

InflaWMix: An inflammatory biomarker signature predicts treatment outcomes in Waldenström's macroglobulinemia

Kevin C. Miller¹, Jennifer Lue², Andrew R. Branagan¹, Gilles Salles², Sandeep Raj³, M. Lia Palomba²

1 – Center for Multiple Myeloma, Mass General Brigham Cancer Institute, 2 – Lymphoma Service, Memorial Sloan Kettering Cancer Center, 3 – Adult Bone Marrow Transplant Service, Memorial Sloan Kettering Cancer Center

Introduction: In Waldenström's macroglobulinemia (WM), standard up-front therapy is fixed-duration bendamustine-rituximab (BR) or continuous Bruton's tyrosine kinase inhibition (BTKi). Tumor genomics play a role in treatment decisions, but novel biomarkers are needed to guide individualized treatment based on both host and disease features. Recently, an "inflammatory" WM subgroup defined by a single analyte, elevated C-reactive protein (CRP), was identified (Debureau et al., *Blood* 2025). Inflamed WM patients have been found to have divergent outcomes with prior-era therapies, but the impact of host inflammation with current standard-of-care treatment remains unclear. Our group previously derived a flexible machine-learning inflammatory signature from laboratory measures in relapsed/refractory lymphoma that predicted response and survival after CAR T-cell therapy and outperformed CRP alone (Raj et al., *Nat Med* 2025). Using similar methodology, we present InflaWMix (Inflammatory WM Mixture Model), testing the hypothesis that dysregulated systemic inflammation impacts the efficacy of standard-of-care treatments in WM.

Methods: We retrospectively studied patients with IgM WM treated with BR or single-agent BTKi at Memorial Sloan Kettering Cancer Center from 2015–2025. Outcomes were annotated per IWWM-11 criteria. *MYD88* and *CXCR4* were analyzed by next-generation sequencing (MSK-IMPACT). An unsupervised Gaussian mixture model was derived from eight scaled routine pre-treatment laboratory parameters among patients with complete baseline data, then refined to the best two-cluster, five-marker model by the Bayesian information criterion. Progression-free survival (PFS) was estimated by the Kaplan-Meier method and compared with log-rank test; hazard ratios (HR) were estimated by Cox proportional hazards regression (Wald test).

Results: Of 155 IgM WM patients screened, 125 with complete immediate pre-treatment laboratory data were included in the model. Sixty-six (53%) were male; median age at treatment initiation was 71 (range 45–92). The *MYD88* mutation was present in 99/117 (85%) and *CXCR4* in 35/80 (44%) of those sequenced. Sixty-three (50%) received BTKi (zanubrutinib n=37, ibrutinib n=18, acalabrutinib n=8) and 62 (50%) received BR. Thirty-eight patients (30%) had received anti-WM therapy prior to index BTKi or BR. Median follow-up was 41.6 months (95% CI 37.1–51.8).

The final derivation model comprised platelet count, absolute neutrophil count, absolute monocyte count, alkaline phosphatase, and IgG. One cluster (n=32), characterized by uniformly higher values across these markers, was designated as "inflammatory" post hoc; the remainder (n=93) were designated "non-inflammatory" (**Fig 1A–B**). The two clusters did not significantly differ in age, treatment type, prior therapy, or mutation status. CRP was not routinely obtained and could not be compared among clusters. However, among 31 patients (25%) with baseline ferritin, the median ratio to the sex-specific upper limit of normal was two-fold higher in the inflammatory cluster (0.56 vs 0.27, p=0.120).

Inflammatory patients had inferior PFS (median 65.8 months vs not reached; log-rank $p=0.018$). In a multivariable model including treatment type and receipt of prior anti-WM therapy, the inflammatory signature was significant for PFS (HR 2.35, 95% CI 1.13–4.88, $p=0.022$) (**Fig 1C**), and also remained independently associated with PFS after adjustment for rIPSSWM (HR 3.74, 95% CI 1.47–9.48, $p=0.006$) or MSS-WM (HR 2.24, 95% CI 1.05–4.80, $p=0.038$) scores, or *MYD88* mutation status (HR 2.48, 95% CI 1.18–5.19, $p=0.016$). In treatment-stratified analyses, the inflammatory cluster was associated with inferior PFS among BR-treated patients (HR 3.99, 95% CI 1.52–10.4, $p=0.005$) but not among BTKi-treated patients (HR 1.02, 95% CI 0.28–3.68) (**Fig 1D–E**).

Conclusion:

InflaWMix, an unsupervised model of readily available, point-of-care laboratory values, identifies a WM subgroup with higher inflammatory markers and inferior PFS. Its prognostic value was independent of established staging systems and *MYD88* genotype, indicating that it captures risk not reflected in tumor burden or genomics. The adverse association was most pronounced among BR-treated patients and was attenuated with BTKi, raising the hypothesis that inflammatory patients may derive relatively greater benefit from continuous BTK inhibition. Validation of the model in external cohorts and integrated multi-omic investigation of the underlying biology are underway. These findings could facilitate precision treatment selection in WM.

Figure 1.

