Bone Marrow Tumor Burden as a Predictor of Time to Progression in Asymptomatic Waldenstrom Macroglobulinemia: Evidence from a 20- year Follow-up Italian Cohort

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Short Report

Keywords: Waldenstrom Macroglobulinemia, Lymhoplasmacytic Lymphoma, Non Hodgkin Lymphoma, Bone Marrow, Smoldering Waldenström Macroglobuliemia

Posted Date: September 30th, 2025

DOI: https://doi.org/10.21203/rs.3.rs-7401332/v1

Additional Declarations: No competing interests reported.

Abstract

While data suggest that bone marrow (BM) disease burden in asymptomatic Waldenström Macroglobulinemia (WM) may be related to time to progression, no consensus has yet been reached regarding the optimal thresholds.

A 25% BM infiltration threshold was used to stratify our cohort of 150 asymptomatic WM into high- and low-disease burden subgroups. The primary outcomes evaluated were time to progression (TTP) and overall survival (OS).

We found that the high BM tumor burden subgroup exhibited distinct clinical and biological features, including lower hemoglobin levels, higher serum IgM concentrations, increased monoclonal component levels, higher frequency of CXCR4 mutations, and a lower prevalence of peripheral neuropathy. This subgroup also demonstrated significantly shorter median TTP compared with patients with lower BM involvement (64 months vs. 137 months, $p = 0.01$). Factors associated with shorter TTP included advanced age (hazard ratio [HR] 1.04), lower hemoglobin levels (HR 1.02), elevated serum MC (HR 1.06), increased IgM concentrations (HR 1.06), and the presence of cytogenetics aberrations (HR 2.5). In multivariate analysis, only elevated serum IgM (HR 1.09) remained an independent predictor of shorter TTP, whereas cytogenetic abnormalities showed only a trend toward significance (HR 2.4).

In the OS analysis, no significant differences were observed between the two subgroups.

Finally, a higher BM tumor burden at diagnosis is associated with shorter TTP in asymptomatic WM. Elevated serum IgM independently predicted inferior TTP. Our results are consistent with previously published series and the 5th WHO Lymphoid Neoplasm Classification, underscoring the prognostic significance of BM disease burden in WM.

Introduction

Waldenström Macroglobulinemia (WM) is a rare indolent B -lymphoma characterized by bone marrow (BM) infiltration of clonal lymphoplasmacytic cells secreting an IgM monoclonal paraprotein.[1] A wide range of clinical manifestations have been described in this entity.[2,3,4,5]

The 5th edition of the World Health Organization (WHO) Classification of Tumors of Haemopoietic and Lymphoid Tissues retains a 10% threshold of BM infiltration as a diagnostic criterion, whereas the 2022 International Consensus Classification (ICC) does not require a minimal percentage, considering the demonstration of lymphoplasmacytic aggregates in BM biopsy as sufficient for diagnosis.[6,7]

These divergent definitions raise the question of whether the degree of BM lymphoplasmacytic infiltration has prognostic value, comparable to other well-established prognostic variables in WM, such as MYD88, CXCR4, TP53 mutational status or karyotype complexity. Together, these molecular features

have clearly demonstrated the central prognostic and therapeutic implications of the WM genomic landscape.[8,9,10]

Previous studies have investigated the prognostic role of BM disease burden in asymptomatic WM.

Kyle et al. first reported in a cohort of 48 asymptomatic patients that a higher progression rate at 5 years was observed in those with > 50% lymphoplasmacytic BM infiltration; notably, BM infiltration was the only independent predictor of progression in multivariate analysis.[11]

Bustoros et al. subsequently proposed a four-variables score (including albumin serum level, serum b2-microglobulin level, BM infiltration percentage, and serum IgM level) for predicting time to progression, identifying a BM infiltration threshold of 70% as independently prognostic.[12]

Similarly, the Spanish group developed a prognostic model using the same variables but applying different thresholds (including BM infiltration cutoff of 20%), again with the aim of predicting progression in asymptomatic WM.[13]

The discrepancies between the current classifications, together with the heterogeneity of BM infiltration thresholds across published studies, make it difficult to establish whether BM disease burden truly carries prognostic significance. This uncertainty particularly affects its potential role as a marker of disease burden in relation to survival outcomes such as TTP and OS.

Given these considerations, we analyzed our Center's WM cohort to investigate whether BM disease burden predicts TTP and OS in asymptomatic WM patients. In addition, we investigated associated clinical and molecular correlations.

Methods

A cohort of 150 asymptomatic WM patients at diagnosis was selected out of 230 consecutive WM patients admitted and diagnosed between 2005 and 2025 at the Hematology and Pathology Units of the University of Padua Hospital, Italy, according to the 2022 ICC definition. The study was carried out after approval of the Ethic Committee of Azienda Ospedale-Università di Padova (protocol # 4089/AO/17).

The primary aim of the study was to assess the impact of BM lymphoplasmacytic infiltration at disease onset in predicting both progression from asymptomatic to symptomatic WM and death from any cause. Accordingly, the two endpoints of the study were time to progression (TTP) and overall survival (OS). Patients were stratified into high- versus low-tumor burden groups using the median BM infiltration value cutoff.

Categorical and continuous variables were compared using the Chi-Square test or Mann-Whitney U test, as appropriate. Cox proportional hazard regression models were applied for univariate and multivariate analyses to identify factors associated with TTP and OS. Missing data were excluded from the analysis.

Survival curves were generated with the Kaplan-Meier method and compared with the log-rank test. A two-sided *p*-value <0.05 was considered statistically significant. Statistical analysis was performed using RStudio (version 2022.07.2).

All BM samples were analyzed and reviewed at the Pathology Unit of the University of Padova Hospital. *MYD88* and *CXCR4* mutational status was determined by highly sensitive allele-specific PCR (AS-PCR), and cytogenetic analysis was performed using chromosome binding analysis (CBA).

Results

The median BM infiltration in the asymptomatic cohort at diagnosis (n=150) was 25%, which was used as the cutoff to stratify patients into high (³25%, n = 82) and low (<25%, n = 68) BM tumor burden subgroups. The median follow was 90 months (95% CI, 57-123)

Patients in the high BM infiltration subgroup displayed distinct clinical features compared with those in the low subgroup: lower hemoglobin levels (126.6 vs 134.5 g/L, *p*=0.001), higher serum IgM concentrations (19.0 vs 10.1 g/L, *p*<0.001), higher monoclonal component (MC) levels (14.6 vs 7.7 g/L, *p*<0.001), a higher frequency of *CXCR4*mutations (23% vs 13%, *p*<0.001), and a lower prevalence of peripheral neuropathy (13% vs 30%, *p*=0.009) (Table1).

No significant differences were observed between subgroups in age at diagnosis, platelet count, serum C-reactive protein, serum creatinine, $MYD88^{L265P}$ status, cytogenetic aberrations, or the occurrence of secondary malignancies.

With regard to survival outcomes, median TTP was significantly shorter in the high BM burden group (64 months; 95% CI, 38-105) compared with the low group (137 months; 95% CI, 121 - NA) (HR 1.85; 95% CI, 1.14-3.01, *p* = 0.01)(Figure 1A; Table3).

In univariate Cox-regression analysis, factors associated with shorter TTP included advanced age (HR 1.04), lower Hb (HR 1.02), elevated serum MC (HR 1.06), higher serum IgM (HR 1.06) and presence cytogenetics aberrations (HR 2.5). In multivariate analysis, only elevated serum IgM remained an independent predictor of shorter TTP (HR 1.09), while cytogenetic aberrations retained only a trend toward significance (HR 2.4) (Table2).

In contrast, BM tumor burden had no significant impact on overall survival: median OS was 200 months (95% CI, 178 – NA) in the high subgroup and 251 months (95% CI, 203 – NA) in the low subgroup (HR 1.63; 95% CI, 0.63-4.22; p = 0.31) (Figure 1B; Table3).

Discussion

In our cohort, a BM infiltration threshold of approximately 25% was identified as a value that evenly stratified asymptomatic patients at diagnosis.

As expected, anemia, as well as elevated serum IgM and MC levels were more frequent in patients with higher BM tumor burden. In addition, the higher prevalence of *CXCR4* mutations in this group may reflect homing signals that facilitate lymphoplasmacytic cell trafficking from peripheral blood to the BM, as previously suggested.[14]

The lower prevalence of peripheral neuropathy in patients with higher BM infiltration and shorter TTP is less straightforward. Clinical practice and published evidence suggest that anti-MAG peripheral neuropathy is often observed in the setting of IgM-MGUS or asymptomatic WM, therefore an underlying indolent biology could be more associated with this manifestation of disease.[3]

While elevated serum IgM levels in patients with higher BM involvement expectedly mirror an increased tumor burden and predict shorter TTP, the prognostic impact of cytogenetic abnormalities appears more complex. Interestingly, these aberrations were not more prevalent in the high-infiltration group but correlated with shorter TTP in patients with ≥25% bone marrow infiltration, at least at univariate analysis. Although the unfavorable prognostic role of karyotype complexity has been documented in WM, this study provides to our knowledge, the first evidence that it may influence progression specifically in asymptomatic WM.[9,15]

Our findings show that asymptomatic WM patients with ≥25% BM infiltrations experience shorter TTP but no significant differences in OS. This observation aligns with 5th WHO Classification, which retains a threshold of BM infiltration (10%) as part of the diagnostic definition, in contrast with the ICC 2022, which does not specify a cutoff. Moreover, our proposed threshold is consistent with those reported by *Kyle et al., Moreno et al., and Bustoros et al*. Together, these data support the view that the extent of BM lymphoplasmacytic infiltration carries prognostic significance in WM.

The limitations of this study include its retrospective design and the relatively small sample size. However, the centralization of the histopathological and molecular BM analysis reduces inter-observer variability and strengthens the reliability of our findings.

In conclusion, we observed that asymptomatic WM patients with high BM tumor burden at diagnosis (³25%) have significantly shorter TTP. This subgroup was characterized by a higher prevalence of hyperviscosity, anemia and *CXCR4* mutations, but a lower frequency of peripheral neuropathy. Elevated serum IgM levels at diagnosis emerged as the only independent predictor of inferior TTP. These results are consistent with prior studies, underscoring the prognostic value of BM disease burden. Prospective external validation will be essential to confirm these observations and further clarify the role of BM infiltration in WM prognostication.

Declarations

Author contributions

ND, FP conceptualization, writing original draft, data analysis; FP editing and supervision; GL, MD, GS, MC, AC, FA, SZ, FV, SM, AV, LT data collection and editing; LB provided molecular analysis; MP histopathological review.

Data availability statement

The data that support the findings of this study are available upon reasonable request to the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Conflict of interest

The authors have no conflicts of interest to declare.

Ethic statement and consent to participate declaration

This study was conducted in accordance with the declaration of Helsinki. In addition, the authors declare that each patient has signed written informed consent to participate to this study.

Clinical trial Number

Clinical trial number: not applicable.

Consent to publish declaration

The authors give the permission of the publication of the results reported in this manuscript.

Funding statement

The authors declare that no source of funding was required for this article.

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Tables

Table 1. Baseline features comparing low (<25%) **versus high bone marrow tumor burden** (³25%) **in asymptomatic Waldenstrom Macroglobulinemia patients.**

	Low Bone Marrow Tumor burden (<25%) for aWM	High Bone Marrow Tumor burden (³25%) for aWM	P value
Age (years, IQR)	70 (60-75)	71 (62-75)	n.s.
Hb (g/L, IQR)	134.5 (121.3-145.7)	126.6 (117.2-136.3)	**0.001**
PLT (x10^9/L, IQR)	247.0 (210.0-300.0)	244.0 (205.0-347.0)	n.s.
IgM (g/L, IQR)	10.1 (4.7-17.6)	19.0 (10.7-25.0)	**< 0.001**
MC (g/L, IQR)	7.7 (5.4-13.4)	14.6 (8.1-21.7)	**< 0.001**
CRP (mg/L, IQR)	2.9 (2.9-5.4)	3.6 (2.9-10.0)	n.s.
Serum creatinine (mmol/L, IQR)	76.0 (67.0-90.0)	80.0 (65.5-88.5)	n.s.
MYD88^{L265P} (n, %)	46/51 (0.90)	52/59 (0.88)	n.s.
CXCR4^{MUT} (n, %)	4/31 (0.13)	7/31 (0.23)	**< 0.0001**
Cytogenetic aberrations (n, %)	7/22 (0.32)	21/48 (0.44)	n.s.
Neuropathy (n, %)	20/67 (0.30)	10/80 (0.13)	**0.009**
Second cancer (n, %)	11/67 (0.16)	17/82 (0.21)	n.s.

Abbreviations: aWM = asymptomatic Waldenstrom Macroglobulinemia; Hb = hemoglobin; PLT = platelets; IQR = interquartile range; MC = monoclonal component; CRP = C reactive protein; n.s.= not significant

Table 2. Cox proportional hazard model regarding Time to progression (TTP) outcome in high bone marrow tumor burden (³25%) in asymptomatic WM patients

	Univariate TTP		Multivariate TTP	
	HR CI 95%	P val	HR CI 95%	P val
Age	1.04 (1.01-1.07)	**0.001**	n.s.	n.s.
Hb	1.02 (0.98-0.99)	**< 0.001**	n.s.	**n.s.**
IgM	1.06 (1.04-1.09)	**< 0.001**	1.09 (1.02-1.17)	**0.02**
MC	1.05 (1.03-1.09)	**< 0.001**	n.s.	n.s.
Cytogenetic abnormalities	2.5 (1.16-5.5)	**0.02**	2.4 (0.98-5.69)	0.05

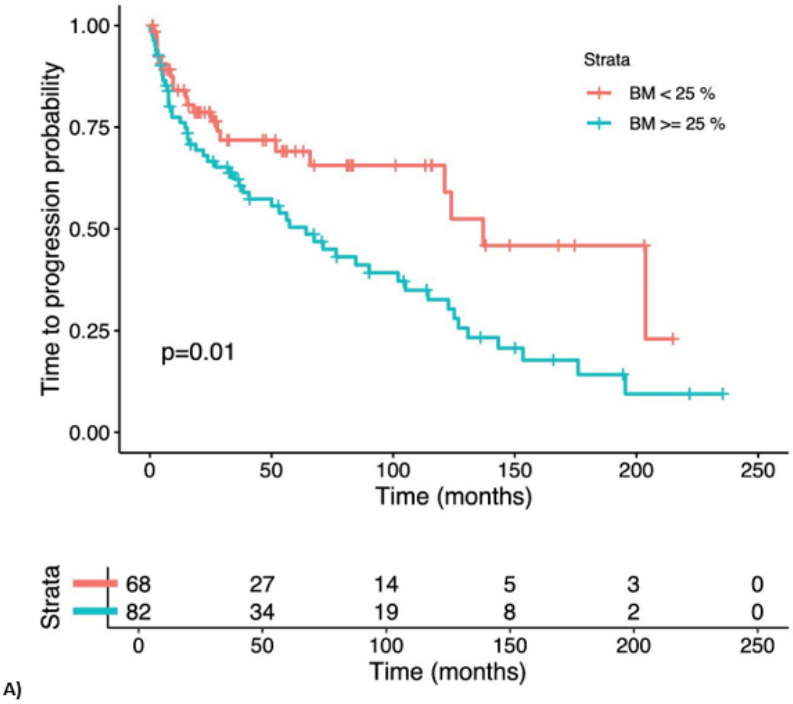
Abbreviations: TTP = time to progression, HR = Hazard ratiom, CI = confidence interval, Hb = hemoglobin; MC = monoclonal component; TTFT = time to first treatment

Table 3. Median TTP and OS comparing high (³25%) vs low (<25%) bone marrow tumor burden for asymptomatic WM patients.

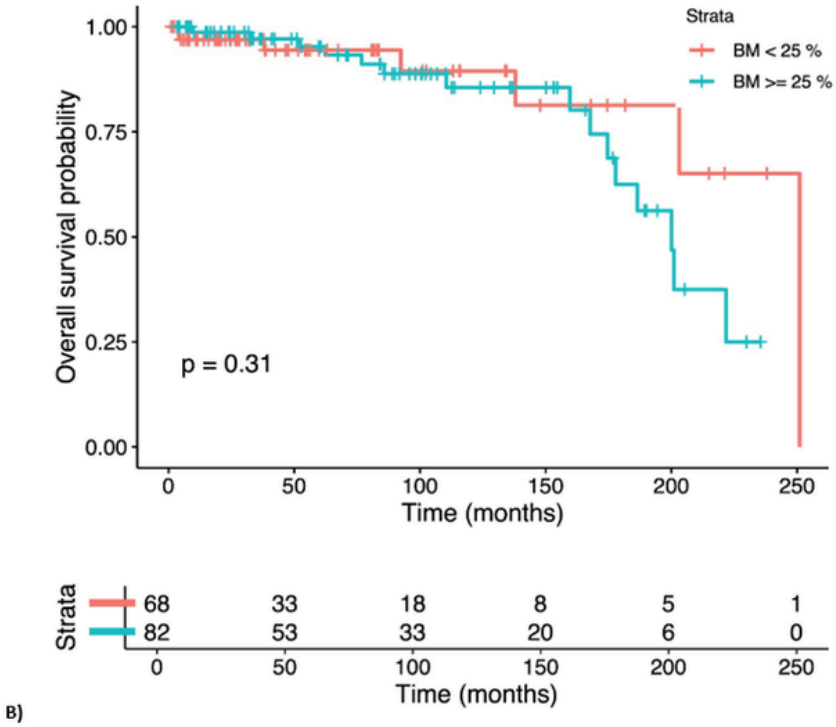
Subgroups	Median TTP (months)	HR (CI 95%), P value	Median OS (months)	HR (CI 95%), P value
High bone marrow tumor burden (³25%)	64	1.85 (1.14-3.01)	200	1.63 (0.63-4.22)
Low bone marrow tumor burden (<25%)	137	0.01	251	0.31

Abbreviations: TTP = time to progression, HR = Hazard ratiom, CI = confidence interval

Figures



A)



B)

Figure 1

Kaplan Meier curves of Time to Progression (TTP) and Overall Survival (OS) considering low (<25%) vs high bone marrow tumor burden (³25%)