLL-type MBL and CHIP and their combined effect remains unknown.

METHODS

- In Mayo Clinic MBL Biobank, we screened 10,330 adults for MBL using flow cytometry. Individuals were over the age of 40 with no prior history of hematologic malignancies.
- CHIP was screened on 291 genes related to myeloid (56 genes) or lymphoid malignancies (235 genes).
- Among individuals residing in the 27 counties surrounding Rochester, MN, we identified incident hematologic malignancies using ICD codes and the Rochester Epidemiology Project, a population based medical records linkage system. All diagnoses were manually reviewed for confirmation.
- Cox regression (adjusted for age and sex) was used to calculate hazard ratios and 95% confidence intervals (CIs).

RESULTS

- Non-CLL-type MBL was detected in 249 (2.8%) individuals; 121 (49%) were male, and median age was 78 years (range, 47-95).
- We identified 757 (8.6%) individuals with CHIP in at least one of the 291 genes tested.
- The most frequently mutated CHIP genes were *DNMT3A*, *TET2*, *ASXL1*, *PPM1D*, and *TP53*. A total of 47 (0.5%) individuals had both non-CLL-type MBL and CHIP **(Figure 1)**; the four genes with the highest number of CHIP variants in these individuals were *DNMT3A* (n=16), *TET2* (n=10), *ASXL1* (n=3), and *ATM* (n=3).
- An association between non-CLL-type MBL and any CHIP (OR=1.6, 95%CI:1.2-2.3, P=0.006) was observed **(Figure 2)**. When analyzing CHIP in genes related to myeloid malignancies, the association with non-CLL-type MBL was also significant (OR=1.6, 95%CI:1.1-2.3, P=0.012).
- With a median follow-up of 5.4 years, 104 individuals developed incident hematologic malignancies (66 lymphoid and 38 myeloid malignancies). Non-CLL-type MBL (HR=3.5, 95%CI:1.9-6.5, P<0.001) and CHIP (HR=3.2, 95%CI:2.1-5.1, P<0.001) were each associated with increased risk of incident hematologic malignancies.

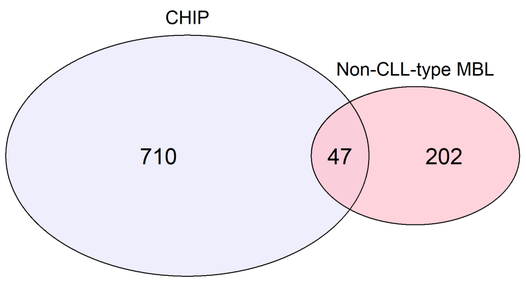


FIGURE 1. Venn diagram of the co-existence of non-CLL-type MBL and CHIP.

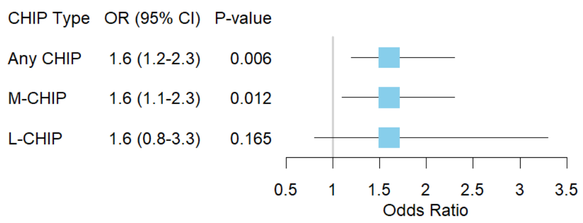
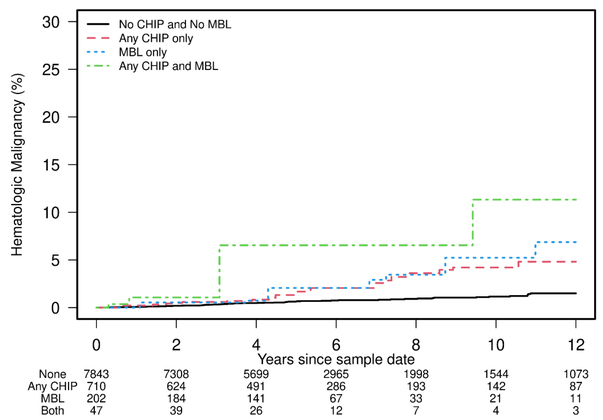


FIGURE 2. Non-CLL-type MBL is associated with CHIP.



RESULTS CONTINUED

- Co-existence of both precursor conditions was associated with a substantially higher risk of incident hematologic malignancies (HR=10.3, 95%CI:4.0-26.2, P<0.001) compared to individuals with neither precursor condition **(Figure 3)**. Among individuals with non-CLL-like MBL, any CHIP was a borderline significant predictor for incident hematologic malignancy (HR=3.6, 95%CI:1.0-12.9, P=0.049).
- Compared to individuals with no precursor conditions, OS was not significantly different in those with non-CLL-type, those with CHIP-only, or those with both CHIP and non-CLL-type MBL.

CONCLUSIONS

- In the largest screening cohort to date evaluating the relationship of CHIP and non-CLL-type MBL, we found that non-CLL-type MBL and CHIP are associated with each other and co-existence is associated with a substantially higher risk of incident hematologic malignancies.
- Individuals with non-CLL-type MBL were more likely to have CHIP variants in *DNMT3A*, *TET2*, *ASXL1*, and *ATM*.
- Among individuals with non-CLL-type MBL, the presence of any CHIP was associated with increased risk of developing hematologic malignancy.

Condition	HR (95% CI)	P-value
Non-CLL-type MBL	3.5 (1.9-6.5)	<0.001
CHIP	3.2 (2.1-5.1)	<0.001
Non-CLL-type MBL + CHIP	10.3 (4.0-26.2)	<0.001

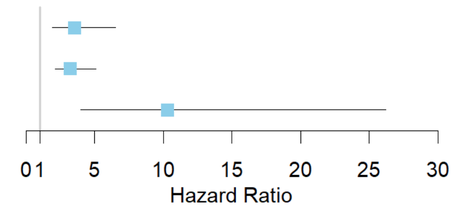


FIGURE 3. The co-existence of non-CLL-type MBL and CHIP significantly increases the risk of incident hematologic malignancies (A) Upper panel: Cumulative incidence of hematologic malignancy (B) Lower panel: Forest plot showing the hazard ratio and confidence intervals in different comparison groups.