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Ethnicity in systemic AL amyloidosis

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Systemic AL amyloidosis is a light-chain misfolding disorder leading to extracellular protein deposition in organs and most patients have cardiac involvement. It is caused by an underlying plasma cell dyscrasia. Health disparities amongst 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 analysed. 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). Socioeconomic deprivation was measured by the index of multiple deprivation (IMD) 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/Fisher's exact tests or Wilcoxon Mann-Whitney/Kruskal-Wallis tests. Overall survival (OS) was defined from diagnosis to death/last follow-up. Statistical analyses were conducted using STATA v18 (STATAcorp, Texas). Written consent was obtained from all patients and ethical approval was obtained.

One-thousand-three-hundred-and-eighty-seven patients were seen between 2010-2022. Self-reported ethnicity data was available in 1352 (806 male, 546 female): 1230 (90%) White and 122 (10%) comprised ethnic minorities (EM). The EM group were distributed as: 72 Black (5%), 30 Asian (2%), 20 Other/mixed (2%). Baseline characteristics are shown (table 1).

Median age at presentation was 67 years (range 29-89), with EM presenting at a younger age (67 v 57 v 60 v 64 years, for White, Black, Asian, Other/mixed, respectively, $p<0.001$). Sixty-five percent had cardiac involvement, with median bone marrow plasma cell infiltrate 10% (range 0-95) and difference in involved and uninvolved free light chain (dFLC) concentration 189mg/L (range 0-15898). Black and Asian patients had a greater bone marrow plasma cell infiltrate than White patients (18 v 10%, $p=0.01$). 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 sociodemographic differences amongst ethnic categories. Those from an EM group had a significantly lower presenting NT-proBNP most prominently in Black/Asians (White 1611ng/L v Black 1002ng/L v Asian 752ng/L v Other/Mixed 1309ng/L, $p=0.02$). On echocardiography, the EM group had a significantly poorer global longitudinal strain (GLS) compared to White patients (White -14.9% v Black -11.4% v Asian -12.6% v Other/Mixed -12.8%, $p=0.05$). Left ventricular (LV) septal measurement ($p=0.26$) and LV ejection fraction ($p=0.65$) were not significantly different. Only nine patients from the Black cohort were classified as having stage IIIb although the numbers are too small for meaningful statistical comparisons. There was no significant correlation between body mass index (BMI) and NT-proBNP (Spearman rho -0.11). Those from an EM had a poorer relative deprivation index decile (White 7 v Black 3, Asian 7, Mixed/Other 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 compared with Black patients at early (6 month: cut-off for White patients 3435ng/L, AUC 0.69 v Black patients

2402ng/L, AUC 0.75, respectively) and late (5 years: cut-off 1841ng/L v 973ng/L, AUC 0.61 and 0.78 for White and Black patients, respectively) timepoints.

The majority (93%) were treated with a first-line bortezomib-based chemotherapy and 6% a daratumumab-bortezomib-based regimen. At a median follow-up of 72 months (95% confidence interval [CI]: 69-75), estimated median OS was 89 months (95% CI: 74-not reached). Independent predictors for OS in a multivariable model were: age (HR 1.04 95% CI:1.02-1.06 p<0.001), NT-proBNP (per 1000ng/L, HR 1.02 95% CI:1.00-1.04 p=0.02), GLS (per %, HR 1.11 95% CI: 1.07-1.49). High-sensitivity troponin T (per 10ng/L p=0.09), dFLC (per 10ng/L p=0.76), ethnicity (p=0.74), deprivation index (p=0.56) and BMI (p=0.38) were not independently prognostic in this multivariable model. dFLC remained non independent at 180 mg/L threshold (p=0.32) on multivariable analysis.

At 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: 0.29-0829, p=0.008), without interaction between ethnicity and cardiac response (p=0.46) (figure 1). The VGPR/CR rate for White, Black, Asian, Other was 57/526 (11%), 6/28 (21%), 2/11 (15%), 1/6 (17%), respectively.

In this study, EM 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, 2% Other ethnicities. The proportion of patients with AL amyloidosis by ethnicity in our cohort is broadly similar although the proportion of Asian patients were lower than census data. We noted key differences in the patients from EM: a significantly younger age than White patients; Black patients presented a decade earlier than White patients. Those from an EM had a poorer deprivation index which has been described in other series (3), however 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 White patients despite worse GLS. Whilst this disparity in NT-proBNP has been previously recognised in Black patients with

heart failure, who had a lower NT-proBNP compared to White patients, the correlation with worse cardiac function in AL has significant clinical implications. This variability of NT-proBNP 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 small patient numbers, comparisons for disease stage and OS should be cautiously interpreted. Body mass index is known to have an inverse relationship with NT-proBNP in healthy patients (4) and those with heart failure (5), however did not differ significantly across ethnicities in our cohort.

NT-proBNP is a strong predictor for OS and forms the basis risk models for outcomes in AL (6-8). A reduction in NT-proBNP following treatment is directly associated with improved OS (2). All staging and response studies in AL amyloidosis to date have not reported ethnicity in the original models. The significantly lower NT-proBNP may impact staging in patients from EM and potentially "falsely" down-stage patients leading to inappropriate treatment decisions. In our cohort, 6-month cardiac response (CR/VGPR) was discriminatory for OS across all ethnicities although the optimal thresholds and kinetics per ethnic category have not been determined.

Despite the lower presenting NT-proBNP, those from EM 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 >30000 patients from the United States with AL and ATTR (11). However, due to ATTR V122I mutation having a more aggressive disease-profile in ATTR, the generalisability for AL remains unclear. United States electronic records of 4028 patients demonstrated Black patients had more pre-existing cardiomyopathy, heart failure, arrhythmias and chronic kidney disease prior to AL diagnosis (12), suggesting Black patients may be

diagnosed at a later stage or take longer to establish a diagnosis. The Boston Amyloidosis centre (3) found that EM presented at a younger age by around 5 years, consistent with population-based data in multiple myeloma suggesting potential different disease biology (13-15). Hispanics had a significantly higher baseline BNP than 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 OS. In the largest inpatient review of US hospitalisations (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 v White patients was shown in a model adjusted for age, gender, income, primary payor and comorbidities.

We demonstrate that EM patients present at a younger age, a lower NT-proBNP and worse GLS despite a similar LV wall thickness. We raise concern that staging systems for AL amyloidosis based on NT-proBNP 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/under treatment of patients. Limitations of this study include the relatively small number of EM patients which raises the possibility of an under-representation due to potential barriers to healthcare utilisation or incorrect diagnoses being made, as is associated with poorer deprivation indices. In light of the relatively smaller numbers, data should be cautiously interpreted. Further analysis of across ethnicities with larger international patient cohorts is warranted including reporting in future prognostic models.

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Table 1. Characteristics of patients with AL amyloidosis by ethnicity

Variable (% or range)	White n=1230	Black n=72	Asian n=30	Other/mixed n=20	p value
Age, years	67 (29-89)	57 (35-82)	60 (40-76)	64 (44-78)	<0.001
Gender					
Male	736 (60)	37 (51)	20 (67)	13 (65)	0.81
Female	494 (40)	35 (49)	10 (33)	7 (35)	
Index of multiple deprivation, decile	7 (1-10)	3 (1-10)	7 (2-10)	5 (1-10)	<0.001
Body mass index	26 (14-55)	27 (19-48)	26 (18-38)	24 (19-36)	0.74
Lambda AL type	967 (79)	59 (82)	23 (77)	14 (70)	0.70
NT-proBNP, ng/L	1611 (12-93602)	1002 (42-24534)	752 (37-18804)	1309 (25-24179)	0.02
Hs-Troponin T, ng/L	55 (0-742)	42 (0-558)	54 (13-259)	45 (3-340)	0.75
dFLC, mg/L	192 (0-15898)	188 (2-10000)	154 (1-2816)	181 (0-959)	0.89
M-protein, g/L	1 (0-45)	0 (0-37)	4 (0-36)	2 (0-32)	0.46
Bone marrow plasma cell infiltrate, % (n=687)	10 (0-95)	18 (0-80)	18 (3-70)	10 (5-30)	0.01
Number of organs affected	2 (1-5)	2 (1-5)	1 (1-4)	2 (1-3)	0.62
Organ involvement					
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					
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	13 (6-24)	14 (8-19)	14 (8-18)	14 (8-18)	0.26
LVEF, %	58 (20-80)	55 (21-73)	58 (30-70)	60 (38-68)	0.65
Global longitudinal strain, %	-14.7 (-28 - -3.1)	-11.4 (-23.1 - -3)	-12.6 (-21.6 - -7.3)	-12.8 (-25.6 - -10.8)	0.05
NYHA (n=1112)					
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 (n=906)	396 (20-700)	368 (29-622)	389 (19-543)	391 (168-529)	0.71
24hr urinary protein, g	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	96 (26-1077)	103 (52-1124)	90 (47-423)	100 (57-613)	0.29
ALP, U/L	91 (16-2389)	92 (31-968)	82 (43-620)	79 (45-258)	0.27
Albumin, g/L	34 (8-480)	37 (15-48)	36 (17-46)	35 (15-47)	0.32

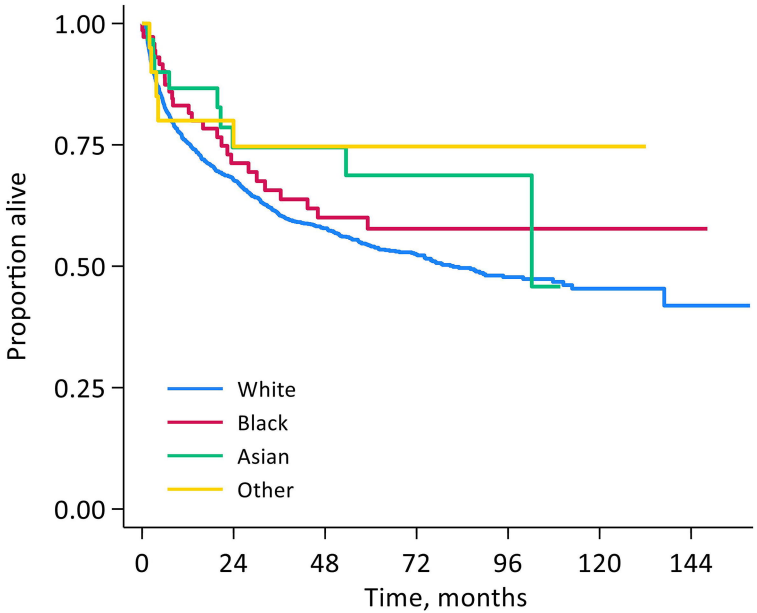
Hs-Troponin T; high sensitivity troponin T; dFLC, difference in involved and uninvolved free light chain; LVS, left ventricular septum thickness; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association classification; 6MWD, Six-minute walk distance; ALP, alkaline phosphatase

Figure 1. Overall survival of the cohort

a) Overall survival by ethnicity

b) Overall survival by depth of cardiac response at 6-month landmark

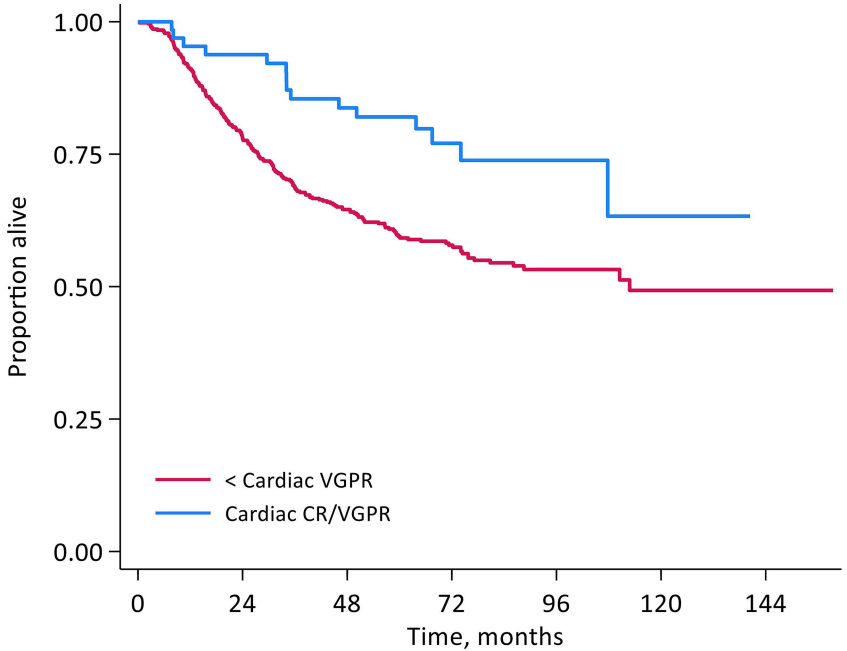
a)



Number at risk

White	1230	761	586	322	139	37	3
Black	72	40	32	20	12	2	1
Asian	30	18	17	10	4	0	0
Other	20	15	14	8	3	2	0

b)



Number at risk

< Cardiac VGPR	507	371	275	150	56	17	2
Cardiac CR/VGPR	66	57	49	25	12	2	0