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SHORT REPORT

Haematological Malignancy – Clinical

Prognostic impact of nodal involvement in Waldenström macroglobulinaemia

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Summary
The clinical and prognostic implications of nodal involvement (NI) in Waldenström macroglobulinaemia (WM) are largely unknown. In this study, we explored the impact of NI on clinical presentation and outcome in a population-based cohort of 469 patients with WM, consecutively diagnosed between 2000 and 2022. NI was detected in 34% of patients and was associated with symptomatic disease, adverse prognostic factors, an increased risk of transformation, and lymphoma-related death. Our findings indicate that NI is of prognostic significance in WM, suggesting a need for enhanced surveillance in these patients.

KEYWORDS
extra-medullary disease, histological transformation, non-Hodgkin's lymphoma, prognosis, Waldenström's macroglobulinaemia

INTRODUCTION

Waldenström macroglobulinaemia (WM) is characterized by clonal expansion of mature B cells in the bone marrow (BM) and the presence of an immunoglobulin M (IgM) monoclonal protein.[1] Although the BM is the primary site of disease, patients with WM may also present with extra-medullary disease, including both nodal and extra-nodal manifestations.[2,3] In other indolent B-cell lymphomas, the nodal tumour burden is a predictor of adverse outcomes and an indicator of a need for treatment.[4,5] However, the clinical significance and prognostic impact of nodal involvement (NI) in patients with WM remains largely unknown. We present data from a population-based study that systematically aimed to determine the clinical characteristics and outcomes of patients with NI.

PATIENTS AND METHODS

The study cohort covered patients with WM diagnosed in Region Zealand between 2000 and 2022. Region Zealand covers ~850 000 citizens, corresponding to 15% of the Danish population. The diagnosis of WM was made in accordance with consensus guidelines and included diagnostic evaluation by an expert hematopathologist.[1] Clinical data were collected from medical records. NI included clinically or radiologically detected lymphadenopathy and splenomegaly. WM-directed first-line therapies were recorded, and response to treatment was evaluated according to consensus criteria.[6] Patients with discordant lymphoma at primary diagnosis, other than diffuse large B-cell lymphoma (DLBCL), were excluded.

Clinical characteristics were reported using descriptive statistics. Chi-square or Mann–Whitney tests were used for

comparison between groups. Time-to-event curves were generated using the Kaplan–Meier method and differences were compared using the log-rank test. Lymphoma-related survival (LRS) was calculated from the date of diagnosis to the date of death caused by lymphoma or the date of last follow-up, and patients who died from treatment-related complications or other causes other than lymphoma were censored. Univariate and multivariate analyses were performed using a Cox proportional hazards regression model.

RESULTS

We identified a total of 469 patients with WM, and their baseline characteristics are summarized in Table S1. The number of patients with NI was 160/469 (34%). Computed tomography (CT) or fluorine-18-fluorodeoxyglucose positron emission tomography (FDG-PET) was performed in 427/469 (91%) patients (Table S1). In 48/160 (30%) patients, NI was further confirmed through tissue biopsy. NI was present at the time of WM diagnosis in 143/160 (89%) patients and detected at progression or relapse in 17/160 (11%) cases. Splenomegaly was present in 16/143 (11%) patients simultaneously with NI at the time of WM diagnosis. *MYD88*^{L265P} mutational status was available in 262/469 (56%) patients, primarily from the late study period, and the *MYD88*^{L265P} mutation was identified in 252/262 (96%) of these cases. *MYD88*^{WT} was detected in 9/178 (5%) patients without NI and 1/84 (1%) patients with NI.

The number of symptomatic patients treated at diagnosis was significantly higher among patients with NI compared

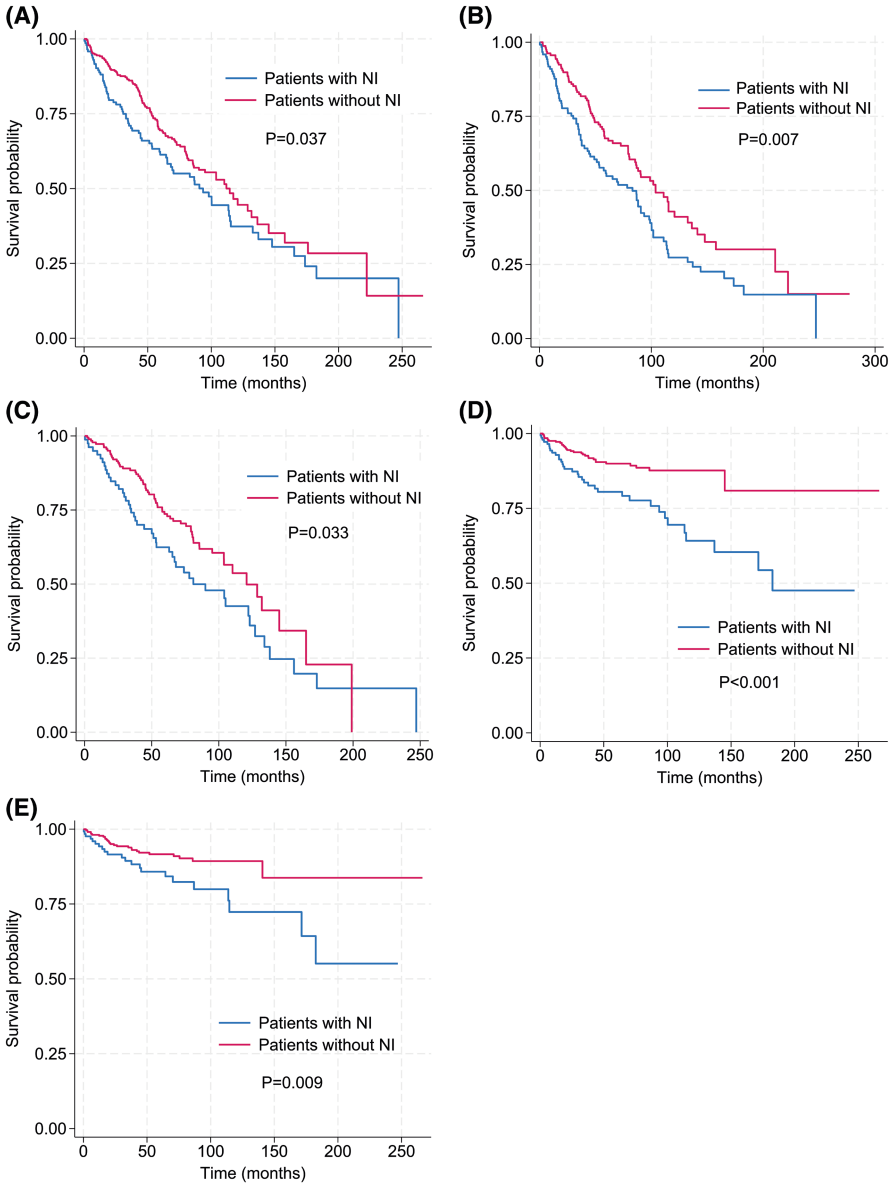

FIGURE 1 Survival analysis of Waldenström macroglobulinaemia patients with and without nodal involvement (NI). (A) Overall survival of the entire cohort ($n = 469$). (B) Overall survival of symptomatic patients ($n = 282$). (C) Overall survival of patients with available *MYD88*^{L265P} mutational status ($n = 262$). (D) Lymphoma-related survival of the entire cohort ($n = 469$). (E) Lymphoma-related survival of patients without transformation ($n = 448$).

with those without NI (Table S1). Details on treatments, including the distribution of therapies between the NI and non-NI groups, are shown in Table S2. Response assessment was available in 254/282 (90%) patients. Complete remission or very good partial remission was achieved in 36% of patients with NI and 37% of patients without NI. Partial remission was achieved in 32% and 40% of patients with and without NI, respectively. In asymptomatic patients who were not treated within 3 months following WM diagnosis, the median time to treatment was 2.4 years (95% CI 1.8–4.5) in patients with NI and 4.8 years (95% CI 4.6–5.6) in patients without NI ($p = 0.002$). The median number of treatment lines from diagnosis to follow-up was 2 (range 0–10) in the NI group and 1 (range 0–7) in the non-NI group ($p < 0.001$).

The median (range) follow-up time in surviving patients was 74 months (11–277). The 5- and 10-year overall survival (OS) estimates for the total group of patients with WM were 63% and 44%. Median OS was significantly shorter for patients with NI at primary diagnosis when compared with patients without NI (94 months [95% CI 65–114] vs. 115 months [95% CI 90–132]) (Figure 1A). The number of symptomatic patients was higher in the NI group; however, a similar trend was found when analysing only symptomatic patients treated at diagnosis (median OS 83 months [95% CI 53–94] vs. 104 months [95% CI 87–121]) (Figure 1B). We also performed an analysis in patients with *MYD88*^{L265P} status available which confirmed a shorter survival in patients with NI (median OS 81 months [95% CI 63–122] vs. 121 months [95% CI 104–145]) (Figure 1C). LRS was also significantly inferior in patients with NI at primary diagnosis (183 months [95% CI 137–183]) compared with patients without NI (median LRS not reached) (Figure 1D). In the univariate Cox regression model of the entire WM group, we found that NI was significantly associated with OS and LRS (Table 1). In the multivariate model, NI remained a significant predictor of inferior LRS.

Histological transformation (HT) to DLBCL was found in 17/143 (11.9%) patients with NI and 4/326 (1.2%) without NI ($p < 0.001$). In patients with NI and HT, biopsies with DLBCL were obtained from lymph nodes (9/17), BM (2/17), or other extra-medullary sites (6/17). The *MYD88*^{L265P} mutational status was available in 12 transformed patients, and the mutation was detected in all cases. In 6/17 (35%) patients with NI, HT occurred within 6 months after the primary diagnosis of WM with two cases of concurrent diagnoses of WM and DLBCL. No patients without NI had HT at the time of primary WM diagnosis. Median (range) time to transformation in patients with and without NI was 12 months (0–98)

TABLE 1 Cox regression model of overall survival (OS) and lymphoma-related survival (LRS) for patients with Waldenström macroglobulinaemia.

	OS			LRS		
	HR	**95% CI**	***p*-Value**	**HR**	**95% CI**	***p*-Value**
Univariate						
Nodal involvement	1.36	1.01–1.83	**0.041**	2.32	1.58–3.42	**<0.001**
Sex (male)	0.98	0.73–1.32	0.912	0.94	0.63–1.39	0.746
Age (≥65 years)	3.00	1.92–4.69	**<0.001**	2.45	1.38–4.37	**0.002**
Hgb (≤11.5 g/dL)	2.19	1.63–2.94	**<0.001**	2.30	1.56–3.39	**<0.001**
Platelets (<100 × 10^9/L)	1.20	0.71–2.06	0.492	0.90	0.39–2.06	0.799
IgM (>20 g/L)	1.07	0.80–1.44	0.657	1.48	1.00–2.20	**0.050**
LDH (>ULN)	1.21	0.86–1.44	0.278	1.56	1.01–2.41	**0.046**
β2M (>3 mg/L)	2.35	1.75–3.16	**<0.001**	2.16	1.46–3.19	**<0.001**
Albumin (<35 g/L)	2.06	1.54–2.76	**<0.001**	2.31	1.57–3.40	**<0.001**
Symptomatic at diagnosis	1.35	0.99–1.83	0.060	2.61	1.62–4.21	**<0.001**
B-symptoms	1.95	1.38–2.75	**<0.001**	2.02	1.28–3.19	**0.003**
BM infiltration (≥30%)	1.12	0.83–1.52	0.449	1.02	0.69–1.51	0.927
Multivariate						
Nodal involvement	1.04	0.75–1.44	0.817	1.77	1.07–2.92	**0.019**
Age (≥65 years)	2.93	1.83–4.67	**<0.001**	2.24	1.11–4.56	**0.010**
Hgb (≤11.5 g/dL)	1.54	1.10–2.14	**0.011**	1.28	0.75–2.17	0.372
IgM (>20 g/L)	-	-	-	1.63	0.99–2.69	0.057
LDH (>ULN)	-	-	-	2.07	1.25–3.43	**0.010**
β2M (>3 mg/L)	1.59	1.16–2.18	**0.004**	1.41	0.80–2.48	0.241
Albumin (<35 g/L)	1.60	1.17–2.19	**0.003**	1.39	0.84–2.32	0.204
Symptomatic at diagnosis	-	-	-	2.14	1.16–3.96	**0.015**
B-symptoms	1.33	0.91–1.95	0.145	1.21	0.70–2.09	0.503

Abbreviations: BM, bone marrow; Hgb, haemoglobin; IgM, immunoglobulin M; LDH, lactate dehydrogenase; ULN, upper limit of normal range; β2M, beta-2 microglobulin.
Bold values indicates statistically significant *p*-values.

and 26 months (5–135) respectively ($p = 0.3$). To evaluate the expected effect of transformation on lymphoma-related death, we compared LRS in patients with and without NI excluding patients with HT from the analysis. LRS remained significantly shorter in patients with NI, but the difference was less pronounced (Figure 1E).

DISCUSSION

We report that approximately one in three WM patients had NI at primary diagnosis, whilst the appearance of NI at relapse or progression was rare. In a Spanish population, and according to data from the Greek Myeloma Study Group, lymphadenopathy and splenomegaly were reported in less than a third of symptomatic patients at the time of WM diagnosis.[7,8] However, two studies examining the role of FDG-PET in symptomatic patients found lymphadenopathy in up to 60% of cases, indicating that the true incidence of NI might be higher than previously assumed.[9,10]

Roughly two-thirds of WM patients are symptomatic with a need for treatment at diagnosis.[8,11] In comparison, we found equivalent rates of symptomatic disease across all patients, but significantly more symptomatic cases among patients with NI. The time to first treatment was shorter for asymptomatic patients with NI compared with those without NI. Additionally, patients with NI typically received more lines of treatment throughout the course of their disease. In other low-grade B-cell lymphomas, a large nodal tumour burden has been associated with an a priori need of treatment.[4] However, WM is defined by malignant infiltration of the BM, and indications for treatment are mainly driven by cytopenias and complications associated with the monoclonal IgM.[1,8] Our findings suggest that the importance of nodal manifestations may have been underestimated with an increased rate of symptomatic disease and need of treatment in patients with NI.

We also observed a significantly higher rate of transformation to DLBCL in patients with NI and approximately a third of transformation events occurred within the first 6 months after the diagnosis of WM. HT generally occurs in about 1%–4% of WM patients, with lymph nodes being the most frequent site of transformation.[12,13] In our study, biopsy-proven transformation was equally distributed between nodal and extra-nodal sites. Another intriguing finding was a significantly shorter OS and LRS associated with NI. In our multivariate model, NI did not maintain its significance as an independent predictor of OS but remained a significant variable for LRS. Our results indicate that NI is accompanied by a more aggressive lymphoma phenotype with an increased risk of transformation and lymphoma-related death. Our data also demonstrate that the higher rate of transformation only accounts for part of the increased risk of lymphoma-related death. Lymphadenopathy has also been included in prognostic models that predict long-term outcome in other indolent lymphomas.[5] In contrast, extramedullary involvement is not part of prognostic scores for WM.[14,15] The findings of our study reveal a likely prognostic impact of NI that needs to be validated in further studies.

Our study has some limitations, including its retrospective nature and the partial lack of molecular data. Additionally, the treatment landscape for WM has evolved in recent years, which may influence the prognostic implications of NI compared with our data spanning two decades. Future studies incorporating quantitative data on nodal tumour burden and more comprehensive molecular data are warranted.

The impact of nodal disease has been relatively neglected in WM. Our study provides novel insights, suggesting that nodal tumour burden, alongside BM disease, holds significant clinical and prognostic relevance in WM. Specifically, NI is associated with an increased need for treatment, inferior lymphoma-specific survival, and an increased risk of transformation. These findings indicate a need for heightened surveillance in these patients and the inclusion of NI in future studies.

AUTHOR CONTRIBUTIONS

SØ wrote the manuscript; SØ and LM collected data; MØP and LMRG performed pathological reviews; all authors contributed to the design of the study, interpretation of data, and the editing of the manuscript; all authors read and approved the final manuscript.

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The authors have nothing to report.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data from this study are available from the corresponding author upon reasonable request and with the appropriate approvals from the Danish Research Ethics Committee.

ETHICS APPROVAL STATEMENT

The study was approved by the Danish National Research Ethics Committee (ID: 2113049) and the Region Zealand Data Protection Agency (ID: REG-020-2022).

PATIENT CONSENT STATEMENT

Exemption from obtaining informed consent was granted by the Danish National Ethics Committee.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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