# Beyond Time to First Treatment: Unmutated IGHV and Bone Marrow Failure-Driven Progression in CLL

**M. Bacanu[1,2], M. Omer[1], E. Pirvu[1], D. Grasu[1], A.D. Malenda[1,2], V.M. Popov[1], M. Andreescu[1,2]**

1. Hematology I, Colentina Clinical Hospital, Bucharest, Romania
2. Faculty of Medicine, UTM, Bucharest, Romania

## INTRODUCTION

Chronic lymphocytic leukemia is characterized by marked biological heterogeneity and variable progression kinetics. Unmutated IGHV is a well-established adverse prognostic marker associated with shorter time to first treatment. However, whether IGHV status also influences the clinical pathway leading to treatment initiation remains less clearly defined.

## AIM

To assess whether IGHV mutational status is associated not only with early treatment requirement, but also with distinct IWCLL-defined clinical indications leading to therapy initiation in a real-world cohort of patients with chronic lymphocytic leukemia.

## METHOD

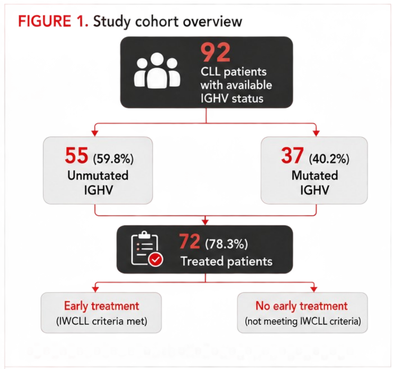
- Retrospective real-world analysis
- **Inclusion criteria:** consecutive patients diagnosed with CLL and available IGHV mutational status
- **Exclusion criteria:** patients without available IGHV status or insufficient clinical data for treatment-timing assessment
- **92 CLL patients** included from a tertiary hematology center in Eastern Europe
- Early treatment: therapy started **<90 days from diagnosis**
- IWCLL 2018 indications grouped as: **marrow failure, tumor burden, B symptoms, rapid lymphocytosis**
- Associations were evaluated using **chi-square testing** and **multivariable logistic regression**

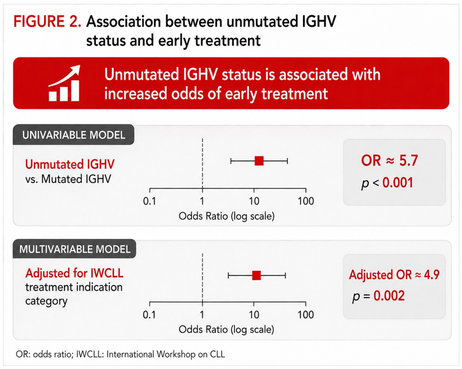
## CONCLUSIONS

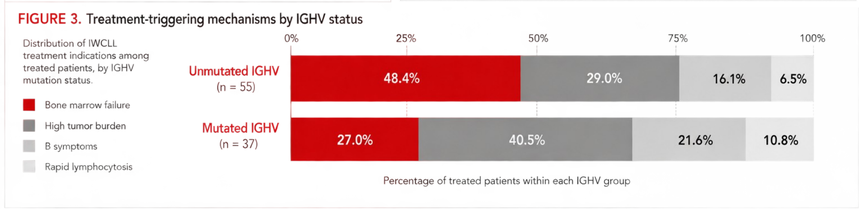
- Unmutated IGHV was independently associated with early treatment requirement.
- Our findings suggest that IGHV status may influence not only treatment timing, but also the clinical pathway leading to therapy.
- Bone marrow failure–driven progression in unmutated IGHV cases warrants further evaluation in larger cohorts with integrated molecular and microenvironmental profiling.

## RESULTS

- Unmutated IGHV was strongly associated with early treatment requirement (**OR≈5.7, p<0.001**) and remained an independent predictor in multivariable analysis (**adjusted OR≈4.9, p=0.002**).
- Among unmutated IGHV patients requiring early therapy, **bone marrow failure** was the leading indication (**48.4%**). Across the treated cohort, bone marrow failure was also the most frequent treatment indication overall (**38.9%**).
- Stratification by IGHV status suggested divergent treatment-triggering patterns: unmutated cases more frequently progressed through **bone marrow failure**, whereas mutated cases more often required therapy because of **tumor burden** or **B symptoms**, with a trend toward statistical significance (**p=0.058**).




## ACKNOWLEDGEMENTS

The authors thank the Hematology I Department, Colentina Clinical Hospital, for their support in data collection and clinical care.

## CONTACT INFORMATION

**Corresponding author:** Bacanu Maria
**Email:** bacanu.maria@yahoo.com
**Institution:** Colentina Clinical Hospital, Bucharest, Romania

## REFERENCES

1. Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Döhner H, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. *Blood*. 2018;131(25):2745-2760.
2. Baliakas P, Mattsson M, Stamatopoulos K, Rosenquist R. Prognostic indices in chronic lymphocytic leukaemia: where do we stand, how do we proceed? *J Intern Med*. 2016;279(4):347-357.
3. Landau DA, Tausch E, Taylor-Weiner AN, Stewart C, Reiter JG, Bahlo J, et al. Mutations driving CLL and their evolution in progression and relapse. *Nature*. 2015;526(7574):525-530.