Ethnicity in systemic AL amyloidosis may impact risk stratification

Systemic AL amyloidosis is a light-chain misfolding disorder leading to extracellular protein deposition in organs and most affected patients have cardiac involvement. It is caused by an underlying plasma cell dyscrasia. Health disparities among ethnic groups are well-documented in multiple myeloma however data on ethnicity in AL amyloidosis are limited. Baseline biomarker-based staging in AL amyloidosis underpins the prognosis and treatment paradigms. There are crucially important racial differences in N-terminal pro B-type natriuretic peptide (NT-proBNP) levels in patients with heart failure and healthy controls[1] which may substantially impact assessment of patients with AL amyloidosis. We compared the disease characteristics and outcomes of patients across ethnic groups from the United Kingdom (UK).

Patients enrolled in a prospective observational study at the UK National Amyloidosis Centre from 2010–2022 were analyzed. The diagnosis of AL amyloidosis was confirmed by histology and typed with immunohistochemistry or mass spectrometry. If unavailable, for those with cardiac involvement alone, a negative DPD-Tc99m bone scan was required if biopsy confirmed amyloidosis. Cardiac involvement was defined as per the International Society of Amyloidosis. Cardiac staging was undertaken using the European modification of the Mayo 2004 staging system (Mayo I-IIIb). Six-month cardiac response was assessed, as outlined elsewhere.[2] Socio-economic deprivation was measured by the index of multiple deprivation decile, the established measure of relative UK deprivation from the Department of Communities and Local Government. It is a composite index derived from household postcodes (1-10: most to least deprived), based on seven sub-domains representing deprivation in income, employment, education, health, crime, housing and living environment. Baseline characteristics were compared using χ^2 or Fisher exact tests or Wilcoxon Mann-Whitney/Kruskal-Wallis tests. Overall survival was defined from diagnosis to death or last follow-up. Statistical analyses were conducted using STATA version 18 (STATAcorp, College Station, TX, USA). Written consent was obtained from all patients and ethical approval was obtained.

Between 2010-2022, 1,387 patients were seen. Self-reported ethnicity data were available for 1,352 (806 male, 546 female) of whom 1,230 (90%) were White and 122 (10%) were from ethnic minorities. The ethnic minorities comprised 72 Black (5%), 30 Asian (2%) and 20 Other/mixed (2%) patients. The baseline characteristics of the patients in this study are shown in Table 1.

The median age of patients at presentation was 67 years (range, 29-89 years), with ethnic minorities presenting at a younger age (67 *vs*. 57 *vs*. 60 *vs*. 64 years, for White, Black, Asian, Other/mixed, respectively; *P*<0.001). Sixty-five percent had cardiac involvement, with the median bone marrow plasma cell infiltrate being 10% (range, 0-95%) and the difference in involved and uninvolved free light chain (dFLC) concentration being 189 mg/L (range, 0-15,898 mg/L). Black and Asian patients had a greater bone marrow plasma cell infiltrate than White patients (18 *vs*. 10%; *P*=0.01). The median dFLC did not differ significantly across ethnicities (*P*=0.89). The pattern of organ involvement was similar across groups (median 2 [range, 1-5] organs).

There were important biological and socio-demographic differences among ethnic categories. Those from an ethnic minority group had a significantly lower presenting NT-proBNP, this being most marked in Blacks and Asians (White 1,611 ng/L *vs*. Black 1,002 ng/L *vs*. Asian 752 ng/L *vs*. Other/mixed 1,309 ng/L; *P*=0.02). On echocardiography, patients in the ethnic minority group had a significantly poorer global longitudinal strain (GLS) compared to White patients (White -14.9% *vs*. Black -11.4% *vs*. Asian -12.6% *vs*. Other/mixed -12.8%; *P*=0.05). Left ventricular septal thickness (*P*=0.26) and left ventricular ejection fraction (*P*=0.65) were not significantly different. Only nine patients from the Black cohort were classified as having stage IIIb cardiac involvement although the numbers are too small for meaningful statistical comparisons. There was no significant correlation between body mass index and NT-proBNP level (Spearman rho -0.11). Those from an ethnic minority had a poorer relative deprivation index decile (White 7 *vs*. Black 3, Asian 7, Other/mixed 5; *P*<0.001).

We generated optimal NT-proBNP cut-offs for predicting survival using time-dependent receiver operative characteristics curves. The NT-proBNP threshold was higher for White patients than for Black patients at early timepoints (6 months: cut-off for White patients 3,435 ng/L, area under the curve [AUC] 0.69 *vs*. cut-off for Black patients 2,402 ng/L, AUC 0.75) and late timepoints (5 years: cut-off 1,841 ng/L *vs*. 973 ng/L, AUC 0.61 and 0.78 for White and Black patients, respectively).

The majority of patients (93%) were treated with first-line botezomib-based chemotherapy and 6% with a daratumumab-botezomib-based regimen. At a median follow-up of 72 months (95% confidence interval [CI]: 69-75), the estimated median overall survival was 89 months (95% CI: 74-not reached). Independent predictors for overall survival in a multivariable model were: age (per year, hazard ratio [HR]=1.04, 95% CI: 1.02-1.06; *P*<0.001), NT-proBNP (per 1,000 ng/L, HR=1.02, 95% CI: 1.00-1.04; *P*=0.02), GLS

Table 1. Characteristics of patients with AL amyloidosis by ethnicity.

Variable	White N=1,230	Black N=72	Asian N=30	Other/mixed N=20	P
Age in years, median (range)	67 (29-89)	57 (35-82)	60 (40-76)	64 (44-78)	<0.001
Gender, N (%)					
Male	736 (60)	37 (51)	20 (67)	13 (65)	0.81
Female	494 (40)	35 (49)	10 (33)	7 (35)	
IMD, decile, median (range)	7 (1-10)	3 (1-10)	7 (2-10)	5 (1-10)	<0.001
Body mass index, median (range)	26 (14-55)	27 (19-48)	26 (18-38)	24 (19-36)	0.74
Lambda AL type, N (%)	967 (79)	59 (82)	23 (77)	14 (70)	0.70
NT-proBNP, ng/L, median (range)	1,611 (12-93,602)	1,002 (42-24,534)	752 (37-18,804)	1,309 (25-24,179)	0.02
hs-Troponin T, ng/L, median (range)	55 (0-742)	42 (0-558)	54 (13-259)	45 (3-340)	0.75
dFLC, mg/L, median (range)	192 (0-15,898)	188 (2-10,000)	154 (1-2,816)	181 (0-959)	0.89
M-protein, g/L, median (range)	1 (0-45)	0 (0-37)	4 (0-36)	2 (0-32)	0.46
Bone marrow plasma cell infiltrate, %, 687 evaluated, median (range)	10 (0-95)	18 (0-80)	18 (3-70)	10 (5-30)	0.01
N of organs affected, median (range)	2 (1-5)	2 (1-5)	1 (1-4)	2 (1-3)	0.62
Organ involvement, N (%)					
Heart	795 (65)	54 (75)	16 (53)	12 (60)	0.16
Kidney	861 (70)	39 (59)	15 (56)	15 (75)	0.09
Liver	154 (13)	11 (17)	4 (14)	1 (5)	0.51
Mayo stage, N (%)					
Stage I	205 (17)	13 (18)	5 (17)	5 (25)	0.44
Stage II	421 (34)	28 (39)	13 (43)	5 (25)	
Stage IIIa	419 (34)	21 (30)	7 (23)	7 (35)	
Stage IIIb	182 (15)	9 (13)	5 (17)	3 (15)	
Unknown	3	1	0	0	
LVS, mm, median (range)	13 (6-24)	14 (8-19)	14 (8-18)	14 (8-18)	0.26
LVEF, %, median (range)	58 (20-80)	55 (21-73)	58 (30-70)	60 (38-68)	0.65
GLS, %, median (range)	-14.7 (-28 to -3.1)	-11.4 (-23.1 to -3)	-12.6 (-21.6 to -7.3)	-12.8 (-25.6 to -10.8)	0.05
NYHA, 1,112 evaluated, N (%)					
Class I	349 (33)	24 (44)	9 (43)	6 (35)	0.09
Class II	572 (54)	24 (44)	12 (57)	9 (53)	
Class III	126 (12)	6 (11)	0	1 (6)	
Class IV	4 (0)	1 (2)	0	1 (6)	
6MWD, m, 906 evaluated, median (range)	396 (20-700)	368 (29-622)	389 (19-543)	391 (168-529)	0.71
24-hr urinary protein, g, median (range)	3.0 (0-36)	1.6 (0-14.1)	0.6 (0-13.2)	3.1 (0.1-19.8)	0.10
Creatinine, μmmol/L, median (range)	96 (26-1,077)	103 (52-1124)	90 (47-423)	100 (57-613)	0.29
ALP, U/L, median (range)	91 (16-2,389)	92 (31-968)	82 (43-620)	79 (45-258)	0.27
Albumin, g/L, median (range)	34 (8-480)	37 (15-48)	36 (17-46)	35 (15-47)	0.32

IMD: index of multiple deprivation; NT-proBNP: N-terminal pro B-type natriuretic peptide; hs-Troponin T: high sensitivity troponin T; dFLC: difference in involved and uninvolved free light chains; M-protein: monoclonal protein; LVS: left ventricular septum thickness; LVEF: left ventricular ejection fraction; GLS: global longitudinal strain; NYHA: New York Heart Association classification; 6MWD: six-minute walk distance; ALP: alkaline phosphatase.

(per %, HR=1.11, 95% CI: 1.07-1.49; *P*<0.001). High-sensitivity troponin T (per 10 ng/L; *P*=0.09), dFLC (per 10 ng/L; *P*=0.76), ethnicity (*P*=0.74), deprivation index (*P*=0.56) and body mass index (*P*=0.38) were not independently prognostic in this multivariable model. dFLC remained non-independent at a 180 mg/L threshold (*P*=0.32) on multivariable analysis.

At the 6-month landmark, cardiac response was assessed in those with a baseline NT-proBNP >650 ng/L (N=573). Achievement of cardiac very good partial/complete response (VGPR/CR, defined by >60% reduction in NT-proBNP)[2] predicted improved survival (HR=0.49, 95% CI: 0.29-0.83; *P*=0.008), without interaction between ethnicity and cardiac response (*P*=0.46) (Figure 1). The VGPR/CR rates for White, Black, Asian, and Other patients were 57/526 (11%), 6/28 (21%), 2/11 (15%) and 1/6 (17%), respectively.

In this study, ethnic minorities accounted for 10% of patients with AL amyloidosis. From 2021 census figures, the UK population consists of 82% White, 9% Asian, 4% Black, 3% Mixed, and 2% Other ethnicities. The proportion of patients with AL amyloidosis by ethnicity in our cohort is

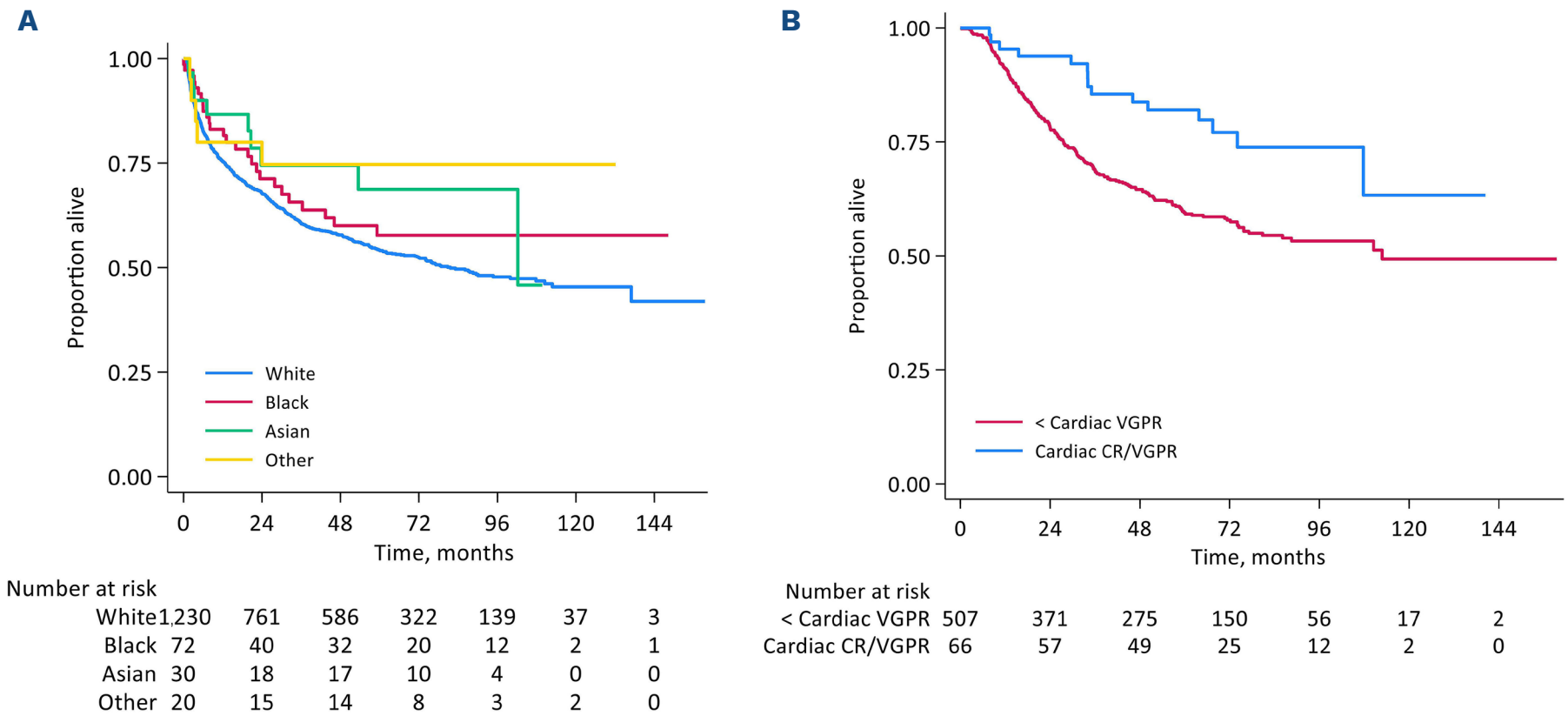

Figure 1. Overall survival of the cohort. (A) Overall survival by ethnicity. (B) Overall survival by depth of cardiac response at 6-month landmark. VGPR: very good partial response; CR: complete response.

broadly similar although the proportion of Asian patients was lower than that in the census data. We noted key differences in the patients from ethnic minorities. Black patients were significantly younger than White ones, presenting a decade earlier than White patients. Those from an ethnic minority had a poorer deprivation index, which has been described in other series,[3] although this did not impact OS in our cohort, which appeared predominantly affected by cardiac biomarkers and age.

The striking difference was a significantly lower NT-proBNP compared with that of White patients despite worse GLS. While this disparity in NT-proBNP levels has been recognized previously in Black patients with heart failure, who had a lower NT-proBNP level than that of White patients, the correlation with worse cardiac function in AL has significant clinical implications. This variability of NT-proBNP concentration may be attributed to impaired natriuretic peptide processing and enhanced clearance of the circulating natriuretic peptides.[1] We additionally note this in Asian patients, too. Due to the small numbers of patients, comparisons for disease stage and overall stage should be interpreted cautiously. Body mass index is known to have an inverse relationship with NT-proBNP level in healthy patients[4] and those with heart failure,[5] but did not differ significantly across ethnicities in our cohort.

NT-proBNP is a strong predictor for overall survival and forms the basis of risk models for outcomes in AL.[6-8] A reduction in NT-proBNP following treatment is directly associated with improved overall survival.[2] None of the staging and response studies in AL amyloidosis to date has reported ethnicity in the original models. The significantly lower NT-proBNP may impact staging in patients from ethnic minorities and potentially "falsely" down-stage patients leading to inappropriate treatment decisions. In our cohort, 6-month cardiac response (CR/VGPR) was discriminatory for overall survival across all ethnicities although the optimal thresholds and kinetics per ethnic category have not been determined.

Despite their lower presenting NT-proBNP, those from ethnic minorities had a poorer GLS. GLS is a functional assessment of global and regional reduction in longitudinal contraction and highly specific and sensitive in amyloid heart disease. It is prognostic at baseline[9] and may be useful for predicting response: a 2% improvement in GLS with NT-proBNP response predicted survival advantage more strongly than NT-proBNP alone.[10]

The influence of ethnicity on outcomes in AL amyloidosis has been explored elsewhere. Age-adjusted amyloidosis-related mortality was greatest for Black patients in a cohort of more than 30,000 patients from the USA with AL and transthyretin (ATTR) amyloidosis.[11] However, due to the *ATTR* V122I mutation having a more aggressive disease profile in ATTR, the generalizability for AL remains unclear. Electronic records of 4,028 USA patients demonstrated that Black patients had more pre-existing cardiomyopathy, heart failure, arrhythmias and chronic kidney disease prior to AL diagnosis,[12] suggesting that Black patients may be diagnosed at a later stage or that it may take longer to establish a diagnosis for them. The Boston Amyloidosis center[3] found that ethnic minorities presented at a younger age by around 5 years, consistent with population-based data in multiple myeloma suggesting potentially differ-

ent disease biology.[13-15] Hispanics had a significantly higher baseline BNP than that of other ethnicities.[3] Differences in sociodemographic domains of education and marital status were disparate in non-Whites; however, when evaluated in a multivariable model, these did not independently impact overall survival. In the largest inpatient review of US hospitalizations,[16] a trend towards lower inpatient mortality but higher intensive care unit use (P=0.09), as well as lower palliative care consultation (P=0.01) in non-Hispanic Black patients *vs*. White patients was shown in a model adjusted for age, gender, income, primary payor and comorbidities. We demonstrate that ethnic minority patients present at a younger age, with a lower NT-proBNP and worse GLS despite a similar left ventricular wall thickness. We raise concern that staging systems for AL amyloidosis based on NT-proBNP concentration and not currently incorporating longitudinal strain may not be universally applicable without re-visiting disparities in biomarkers and their kinetics. There is potential to underestimate risk, causing over- or under-treatment of patients. Limitations of this study include the relatively small number of patients from ethnic minorities which raises the possibility of an under-representation due to potential barriers to healthcare utilization or incorrect diagnoses being made, as is associated with poorer deprivation indices. In light of the relatively smaller numbers, data should be interpreted cautiously. Further analysis across ethnicities with larger international patient cohorts is warranted, including reporting in future prognostic models.

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Contributions

JK and AW designed the research. JK performed the statistical analysis and wrote the manuscript. SR, OC, DF, AM-N, LV, CW, PNH, JG, HJL, SM, MF and AW reviewed the manuscript.

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Data-sharing statement

Data may be made available upon request from the corresponding author.

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