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

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Waldenström Macroglobulinaemia (WM) is a low-grade B-cell lymphoma characterised by lymphoplasmacytic marrow infiltration (1), historically described in white cohorts (2). The aim of this study was to analyse 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 analysed 1168 patients from the UK, demonstrating that ethnic minorities (EM) presented with WM at a younger age, a lower monoclonal protein (M-protein) and with a higher proportion of *MYD88*^{WT} which may suggest different disease biology than white patients. Black patients had a shorter treatment-free survival (TFS) independent 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), however molecular and clinical characteristics are increasingly investigated. Little is, however, 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 characterised in the UK.

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

Self-reported ethnicity was categorised as White, Black, Asian and Mixed/Other according to the UK Office for National Statistics categories (supplementary table 1). Baseline characteristics were compared using χ^2 or Fisher's 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 was 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 significant at p-values <0.05. Statistical analyses were performed using STATA v18.0 (StataCorp, Texas, USA).

Of 1437 patients registered in June 2022, 1200 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 1168 patients (61% male, 39% female) available for analysis. Table 1 summarises the baseline characteristics.

Between June 1978 and December 2022, the underlying diagnosis was WM (n=1026), non-IgM LPL (n=23) or IgM MGCS alone (n=119). Of those with WM, 24% (248/1027) had an additional MGCS disorder. Thirty-eight patients had extranodal LPL infiltration in the central nervous system, Bing-Neel Syndrome (BNS).

The majority was white (1058; 91%) and 110 (9%) were from the following ethnic groups (collectively, EM): 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 EM presented at a younger age compared to white ethnicity for White, Asian, Black and Other ethnicities, respectively (65 vs 59 vs 62 vs 60 years, p<0.001) and with a lower presenting M-protein at WM diagnosis (30 vs 11 vs 26 vs 11g/L, p=0.05). There were no significant differences in the proportion with underlying WM, non-IgM LPL 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

6g/l, for White, Asian, Black, respectively, p=0.26). *MYD88*^{L265P} mutation status was available in 395 patients with WM (34%), of which *MYD88*^{L265P} was detected in 90% (351/395). *CXCR4* mutation was tested in 101 (9%) patients with WM and mutated in 30% (30/101). *MYD88*-mutated WM was observed less frequently in the EM versus white cohorts (90% vs 76% vs 67% vs 100% for White, Asian, Black, Other cohorts respectively, p=0.05).

In those with WM diagnosed since 2015 (n=483), median follow-up time was 48 months (95% CI 44-50). 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 (supplementary tables 2-3). First-line therapy was bendamustine-ritxumab (36%; 102/283) or dexamethasone-rituximab-cyclophosphamide (27%; 76/283) in the majority.

Overall survival estimates did not differ when comparing ethnic groups. Predictors of TFS on univariable analysis were high-risk IPSSWM (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 BNS (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 for shorter TFS after adjustment for multiple comparisons.

There was a significant interaction between age at diagnosis and ethnicity for TFS (p<0.001). Amongst younger patients (<75 years), Black patients had a significantly poorer TFS (age 18-64: HR 14.27, p<0.001; age 65-74: 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 *(21)*. Our study was not a population-based registry. Rather, data were collected from participating centres and are regarded as geographically representative of the UK. EM accounted for 9% of patients with WM. From 2021 census figures, the UK census data consists 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 to true biological differences or indeed acquisition bias. Epidemiological data suggests a higher incidence in white compared with ethnic minority groups (0.74/100,000 v 0.28-0.35/100,000) (2, 8). In our cohort, WM from EM had a lower presenting M-protein and lower frequency of $MYD88^{L265P}$ detected. Ethnicity independently predicted TFS independently of disease-related factors (IPSSWM risk). Disparities in outcome deserve consideration, particularly in the era of increasing clinical trials.

$MYD88^{L265P}$ somatic mutation is present in >90% of WM (9) and CXCR4 in 30-40% (10). IgM myeloma and CAD are characteristically *MYD88* wild-type ($MYD88^{WT}$) (11), whereas cryoglobulinaemia and AL amyloidosis can arise from mutated or unmutated clones (12). Our study found that EM 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% (13). 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 (14), whilst it is established that Black patients have higher age-adjusted prevalence ratio of MGUS in compared with white patients (15). US-based Surveillance, Epidemiology, and End Results (SEER) data of >3000 patients showed African Americans had a 10 year younger age of presentation compared with White patients (5) and data from China report a median of 62 years (16). Those with $MYD88^{WT}$ have been shown to have poorer OS compared with the mutated (17), however this was not independently prognostic in our cohort.

The most established prognostic score for WM is the IPSSWM based on disease parameters at the time of first-line treatment (age, haemoglobin, platelet count, β2-microglobulin, M-protein). A

retrospective report from seven Latin American countries showed the prognostic value for predicting OS and progression-free survival in a 159 patients from 1991-2019 (7). In our cohort, IPSSWM was predictive of OS and TFS, although Black patients had shorter TFS after adjustment of differences in presenting features (IPSSWM, *MYD88* status, presence of BNS). A US study of >3000 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) (18).

We found an interaction between age with ethnicity with higher HR of TFS for Black patients at a younger age. This may be due to biologically aggressive disease not captured by IPSSWM or may be related to healthcare utilisation disparities in younger Black patients. Analysis of SEER data showed an interaction between median OS, race, and age at diagnosis. For those age<65 years, African Americans had the poorest median OS, while among patients aged >75 years Hispanics had the poorest OS, although data was limited by lack of clinical data (5).

There has been an expansion of novel agents via clinical trials including non-covalent BTKi, CXCR4 antagonists, BCL2 inhibitors, radiotherapeutic agents, CAR-T therapy for WM, complement inhibitors for CAD and anti-fibril antibodies for AL amyloidosis. These therapies may overcome poorer prognostic features. It is imperative that all patients have access to these particularly given the evidence of underrepresentation of EM in clinical trials (19).

Confounders including socioeconomic deprivation indices, wealth, education amongst other factors were not accounted for in this study which is a limitation. In our cohort, 16% (237/1437) had missing self-reported ethnicity. There is evidence in the literature that EM may be less likely to self-disclose ethnicity, based upon imputed methods from US survey data (20). 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 delineate these disparities in WM. Further systematic analysis is required to delineate the contribution of socioeconomic factors, molecular analyses and devise strategies to overcome these disparities.

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Table 1. Baseline characteristics

Variable, n (% or range)	**White n=1058**	**Asian n=58**	**Black n=17**	**Other/mixed n=35**	**p value**
Age, years	65 (27-92)	59 (28-80)	62 (39-93)	60 (40-80)	<0.001
Diagnosis					
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					
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					
MYD88^{L265P}	315 (90)	19 (76)	4 (67)	13 (100)	0.03
MYD88^{WT}	36 (11)	6 (24)	2 (33)	0	
WM/LPL:					
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, n=558					
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					
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	34 (3)	1 (2)	3 (18)	0	0.04

Table 2. Predictors for treatment-free survival

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	p value	HR (95% CI)	p value*
IPSSWM				
Int	1.41 (0.95-2.09)	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.
IPSSWM (risk score comprises age, haemoglobin, platelets, β2-microglobulin, IgM)

Table 3. TFS with WM by age and ethnicity

	18-64 years		**65-74 years**		**≥75 years**	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
White	1.00 (reference)	-	1.00 (reference)	-	1.00 (reference)	
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

Supplementary 1. Ethnic categories (UK Census):

Ethnic categories	
Asian or Asian British	• Indian • Pakistani • Bangladeshi • Chinese • Any other Asian background
Black, Black British, Caribbean or African	• Caribbean • African • Any other Black, Black British, or Caribbean background
Mixed or multiple ethnic groups	• White and Black Caribbean • White and Black African • White and Asian • Any other Mixed or multiple ethnic background
White	• English, Welsh, Scottish, Northern Irish or British • Irish • Gypsy or Irish Traveller • Roma • Any other White background
Other ethnic group	• Arab • Any other ethnic group

Supplementary table 2. First-line therapy indications

Indications for treatment	Total	White	Asian	Black˜	Other/mixed#
Bone marrow failure	120	107	10	0	3
M-protein related	112	101	8	0	3
Lymphoma-related	107	94	8	3	2

Bone marrow failure (haemoglobin <100 g/L, platelets <100 × 10^9/L or neutrophils <1 × 10^9/L); M-protein related (hyperviscosity, autoimmune, IgM-associated disorder); lymphoma-related (bulky or symptomatic lymphadenopathy/ organomegaly, B-symptoms).
˜1 patient unknown indication #4 patients unknown indication

Supplementary table 3. First-line therapy

Therapy	Total	White	Asian	Black	Other/mixed
Bendamustine-rituximab	102	89	5	2	6
Dexamethasone-rituximab-cyclophosphamide	76	70	4	0	2
BTKi	15	15	0	0	0
Single agent rituximab	27	25	2	0	0
Bortezomib-based combination	13	11	2	0	0
Methotrexate-cytarabine based combination	12	10	1	1	0
RCHOP	11	11	0	1	0
Chlorambucil	8	9	0	0	0
Other	19	15	2	0	2

RCHOP, Rituximab-cyclophosphamide-doxorubicin-vincrinstine-prednisolone