Ethnic diversity in presentation and outcome of Waldenström macroglobulinemia and IgM monoclonal gammopathy of clinical significance in the United Kingdom

Waldenström macroglobulinemia (WM) is a low-grade B-cell lymphoma characterized by lymphoplasmacytic marrow infiltration,[1] historically described in white cohorts.[2] The aim of this study was to analyze baseline characteristics and outcomes of patients with WM, IgM monoclonal gammopathies of clinical significance (MGCS) and IgM-associated disorders across different ethnic groups in the United Kingdom (UK). We analyzed 1,168 patients from the UK, demonstrating that ethnic minorities presented with WM at a younger age, with a lower monoclonal protein (M-protein) and with a higher proportion of *MYD88*^{WT}, which may suggest a different disease biology from that in white patients. Black patients had a shorter treatment-free survival (TFS) independently of baseline characteristics.

WM may be asymptomatic, symptomatic and/or associated with other IgM MGCS.[3] The International Prognostic Scoring System for WM (IPSSWM) stratifies survival outcomes based on clinical biomarkers,[4] although molecular and clinical characteristics are increasingly investigated. Little, however, is reported on ethnicity. Data from the United States (US)[5,6] and Latin America[7] highlight potential differences in outcomes. Clinical correlates with ethnicity have not been formally characterized in the UK.

We reviewed data from the Rory Morrison WMUK Registry, collating data from patients with WM, non-IgM lymphoplasmacytic lymphoma and IgM MGCS from 21 centers across the UK. Research ethics approval was obtained (REC:17/LOLO/1666). Baseline characteristics, indication for treatment and outcome were recorded. Molecular analysis was performed at local sites and reviewed in nationally designated specialist integrated hematologic malignancy diagnostic services. Sociodemographic data were not collected. Follow-up was recorded to September 2023.

Self-reported ethnicity was categorized as White, Black, Asian and Mixed/Other according to the UK Office for National Statistics categories (*Online Supplementary Table S1*). Baseline characteristics were compared using χ^2 or Fisher exact tests (categorical variables) or Wilcoxon Mann-Whitney/Kruskal-Wallis tests (continuous variables). Survival analysis was performed for patients diagnosed from 2015 onwards, after prospective data entry was initiated in the registry to reduce survivorship bias risk. Overall survival (OS) and TFS were defined as time from diagnosis to death/last follow-up and first-line therapy/death, respectively. OS and TFS estimates were generated using the Kaplan-Meier method and groups were compared using Cox proportional hazards regression and the log-rank test. Differences were considered statistically significant at *P* values <0.05. Statistical analyses were performed using STATA v18.0 (StataCorp, College Station, TX, USA).

Of 1,437 patients registered in June 2022, 1,200 patients had documented ethnicity. Thirty-two were excluded due to incomplete diagnostic information or reclassification to another diagnosis (marginal zone lymphoma/plasmablastic lymphoma, N=4; IgM monoclonal gammopathy of uncertain significance [MGUS] alone, N=28), leaving 1,168 patients (61% male, 39% female) available for analysis. Table 1 summarizes their baseline characteristics.

The underlying diagnosis of the patients registered between June 1978 and December 2022 was WM (N=1,026), non-IgM lymphoplasmacytic lymphoma (N=23) or IgM MGCS alone (N=119). Of those with WM, 24% (248/1,026) had an additional MGCS disorder. Thirty-eight patients had extranodal lymphoplasmacytic lymphoma infiltration in the central nervous system (Bing-Neel syndrome).

Most of the patients were White (1,058; 91%) and 110 (9%) were from the following ethnic groups (collectively, ethnic minorities): 58 Asian (24 Indian, 4 Pakistani, 2 Bangladeshi, 7 Chinese, 16 other, 5 undisclosed), 17 Black (5 African, 9 Caribbean, 1 other, 2 undisclosed), 6 Mixed/multiple, 29 Other ethnic group.

Patients from ethnic minorities presented at a younger age compared to those of white ethnicity (ages for White, Asian, Black and Other ethnicities being 65 *vs*. 59 *vs*. 62 *vs*. 60 years, respectively, *P*<0.001) and with a lower presenting M-protein at WM diagnosis (30 *vs*. 11 *vs*. 26 *vs*. 11 g/L, *P*=0.05). There were no significant differences in the proportion with underlying WM, non-IgM lymphoplasmacytic lymphoma or MGCS alone across all ethnic cohorts (*P*=0.09). In those with IgM MGCS alone, presenting M-protein was similar across ethnic categories (3 *vs*. 5 *vs*. 6 g/L, for the White, Asian, and Black cohorts, respectively, *P*=0.26). *MYD88*^{L265P} mutation status was available for 395 patients with WM (34%), among whom *MYD88*^{L265P} was detected in 90% (351/395). *CXCR4* mutation was tested in 101 (9%) patients with WM and was found to be mutated in 30% (30/101). *MYD88*-mutated WM was observed less frequently in the ethnic minorities than in the white cohort (90% *vs*.

Table 1. Baseline characteristics.

Variable	White N=1,058	Asian N=58	Black N=17	Other/mixed N=35	*P*
Age in years, median (range)	65 (27-92)	59 (28-80)	62 (39-93)	60 (40-80)	<0.001
Diagnosis, N (%)					
WM	929 (88)	50 (86)	14 (82)	33 (94)	0.09
MGCS alone	110 (10)	6 (10)	3 (18)	0	-
Non-IgM LPL	19 (2)	2 (3)	0	2 (6)	-
Presenting M-protein, g/L, median (range)					
WM/LPL	30 (0-87)	11 (0-79)	26 (4-65)	11 (0-57)	0.05
MGCS	3 (0-17)	5 (5-10)	6 (0-12)	-	0.26
WM/LPL, N (%)					
MYD88^{L265P}	315 (90)	19 (76)	4 (67)	13 (100)	0.03
MYD88^{WT}	36 (11)	6 (24)	2 (33)	0	-
WM/LPL, N (%)					
CXCR4 mutated	26 (30)	3 (33)	0	1 (25)	1.00
CXCR4 wild-type	61 (70)	6 (67)	1 (100)	3 (75)	-
WM IPSSWM risk (in 558 patients), N (%)					
High	198 (39)	9 (30)	1 (17)	7 (44)	0.52
Intermediate	154 (30)	7 (23)	3 (50)	5 (31)	-
Low	154 (30)	14 (47)	2 (33)	4 (25)	-
IgM MGCS, N (%)					
CAD/syndrome	39 (4)	6 (10)	1 (6)	0	0.05
Cryoglobulins	105 (10)	11 (19)	1 (6)	1 (3)	0.06
AL amyloidosis	31 (3)	2 (3)	0	1 (3)	0.87
Schnitzler	8 (1)	0	0	0	1.00
Anti-MAG PN	93 (9)	2 (2)	2 (12)	1 (3)	0.30
Non-MAG PN	79 (7)	3 (5)	1 (6)	3 (9)	0.93
Bing-Neel syndrome, N (%)	34 (3)	1 (2)	3 (18)	0	0.04

WM: Waldenström macroglobulinemia; MGCS: monoclonal gammopathy of clinical significance; LPL: lymphoplasmacytic lymphoma; IPSSWM: International Prognostic Scoring System for Waldenström macroglobulinemia; CAD: cold agglutinin disease; MAG: myelin-associated-glycoprotein; PN: peripheral neuropathy.

76% *vs*. 67% *vs*. 100% for White, Asian, Black, Other cohorts, respectively, *P*=0.05).

In those with WM diagnosed since 2015 (N=483), the median follow-up was 48 months (95% confidence interval [95% CI]: 44-50). The median TFS was 15 months (95% CI: 11-21); 283 patients were treated during the follow-up period at a median time to first treatment for those treated of 3 months (95% CI: 2-5 months; range, 0-96 months). Indications for treatment and treatment delivered were similar across all ethnic groups (*Online Supplementary Tables S2* and *S3*). In most cases first-line therapy was bendamustine-ritxumab (36%; 102/283) or dexamethasone-rituximab-cyclophosphamide (27%; 76/283).

OS estimates did not differ when comparing ethnic groups. Predictors of TFS on univariable analysis were high-risk IPSSWM (hazard ratio [HR]=1.78, 95% CI: 1.26-2.52, *P*=0.01), M-protein concentration (HR=1.02, 95% CI: 1.02-1.03, *P*<0.001), and presence of Bing-Neel syndrome (HR=2.70, 95% CI: 1.60-4.56, *P*<0.001) (Table 2). On multivariable analysis, IPSSWM (high-risk: HR=1.99, 95% CI: 1.24-3.16, *P*=0.004) and Black ethnicity (HR=7.51, 95% CI: 2.21-26.52, *P*=0.02) were predictors of shorter TFS after adjustment for multiple comparisons.

There was a significant interaction between age at diagnosis and ethnicity for TFS (*P*<0.001). Among younger patients (<75 years), Black patients had a significantly poorer TFS (age 18-64 years: HR=14.27, *P*<0.001; age 65-74 years: HR=19.78 *P*=0.005), which was not significant in those >75 years (HR=0.24, *P*=0.16) (Table 3). There was no interaction between age and ethnicity for OS (*P*=0.08).

There is no universally accepted definition of ethnicity, although it is established as an important surrogate marker for shared exposures for people with similar social, biological and cultural characteristics.[8] Our study was not based on a population-based registry. Rather, data were collected from participating centers and are regarded as geographically representative of the UK. Ethnic minorities accounted for 9% of patients with WM. From 2021 UK census data, the population distribution is 82% White, 9% Asian, 4% Black, 3% Mixed, 2% Other. The proportion of patients with WM by ethnicity in the current cohort is 5% Asian, 1% Black, 1% Mixed, 2% Other. This may be related

Table 2. Predictors of treatment-free survival.

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P**
IPSSWM				
Intermediate	1.78 (1.26-2.52)	0.09	1.79 (1.10-2.91)	0.02
High	1.78 (1.26-2.52)	0.01	1.99 (1.24-3.16)	0.004
Age, per year	1.01 (1.00-1.02)	0.28	-	-
MYD88^{L265P}	0.78 (0.47-1.31)	0.36	1.24 (0.68-2.29)	0.70
M-protein	1.02 (1.02-1.03)	<0.001	-	-
Bing-Neel syndrome	2.70 (1.60-4.56)	<0.001	1.87 (0.91-3.84)	0.09
Ethnicity				
Black	1.77 (0.73-4.30)	0.21	7.51 (2.12-26.52)	0.002
Asian	1.50 (0.90-2.49)	0.12	1.22 (0.60-2.51)	0.58
Other	0.84 (0.45-1.59)	0.60	0.92 (0.29-2.95)	0.89

**P* values corrected by the Holm-Bonferroni method to adjust for multiple comparisons. The IPSSWM risk score comprises age, hemoglobin concentration, platelet count, β2-microglobulin, and IgM. HR: hazard ratio; 95% CI: 95% confidence interval; IPSSWM: International Prognostic Scoring System for Waldenström macroglobulinemia.

Table 3. Treatment-free survival of patients with Waldenström macroglobulinemia by age and ethnicity.

	18-64 years		65-74 years		≥75 years	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
White	1.00 Ref.	-	1.00 Ref.	-	1.00 Ref.	-
Black	14.27 (4.30-47.38)	<0.001	19.78 (2.42-161)	0.005	0.24 (0.03-1.76)	0.16
Asian	1.34 (0.74-2.44)	0.34	2.05 (0.49-8.51)	0.32	1.57 (0.38-6.57)	0.53
Other/mixed	0.54 (0.20-1.48)	0.23	1.70 (0.68-4.21)	0.26	0.55 (0.07-4.00)	0.56

HR: hazard ratio; 95% CI: 95% confidence interval; Ref.: reference.

to true biological differences or indeed acquisition bias. Epidemiological data suggest a higher incidence in white ethnic groups than in ethnic minority groups (0.74/100,000 *vs*. 0.28-0.35/100,000).[2,9] In our cohort, WM patients from ethnic minorities had a lower presenting M-protein and a lower frequency of *MYD88*^{L265P} detected. Ethnicity predicted TFS independently of disease-related factors (IPSSWM risk). Disparities in outcome deserve consideration, particularly in the era of increasing clinical trials.

The *MYD88*^{L265P} somatic mutation is present in >90% of WM[10] and CXCR4 in 30-40%.[11] IgM myeloma and cold agglutinin disease are characteristically *MYD88* wild-type (*MYD88*^{WT}),[12] whereas cryoglobulinemia and AL amyloidosis can arise from mutated or unmutated clones.[13] Our study found that ethnic minorities were more likely to be *MYD88*^{WT}. A study of 32 Korean patients also demonstrated *MYD88*^{L265P} in only 81% and *CXCR4* mutation in 24%.[14] This is consistent with studies in MGUS. A population study of >150,000 healthy patients in Peking Union Medical College demonstrated that Asians had a lower incidence of MGUS compared with White patients and at a lower M-protein concentration,[15] while it is established that Black patients have a higher age-adjusted prevalence ratio of MGUS compared with White patients.[16] US-based Surveillance, Epidemiology, and End Results (SEER) data of >3,000 patients showed that African-Americans presented at a 10-year younger age compared with White patients[5] and data from China report a median of 62 years.[17] Those with *MYD88*^{WT} have been shown to have poorer OS compared with the mutated subjects;[18] however, this factor was not independently prognostic in our cohort.

The most established prognostic score for WM is the IPSSWM, which is based on disease parameters at the time of first-line treatment (age, hemoglobin, platelet count, β2-microglobulin, M-protein). A retrospective report from seven Latin American countries showed the prognostic value of the IPSSWM for predicting OS and progression-free survival in 159 patients from 1991-2019.[7] In our cohort, IPSSWM was predictive of OS and TFS, although Black patients had shorter TFS after adjustment for differences in presenting features (IPSSWM, *MYD88* status, presence of Bing-Neel syndrome). A US study of >3,000 patients showed no significant differences in outcomes across ethnicities after adjustment for multiple comparisons, with no interactions between race and covariates (sex, stage, county median household income, year of diagnosis).[19]

We found an interaction between age and ethnicity with a higher hazard ratio for TFS for Black patients at a younger age. This may be due to biologically aggressive disease not captured by the IPSSWM or may be related to healthcare

utilization disparities in younger Black patients. Analysis of SEER data showed an interaction between median OS, race, and age at diagnosis. For those aged <65 years, African-Americans had the poorest median OS, while among patients aged >75 years Hispanics had the poorest OS, although the analysis was limited by lack of clinical data.[5] There has been an expansion of novel agents being tested in or validated by clinical trials, including non-covalent BTK inhibitors, CXCR4 antagonists, BCL2 inhibitors, radiotherapeutic agents, chimeric antigen receptor T-cell therapy for WM, complement inhibitors for cold agglutinin disease and anti-fibril antibodies for AL amyloidosis. These therapies may overcome poorer prognostic features. It is imperative that all patients have access to these novel agents, particularly given the evidence of underrepresentation of ethnic minorities in clinical trials.[20]

Confounders including socioeconomic deprivation indices, wealth, and education, among other factors were not accounted for in this study which is a limitation. In our cohort, self-reported ethnicity was missing for 16% (237/1,437). There is evidence in the literature that ethnic minorities may be less likely to self-disclose ethnicity, based upon imputed methods from US survey data.[21] Potential mistrust or lack of culturally appropriate communication may be other reasons for disparities. This is particularly important as IgM gammopathies have protean complications and long-term engagement with healthcare services is required.

Our analysis helps to outline disparities in WM. Further systematic analysis is required to delineate the contribution of socioeconomic factors and molecular analyses and to devise strategies to overcome these disparities.

Authors

Jahanzaib Khwaja, Nicole Japzon, Maria Gabriel, Oliver Tomkins, Jindriska Lindsay, Charalampia Kyriakou, Ashutosh Wechalekar and Shirley D'Sa

University College London Hospital, London, UK

Correspondence:
J. KHWAJA - j.khwaja@nhs.net

https://doi.org/10.3324/haematol.2024.285420

Received: March 13, 2024.
Accepted: May 28, 2024.
Early view: June 6, 2024.

Disclosures

JL has received honoraria from Takeda, BMS, and Janssen; has received travel support from BMS, Amgen, Takeda, and BeiGene; and has sat on advisory boards for Amgen, Pfizer, Janssen, and BMS. AW has received honoraria from GSK, Alexion, Attralus, and Janssen and travel support from Takeda. SD'S has received research funding, honoraria for advisory board work and conference support from Janssen and BeiGene, and honoraria for advisory board work from Sanofi. JK, NJ, MG, OT, and CK have no conflicts of interest to disclose.

Contributions

JK and SD'S designed the study. JK, NJ, and MG participated in data collection. JK wrote the paper and performed the statistical analysis. All contributors reviewed the manuscript.

Acknowledgments

We acknowledge the WMUK Rory Morrison Registry, carers and patients.

Data-sharing statement

The data that support the findings of this study may be available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

References

1. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127(20):2375-2390.
2. Gertz MA. Waldenström macroglobulinemia: 2023 update on diagnosis, risk stratification, and management. Am J Hematol. 2023;98(2):348-358.
3. Khwaja J, D'Sa S, Minnema MC, Kersten MJ, Wechalekar A, Vos JM. IgM monoclonal gammopathies of clinical significance: diagnosis and management. Haematologica. 2022;107(9):2037-2050.
4. Morel P, Duhamel A, Gobbi P, et al. International Prognostic Scoring System for Waldenstrom macroglobulinemia. Blood. 2009;113(18):4163-4170.
5. Ailawadhi S, Kardosh A, Yang D, et al. Outcome disparities among ethnic subgroups of Waldenström's macroglobulinemia: a population-based study. Oncology. 2014;86(5-6):253-262.
6. Wang H, Chen Y, Li F, et al. Temporal and geographic variations of Waldenström macroglobulinemia incidence: a large population-based study. Cancer. 2012;118(15):3793-3800.
7. Riva E, Duarte PJ, Valcárcel B, et al. Treatment and survival outcomes of Waldenstrom macroglobulinemia in Latin American patients: a multinational retrospective cohort study. JCO Glob Oncol. 2022;8:e2100380.
8. Mathur R, Grundy E, Smeeth L. NCRM Working Paper Series: availability and use of UK based ethnicity data for health research. March 27, 2013. http://eprints.ncrm.ac.uk/3040/.

Accessed June 5, 2020.
9. McMaster ML. The epidemiology of Waldenström macroglobulinemia. Semin Hematol. 2023;60(2):65-72.
10. Treon SP, Xu L, Yang G, Zhou Y, et al. MYD88 L265P somatic mutation in Waldenström's macroglobulinemia. N Engl J Med. 2012;367(9):826-833.
11. Hunter ZR, Yang G, Xu L, Liu X, Castillo JJ, Treon SP. Genomics, signaling, and treatment of Waldenström macroglobulinemia. J Clin Oncol. 2017;35(9):994-1001.
12. Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: lymphoid neoplasms. Leukemia. 2022;36(7):1720-1748.
13. Khwaja J, Vos JMI, Pluimers TE, et al. Clinical and clonal characteristics of monoclonal immunoglobulin M-associated type I cryoglobulinaemia. Br J Haematol. 2024;204(1):177-185.
14. Shin DW, Kim SM, Kim JA, et al. Characteristics of Waldenström macroglobulinemia in Korean patients according to mutational status of MYD88 and CXCR4: analysis using ultra-deep sequencing. Clin Lymphoma Myeloma Leuk. 2019;19(8):e496-e505.
15. Han JH, Wang JN, Zhang YL, et al. Prevalence of monoclonal gammopathy of undetermined significance in a large population with annual medical check-ups in China. Blood Cancer J. 2020;10(3):34.
16. Landgren O, Gridley G, Turesson I, et al. Risk of monoclonal gammopathy of undetermined significance (MGUS) and subsequent multiple myeloma among African American and white veterans in the United States. Blood. 2006;107(3):904-906.
17. Cao XX, Yi SH, Jiang ZX, et al. Treatment and outcome patterns of patients with Waldenström's macroglobulinemia: a large, multicenter retrospective review in China. Leuk Lymphoma. 2021;62(11):2657-2664.
18. Treon SP, Gustine J, Xu L, et al. MYD88 wild-type Waldenstrom macroglobulinaemia: differential diagnosis, risk of histological transformation, and overall survival. Br J Haematol. 2018;180(3):374-380.
19. Vaughn JL, Spies D, Xavier AC, Epperla N. Racial disparities in the survival of patients with indolent non-Hodgkin lymphomas in the United States. Am J Hematol. 2021;96(7):816-822.
20. Asher S, Kazantzi A, Dekaj F, et al. Under-representation of ethnic minorities in early phase clinical trials for multiple myeloma. Haematologica. 2022;107(12):2961-2965.
21. Dembosky JW, Haviland AM, Haas A, et al. Indirect estimation of race/ethnicity for survey respondents who do not report race/ethnicity. Med Care. 2019;57(5):e28-e33.