JACC: CARDIOONCOLOGY VOL. 6, NO. 3, 2024

ORIGINAL RESEARCH

Race and Socioeconomic Status Impact Diagnosis and Clinical Outcomes in Transthyretin Cardiac Amyloidosis

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ABSTRACT

BACKGROUND Transthyretin amyloid cardiomyopathy (ATTR-CM) is associated with significant mortality. The Val122Ile variant, highly prevalent in Black patients, portends poorer survival compared with other ATTR-CM subtypes. Although Val122Ile is biologically more aggressive, the contribution of race and socioeconomic status (SES) to disease outcomes in patients with ATTR-CM is undefined.

OBJECTIVES The aim of this study was to evaluate the impact of race and SES on clinical outcomes in patients with ATTR-CM.

METHODS Patients with ATTR-CM who received care at Johns Hopkins Hospital between 2006 and 2022 were included. SES was assessed using area deprivation index (ADI). Associations of race and ADI with heart failure (HF) hospitalization and/or death were measured using multivariable logistic or Cox proportional hazards models.

RESULTS Of 282 patients, 225 (80%) were men, and 129 (46%) were Black. Black vs White patients disproportionately constituted the highest ADI (most deprived) category (66% vs 28%; $P = 0.004$), and Black patients were more likely to have HF hospitalization or death over 5 years compared with White patients (log-rank $P < 0.001$). Among those with ADI >25, Black patients had a significantly greater hazard of HF hospitalization or death compared with White patients, independent of disease stage at diagnosis (HR: 2.77; 95% CI: 1.45-5.32; $P = 0.002$).

CONCLUSIONS Black patients with low SES may be at greater risk for underdiagnosis and adverse outcomes compared with White patients. Ongoing efforts are needed to improve outcomes in this subset of patients with ATTR-CM. (J Am Coll Cardiol CardioOnc 2024;6:454-463) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received March 7, 2024; revised manuscript received May 8, 2024, accepted May 8, 2024.

ISSN 2666-0873 https://doi.org/10.1016/j.jaccao.2024.05.001

Transthyretin amyloid cardiomyopathy (ATTR-CM) is an underdiagnosed cause of heart failure (HF) associated with significant morbidity and mortality. ATTR-CM can result from either wild-type or hereditary genetic sequences, which will influence disease course and clinical outcomes. In particular, the pathogenic variant resulting from the substitution of valine for isoleucine at position 122 (Val122Ile), present in approximately 3% to 4% of Black individuals in the United States, is associated with more severe disease at onset and poorer survival compared with other ATTR-CM subtypes.[1-4] It has been hypothesized that this discrepancy in outcomes arises because Val122Ile hereditary transthyretin amyloidosis (ATTRv) is a biologically more aggressive disease; however, the impact of race and socioeconomic status (SES) on disease presentation and outcomes in patients with ATTR-CM is unexplored.[1] We aimed to evaluate the impact of race and socioeconomic conditions on disease severity at presentation and clinical outcomes in patients with ATTR-CM.

METHODS

STUDY POPULATION. This study was conducted with approval from the Johns Hopkins University Institutional Review Board. Patients with ATTR-CM seen at Johns Hopkins Hospital between 2006 and 2022 were included for analysis. A diagnosis of ATTR-CM was defined as either histopathologic via endomyocardial biopsy and confirmed using mass spectrometry (Rochester, Minnesota) or as positive (grade 2 or grade 3) findings on ^{99m}Tc-labeled pyrophosphate scintigraphy (PYP) and negative results on light-chain testing.[5-7] All patients underwent genetic testing including sequencing and deletion and duplication analysis of the TTR gene. Follow-up data were collected for up to 5 years from index visit. Patients were excluded from race analysis if they were not self-reported to be Black or White because of insufficient sample size of other races (n = 18). Patients were excluded from outcome analyses if they were followed for <6 months (n = 83).

STUDY VARIABLES. Clinical, radiologic, hemodynamic, and pathologic data were collected via retrospective chart review. Race was self-reported at the index visit. Individual socioeconomic metrics were collected including work status, insurance status, and marital status. Area-level SES was measured using the national area deprivation index (ADI). ADI is validated for use at the neighborhood level for assessing health outcomes and has been used extensively in research on social determinants of health.[8-10] For comparison of clinical characteristics, ADI was split into 3 groups (group 1, ADI ≤25; group 2, ADI 26-50; and group 3, AD 51-100), with increasing group number corresponding to increasing area-level deprivation; additionally, for outcome analysis, ADI was dichotomized at 25, comparing values ≤25 with those of 26 to 100. We chose this categorization because of insufficient sample size in the highest ADI quantile. Outcome data including HF hospitalization and mortality were collected via the electronic medical record, including the Care Everywhere network (Epic) and the Chesapeake regional health information exchange (Chesapeake Regional Information System for Our Patients). HF hospitalizations were assessed by 2 blinded adjudicators and were determined on the basis of review of the hospitalization record and the use of intravenous diuresis to treat symptoms. HF hospitalization and/or death were combined as the primary endpoint for analysis.

STATISTICAL ANALYSIS. Data were analyzed using SAS version 9.4 (SAS Institute). Data are presented as mean ± SD for normally distributed variables, as median (Q1-Q3) if not normally distributed, and as count (percentage) for categorical variables. Associations between demographic and clinical variables and ADI were measured using the chi-square test or Fisher exact test for categorical variables, Student's *t*-test or the Mann Whitney *U* test for comparing 2 continuous variables, and analysis of variance or the

ABBREVIATIONS AND ACRONYMS

ADI = area deprivation index

ATTR-CM = transthyretin amyloid cardiomyopathy

ATTRv = hereditary transthyretin amyloidosis

ATTRwt = wild-type transthyretin amyloidosis

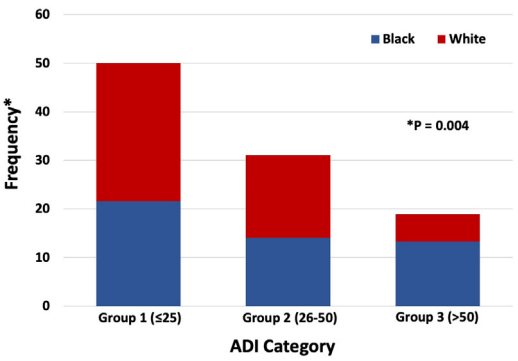
HF = heart failure

NAC = National Amyloidosis Center

PYP = ^{99m}Tc-labeled pyrophosphate scintigraphy

SES = socioeconomic status

FIGURE 1 Percentage of Patients Diagnosed With Transthyretin Amyloid Cardiomyopathy at Johns Hopkins Hospital by Race and ADI



Most patients were diagnosed from a high (less deprived) area deprivation index (ADI) category, and the proportion of Black patients (blue) increased with increasing ADI category compared with White patients (red) (P = 0.004).

JACC: CARDIOONCOLOGY, VOL. 6, NO. 3, 2024
JUNE 2024:454–463

TABLE 1 Baseline Characteristics by Race of Patients With Transthyretin Amyloid Cardiomyopathy

	White (n = 135)	Black (n = 129)	*P* Value
Demographics			
Age, y	75.9 (69.2-82.2)	74.3 (69.5-79.3)	0.18
Male	118 (87.4)	91 (70.5)	0.001
Work status			0.78
Employed	14 (10.4)	14 (10.9)	
Unemployed	4 (3.0)	7 (5.4)	
Retired	101 (74.8)	97 (75.2)	
Unable to work/disability	1 (0.7)	1 (0.8)	
Marital status			0.002
Single	5 (3.7)	9 (7.0)	
Married	111 (82.2)	78 (60.5)	
Separated/divorced	7 (5.2)	15 (11.6)	
Widowed	9 (6.7)	25 (19.4)	
Insurance			0.91
None	2 (1.5)	1 (0.8)	
Medicare	46 (34.1)	39 (30.2)	
Medicaid	5 (3.7)	5 (3.9)	
Private	73 (54.1)	73 (56.6)	
Clinical characteristics			
Amyloid subtype			<0.001
Wild-type	96 (71.1)	23 (18.8)	
Val122Ile	2 (1)	102 (79)	
Val30Met	6 (4.4)	0 (0)	
Thr60Ala	10 (7.4)	0 (0)	
Other	21 (15.6)	4 (3.1)	
Endomyocardial biopsy	110 (82.2)	108 (86.1)	0.40
PYP[a]	64 (47.8)	42 (32.6)	0.012
Grade 0	7 (12.7)	1 (2.6)	0.23
Grade 1	0 (0.0)	0 (0.0)	
Grade 2	6 (10.9)	5 (13.2)	
Grade 3	42 (76.4)	32 (84.2)	
Symptoms			
Dyspnea	69 (53.5)	71 (60.7)	0.52
Orthopnea	12 (9.3)	29 (24.6)	0.005
Fatigue	51 (39.5)	43 (36.8)	0.002
Edema	57 (44.2)	62 (53.0)	0.19
Decreased exercise tolerance	52 (40.3)	50 (42.4)	0.019
NYHA functional class			0.002
I	12 (9.3)	3 (2.6)	
II	58 (45.0)	39 (34.2)	
III	27 (20.9)	48 (42.1)	
IV	1 (0.8)	3 (2.6)	
NAC stage			0.011
1	58 (50.4)	39 (39.0)	
2	50 (43.5)	42 (42.0)	
3	7 (6.1)	19 (19.0)	
On tafamidis	28 (10.6)	23 (8.7)	0.55
On a loop diuretic agent	78 (60.0)	98 (81.7)	<0.001
Furosemide equivalent loop diuretic agent dose, mg	80 (40-120)	40 (20-80)	0.001
eGFR, mL/min/1.73 m^2	66.1 ± 19.2	53.8 ± 20.8	<0.001
Troponin I, ng/mL	1.1 ± 8.9	0.2 ± 0.3	0.36
NT-proBNP, pg/mL	2,438 ± 3,725	2,659 ± 4,801	0.16

Continued on the next page

Kruskal-Wallis test for comparing >2 groups. Associations between race and ADI with disease stage at diagnosis, HF hospitalization, and/or death were measured using multivariable logistic or Cox proportional hazards regression models, adjusted for age, sex, ADI, marital status (married vs not married), coronary artery disease, and National Amyloidosis Center (NAC) stage at diagnosis. Additional Cox proportional hazards models analyzed association modification by race on ADI for risk for HF hospitalization or death, adjusted for age and sex and for age, sex, and NAC stage and included an interaction term between race and ADI. Model results are presented as ORs with 95% CIs or as HRs with 95% CIs. The assumption of proportional hazards was tested using the SAS PHREG procedure with the "proportionality test" function with time-dependent covariates (generated as interactions between the covariate and survival time). Time to events was visualized using Kaplan-Meier curves and compared using log-rank tests. *P* values <0.05 were considered to indicate statistical significance.

RESULTS

BASELINE CHARACTERISTICS. Of the 282 patients with ATTR-CM who were included in the study, 225 (80%) were men, and 129 (46%) were Black. The median age of the Black patients was 74.3 years (Q1-Q3: 69.5-79.3 years), and the median age of the White patients was 75.9 years (Q1-Q3: 69.2-82.2 years). A total of 127 patients (45%) were classified as having wild-type transthyretin amyloidosis (ATTRwt) and 155 (55%) patients as having ATTRv; the most common genotype was p.Val122Ile (n = 110 [39%]). There were 140 patients (49%) in ADI group 1 (least deprived), 89 (32%) in group 2, and 53 (19%) in group 3 (most deprived). There was a significant difference in proportion of Black patients compared with White patients within ADI groups, with Black patients constituting most of ADI group 3 (66% vs 28%; $P = 0.004$) (Figure 1).

COMPARISON OF ATTR-CM DISEASE CHARACTERISTICS BY RACE AND SES. Of the 282 patients included in the study, 264 were either Black or White and were included in the race analysis, and the rest (n = 18) were excluded because of small sample size. Black patients were similar in age, less likely to be male (71% vs 87%, $P < 0.001$) and less likely to have ATTRwt (19% vs 71%; $P < 0.001$) compared with White patients in our cohort (Table 1). Black patients more commonly had Val122Ile disease compared with

White patients (79% vs 1%; $P < 0.001$), though other genotypes were less common in Black patients compared with White patients. Black patients were more likely to be unmarried (single, separated, or widowed; $P = 0.001$) and more likely to be in ADI group 3 compared with White patients (66% vs 28%; $P = 0.004$). There was no difference in work status or insurance status or type by race. In comparing clinical data, Black patients were less likely to undergo PYP for diagnosis (33% vs 48%; $P = 0.012$). Of note, there were 8 patients with grade 0 results on PYP, the majority of whom (n = 7) were White. Of these, 6 patients had a specific variant, Leu58His, that is more prevalent in our region and is associated with a high false-negative rate on PYP. There was no significant difference in comorbidity burden by race including atrial fibrillation, carpal tunnel syndrome, or lumbar spinal stenosis except for a lower burden of coronary artery disease (19% vs 35%; $P = 0.007$) and a lower frequency of indwelling pacemaker (8% vs 20%; $P = 0.004$) at the time of index visit in Black compared with White patients. Black patients were more likely to have had prior HF hospitalizations (49% vs 26%; $P < 0.001$) and more likely to be on loop diuretic agents (82% vs 60%; $P < 0.001$) at a higher median dose (40 mg [Q1-Q3: 20-80 mg] vs 80 mg [Q1-Q3: 40-120 mg]; $P = 0.001$) compared with White patients at the time of index visit. Black patients had significantly worse renal function (estimated glomerular filtration rate 53.8 ± 20.8 mL/min/1.73 m^2 vs 66.1 ± 19.2 mL/min/1.73 m^2; $P < 0.001$) compared with White patients. There was a higher proportion of Black patients classified in NYHA functional class III compared with White patients at time of index visit (42% vs 21%; $P = 0.002$). On electrocardiography, Black patients had significantly lower total QRS voltage compared with White patients (106 ± 32 mV vs 115 ± 34 mV; $P = 0.038$).

On echocardiography, Black patients had significantly lower left ventricular ejection fractions, higher incidence of moderate or severe mitral regurgitation, higher E/A ratios, higher right ventricular systolic pressures, and lower calculated stroke volumes (Table 2). In the subset of patients who underwent right heart catheterization for diagnosis (n = 167; 76 White and 85 Black patients), Black patients had significantly worse hemodynamic status compared with White patients across all parameters, including higher filling pressures, lower cardiac output and cardiac index, lower pulmonary arterial saturation, and higher pulmonary vascular resistance (Table 2).

When comparing the cohort by ADI groups, no significant difference was found in baseline demographics except for a higher proportion of Black

TABLE 1 Continued

	White (n = 135)	Black (n = 129)	*P* Value
Total QRS voltage on ECG, mV	115.3 ± 32.2	105.6 ± 34.3	0.038
Medical history			
Atrial fibrillation	74 (56.9)	51 (43.2)	0.064
Carpal tunnel syndrome	70 (54.3)	57 (48.0)	0.32
Lumbar spinal stenosis	22 (16.9)	16 (13.5)	0.71
Coronary artery disease	45 (35.2)	22 (18.5)	0.008
Pacemaker implanted	26 (20.2)	9 (7.6)	0.004
ICD implanted	7 (5.4)	13 (10.9)	0.12
HF hospitalization <12 mo prior	34 (26.2)	57 (48.7)	<0.001

Values are median (Q1-Q3), n (%), or mean ± SD. [a]Grade was not reported for 13 scans.

ECG = electrocardiography; eGFR = estimated glomerular filtration rate; HF = heart failure; ICD = implantable cardioverter-defibrillator; NAC = National Amyloidosis Center; NT-proBNP = N-terminal pro-brain natriuretic peptide; PYP = ^{99m}Tc-labeled pyrophosphate scintigraphy.

TABLE 2 Baseline Echocardiographic and Hemodynamic Data by Race of Patients With Transthyretin Amyloid Cardiomyopathy

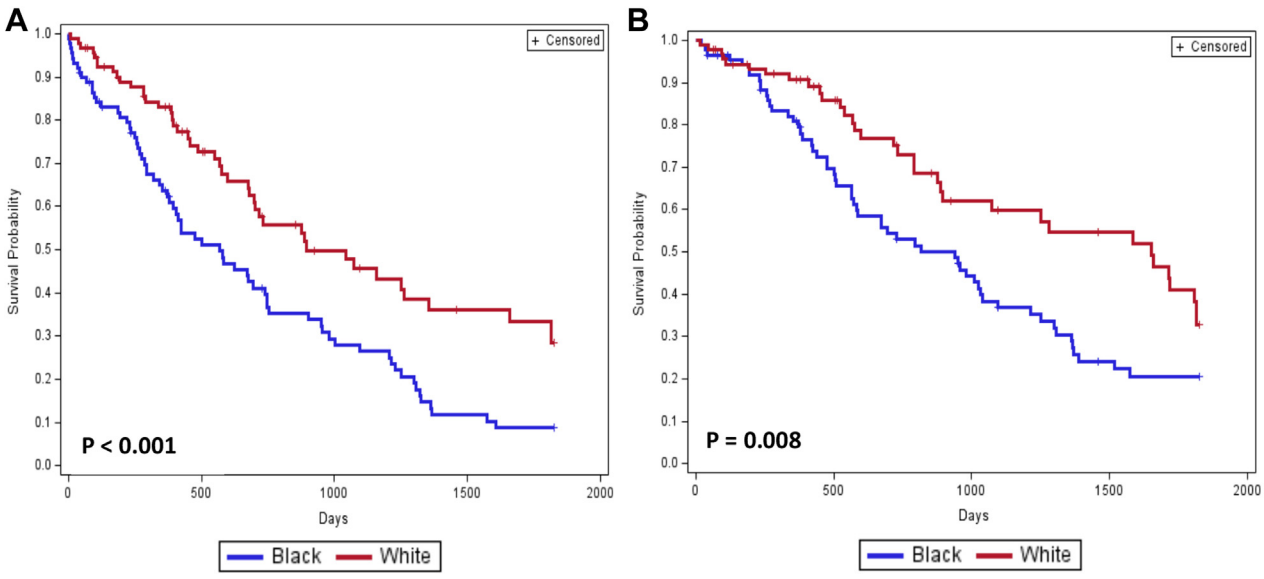
	White (n = 135)	Black (n = 129)	*P* Value
Echocardiography			
Ejection fraction, %	51.5 ± 12.5	41.3 ± 14.3	<0.001
TAPSE, cm	1.6 ± 0.5	1.5 ± 0.5	0.46
LV diastolic dimension, cm	4.3 ± 0.6	4.3 ± 0.8	0.79
IVSd, cm	1.7 ± 0.3	1.7 ± 0.3	0.98
LVPWd, cm	1.6 ± 0.3	1.6 ± 0.4	0.84
LA systolic diameter, cm	4.4 ± 0.8	4.5 ± 0.6	0.76
LVOT VTI, cm	21.8 ± 18.1	14.2 ± 4.5	0.010
E/A ratio	2.0 ± 1.2	2.6 ± 1.3	0.034
E/e′ ratio	18.3 ± 8.0	19.4 ± 8.5	0.56
RV systolic pressure, mm Hg	37.7 ± 11.6	43.4 ± 12.0	0.005
GLS, % (n = 67)	−10.7 ± 4.7	−9.2 ± 3.6	0.20
Right heart catheterization[a]			
Heart rate, beats/min	72.1 ± 14.1	81.2 ± 16	0.001
mRAP, mm Hg	8.7 ± 4.9	11.6 ± 6.5	0.001
RV systolic pressure, mm Hg	40.8 ± 11.8	48.1 ± 13.6	0.001
RV diastolic pressure, mm Hg	8.8 ± 4.4	11.6 ± 6.4	0.002
PA diastolic pressure	18.0 ± 6.8	20.3 ± 6.9	0.037
mPAP, mm Hg	25.7 ± 8.4	29.5 ± 8.2	0.005
PCWP, mm Hg	17.1 ± 6.4	19.6 ± 6.8	0.020
Cardiac output (thermodilution), L/min	4.0 ± 1.1	3.4 ± 1.2	0.002
Cardiac index, L/min/m^2	2.0 ± 0.6	1.7 ± 0.5	0.001
PA saturation, %	63.4 ± 7.4	57.2 ± 8.4	<0.001
SVRI, dyne · s · m^2/cm^5	3,673.3 ± 1,133.4	4,121.6 ± 1,387.1	0.045
PVR, Wood units	2.4 ± 1.1	3.1 ± 1.6	0.002

Values are mean ± SD. [a]Only a subset of patients underwent right heart catheterization (n = 167; 76 White patients and 85 Black patients).

GLS = global longitudinal strain; IVSd = intraventricular septal diastolic dimension; LA = left atrial; LV = left ventricular; LVOT = left ventricular outflow tract; LVPWd = left ventricular posterior wall diastolic dimension; mRAP = mean right atrial pressure; mPAP = mean pulmonary artery pressure; PA = pulmonary artery; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; RV = right ventricular; SVRI = systemic vascular resistance index; TAPSE = tricuspid annular plane systolic excursion; VTI = velocity-time integral.

JACC: CARDIOONCOLOGY, VOL. 6, NO. 3, 2024
JUNE 2024:454–463

FIGURE 2 Kaplan-Meier Curves Depicting the Association Between Race and Heart Failure Hospitalization or Mortality and Mortality Alone



Black patients with transthyretin amyloid cardiomyopathy were more likely to experience (A) heart failure hospitalization or mortality at 5 years (log-rank $P < 0.001$) and (B) mortality alone at 5 years (log-rank $P = 0.008$) compared with White patients.

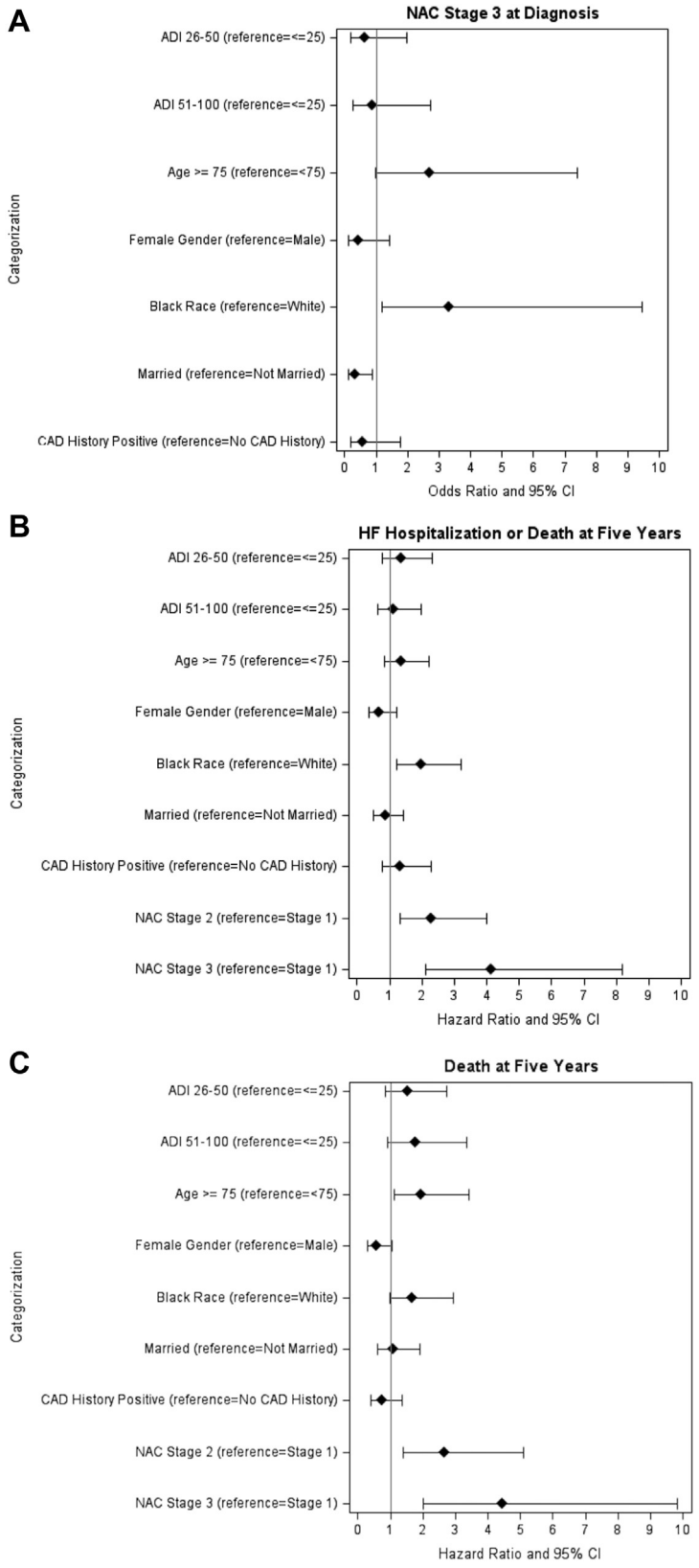
patients in the most deprived ADI group compared with White patients, as noted previously. There were no significant differences in disease characteristics, echocardiographic findings, and hemodynamic data by ADI group (Supplemental Tables 1 and 2).

COMPARISON OF ATTR-CM DISEASE OUTCOMES BY RACE AND SES. Black patients were more likely to experience HF hospitalization or death (log-rank $P < 0.001$) (**Figure 2A**) and death alone over 5 years of follow-up (log-rank $P = 0.008$) (**Figure 2B**). In adjusted analyses, Black race was significantly associated with higher odds of being diagnosed at NAC stage 3 (OR: 3.32; 95% CI: 1.17-9.45; $P = 0.025$), and being married appeared to be protective against this (OR: 0.31; 95% CI: 0.11-0.89; $P = 0.029$), as shown in **Figure 3A**. Black race (HR: 1.97; 95% CI: 1.21-3.21; $P = 0.007$) and NAC stage 2 (HR: 2.29; 95% CI: 1.31-3.98; $P = 0.004$) or 3 (HR: 4.15; 95% CI: 2.10-8.19; $P < 0.001$) were associated with HF hospitalization or death at 5 years (**Figure 3B**). When limiting the outcome to death alone, there was no longer a significant association with Black race, though higher NAC state remained significant, as did age > 75 years (**Figure 3C**). In a sensitivity analysis performed in patients with Val122Ile disease, ADI >25 was a significant predictor of HF hospitalization and death (HR: 1.81; 95% CI: 1.03-3.17; $P = 0.039$) when adjusted for age and sex. Race was not included in this model given the large proportion of patients with Val122Ile disease who were Black. A sensitivity analysis to assess race as a predictor of HF hospitalization or death among those with wild-type disease was not performed, because of insufficient sample size of Black patients (n = 12).

There was no significant difference in HF hospitalization or mortality or in mortality alone by ADI category in unadjusted and adjusted analyses (Supplemental Figure 1). When race was stratified by ADI category (≤25 and >25), there was a significant difference in event-free survival among the groups. Black patients with high ADI had lower event-free survival compared with White patients in either ADI category, with Black patients in the highest ADI category having the lowest event-free survival overall (log-rank $P = 0.001$) (**Figure 4**).

In Cox proportional hazards models, among patients with ADI >25, Black patients had a significantly higher hazard of HF hospitalization or death compared with White patients when adjusted for age and sex (HR: 3.33; 95% CI: 1.88-5.89; $P < 0.001$) and when adjusted for age, sex, and NAC stage (HR: 2.77; 95% CI: 1.45-5.32; $P = 0.002$). Additionally, ADI >25 was associated with a higher hazard of HF hospitalization or death in Black patients (HR: 1.72; 95% CI: 1.04-2.83; $P = 0.034$) when adjusted for age and sex,

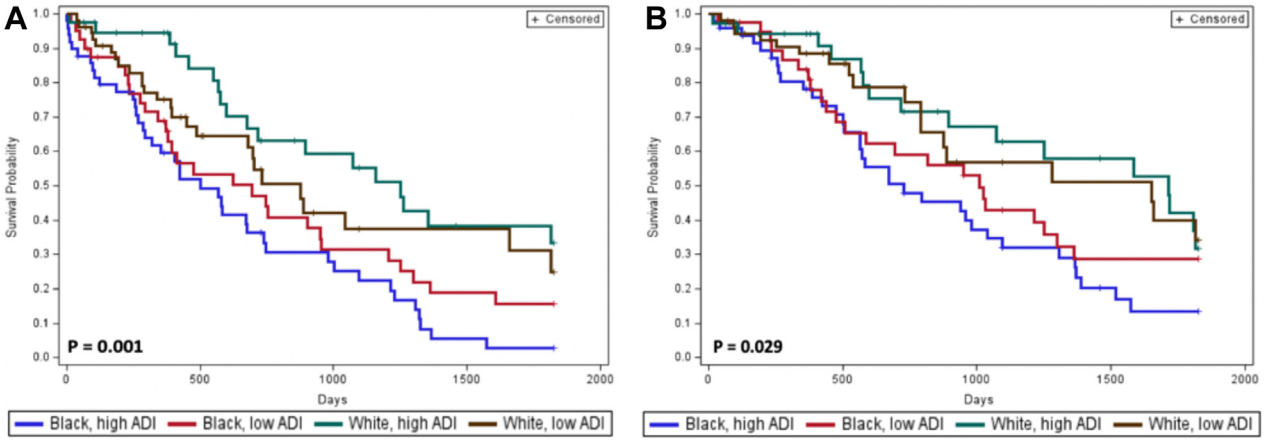
FIGURE 3 **Forest Plots Depicting ORs or HRs, 95% CIs, and *P* Values for Various Outcomes**



(A) Black race was associated with National Amyloidosis Center (NAC) stage 3 at diagnosis. (B) Black race and higher NAC stage were associated with heart failure (HF) hospitalization or death at 5 years. (C) Elderly age and higher NAC stage were associated with death alone at 5 years. ADI = area deprivation index; CAD = coronary artery disease.

JACC: CARDIOONCOLOGY, VOL. 6, NO. 3, 2024
JUNE 2024:454–463

FIGURE 4 Kaplan-Meier Curves Depicting Associations of Race and ADI With Heart Failure Hospitalization or Mortality



Black patients in the highest area deprivation index (ADI) category had the lowest event-free survival overall for both (A) HF hospitalization and mortality (log-rank $P = 0.001$) and (B) mortality alone (log rank $P = 0.029$). Low ADI is defined as ADI ≤25 and high ADI as ADI >25.

whereas in White patients, this was not significant (Table 3). This finding in Black patients was attenuated when additionally adjusting for NAC stage (HR: 1.69; 95% CI: 0.95-2.99; $P = 0.073$). Last, there was a significant interaction between ADI and race in predicting HF hospitalization or death (P for interaction = 0.034), although this effect was attenuated after adjusting for NAC stage ($P = 0.081$). Results of Cox proportional hazards regression models for outcome of HF hospitalization and death alone are shown in Supplemental Tables 3 and 4.

DISCUSSION

This is the first study evaluating the impact of race and SES on disease presentation and outcomes in patients with ATTR-CM. Our findings highlight that Black patients with low SES may be at greater risk for underdiagnosis and have poorer longitudinal outcomes independent of disease severity at diagnosis compared with White patients (Central Illustration). We observed a difference in the proportion of patients diagnosed with ATTR-CM by SES, with most patients diagnosed from a high-SES area and Black patients constituting the majority of individuals diagnosed from a low SES area. Furthermore, Black patients, the majority of whom had Val122Ile disease, had more advanced cardiac disease at diagnosis and worse clinical outcomes compared with White patients. Black patients from the most socioeconomically deprived areas had the poorest event-free survival compared with other groups. Importantly, among patients with ADI >25, the hazard of HF hospitalization or mortality was significantly higher in

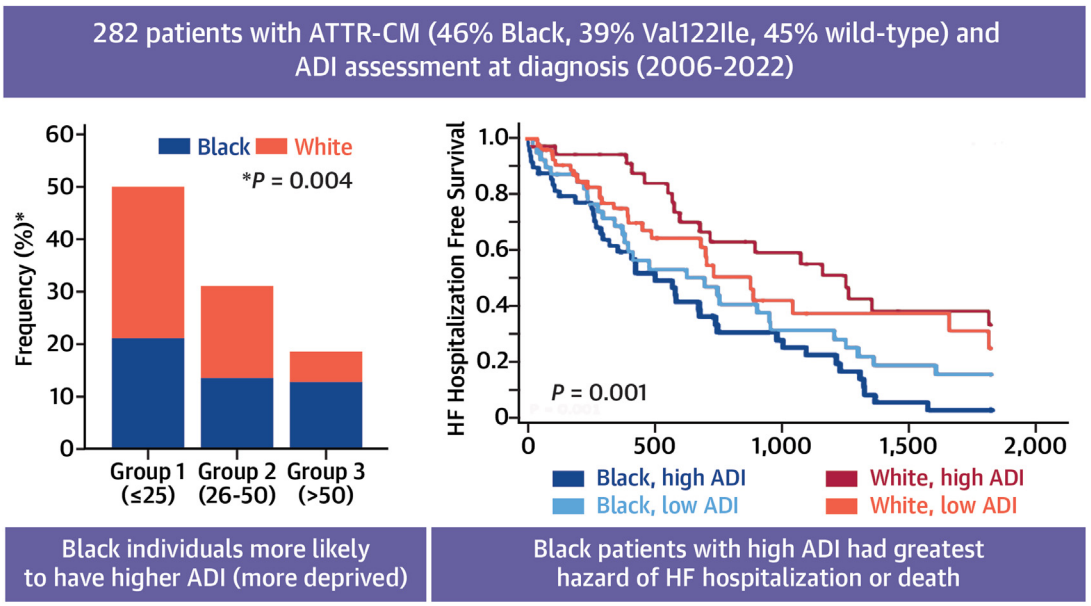
TABLE 3 Cox Proportional Hazards Models With Analysis Between Race and ADI for Composite Outcome

	HF Hospitalization or Mortality					
	Model A[a]			Model B[b]		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Black vs White for ADI ≤25	1.42	0.82-2.46	0.21	0.42	0.42-0.42	0.42
Black vs White for ADI >25	3.33	1.88-5.89	<0.001	2.77	1.45-5.32	0.002
ADI >25 vs ADI ≤25 for Black race	1.72	1.04-2.83	0.034	1.69	0.95-2.99	0.073
ADI >25 vs ADI ≤25 for White race	0.73	0.40-1.35	0.32	0.78	0.41-1.50	0.46
NAC stage 2 vs stage 1				2.29	1.39-3.77	0.001
NAC stage 3 vs stage 1				4.15	2.15-8.02	<0.001

For interaction between race and ADI, $P = 0.034$ (model A) and $P = 0.081$ (model B). [a]Model A was adjusted for age and sex. [b]Model B was adjusted for age, sex, and NAC stage.

ADI = area of deprivation index; HF = heart failure; NAC = National Amyloidosis Center.

CENTRAL ILLUSTRATION **The Impact of Race and Socioeconomic Status on Clinical Outcomes in Patients With ATTR-CM**



Shankar B, et al. J Am Coll Cardiol CardioOnc. 2024;6(3):454–463.

Among patients with transthyretin amyloid cardiomyopathy (ATTR-CM) with high area deprivation index (ADI) (>25), Black patients had worse outcomes independent of disease severity compared with White patients. HF = heart failure.

Black compared with White patients, even when adjusting for disease severity at diagnosis. This difference was not appreciated in patients with low ADI (<25).

These new findings are hypothesis generating and warrant ongoing investigation. It is possible that this difference was observed because of racially influenced determinants of health heightened in patients with high ADI. Other possibilities include a higher burden and/or rate of progression of non-amyloid comorbidities contributing to poorer outcomes. Last, in a broader cohort, the lack of access to treatment compounded with the propensity for Val122Ile to progress at a more rapid rate than wild-type disease could contribute to differences in outcomes in those with high ADI. However, this is unlikely the explanation in our cohort, as no significant difference in tafamidis treatment by race or ADI was observed.

Several prior reports have highlighted an adverse prognosis of Val122Ile cardiomyopathy compared with other forms of ATTR-CM. In data from THAOS (Transthyretin Amyloid Outcome Survey), Val122Ile was the most common ATTR-CM mutation in the United States and was associated with a significantly higher incidence of heart transplantation from time of diagnosis.[4,11] Data from the NAC inclusive of >1,000 patients with ATTR-CM and about 20% with Val122Ile highlight that subjects with Val122Ile have lower left ventricular ejection fractions, higher N-terminal pro-brain natriuretic peptide levels, and shorter 6-minute walk distances at the time of diagnosis.[1] Furthermore, median survival was significantly reduced in the Val122Ile cohort compared with those with ATTRwt cardiomyopathy (31 vs 57 months; $P < 0.001$).[1] Given the access to health care available in the United Kingdom, it was hypothesized that the variation in disease severity at time of diagnosis was because

JACC: CARDIOONCOLOGY, VOL. 6, NO. 3, 2024
JUNE 2024:454–463

Val122Ile is pathologically more aggressive, above other environmental factors such as SES. However, racial disparity, including HF hospitalization and premature death in Black individuals in a broader HF population, has increased over the past several years compared with White individuals, and therefore, pathobiology is unlikely to be the only contributor to this phenomenon observed in Val122Ile ATTR-CM.[12,13] Our findings highlight that within Black patients, there is lower event-free survival by SES category, further supporting this notion. More so, Alexander et al[14] demonstrated large geographic variations in reported mortality due to amyloidosis, including states with the highest proportion of Black individuals having the lowest mortality, likely reflective of the disparities in diagnosis. In a recent single-center cohort study, Khedraki et al[15] investigated disparities by race and genotype categories in ATTR-CM and included 53 patients who were Black with wild-type disease. Similar to our findings, Black patients had worse outcomes than White patients. There were no differences in outcomes between Black patients with Val122Ile and wild-type disease, though the analysis may have been underpowered to detect differences. Our study is unique in that we not only measured genetic and racial factors but also incorporated ADI as a measure of SES on disease outcomes. Given the high risk for adverse outcomes seen in our Black patients as well as in other cohorts, significant global efforts are needed to help mitigate socioeconomic burdens and improve early diagnosis in this vulnerable patient population.

Prior to the U.S. Food and Drug Administration's approval of tafamidis, there were no disease-altering therapies that improved outcomes for ATTR-CM. Since then, there have been several therapies under investigation for the disease.[16-19] Although the current therapeutic landscape for ATTR-CM is promising, the majority of these therapies in later stage development slow progression of disease rather than reversing existing myocardial damage. Contemporary ATTR-CM trials have predominantly enrolled White subjects, with only 14% of patients in the landmark ATTR-ACT (Safety and Efficacy of Tafamidis in Patients With Transthyretin Cardiomyopathy) trial and 9% of patients in APOLLO-B (A Study to Evaluate Patisiran in Participants With Transthyretin Amyloidosis With Cardiomyopathy) being Black.[16,20] As such, there needs to be a greater emphasis on prioritizing racial diversity in ATTR-CM clinical trials, as Black patients are at higher risk for adverse outcomes compared with White patients and in great need of effective treatment.

STUDY LIMITATIONS. This study was conducted at a single center, and therefore its findings need to be replicated at other centers to show external validity. Furthermore, ADI is a population rather than an individual measure of SES. However, it remains a useful aggregating tool that encompasses the multifaceted nature of SES. The ADI was determined on the basis of patients' addresses at the time they were enrolled in the electronic medical record, but these may have changed at the time of chart review, although a sensitivity analysis with patient data from 2017 and later showed no difference in the principal outcomes. Importantly, the combination of pathobiological factors with socioeconomic factors leads to some uncertainty regarding the true effect size of our results. We acknowledge that most of the Black patients in our cohort had the Val122Ile variant, and the White patients had wild-type disease. Given the small proportion of Black patients with wild-type disease, we were unable to perform an analysis by race in those with wild-type disease. This is a known limitation of our study and a clear area in need of further exploration.[15]

CONCLUSIONS

There are limited data on the impact of SES on timely diagnosis and clinical outcomes in patients with ATTR-CM. Our study is the first to demonstrate that Black patients with lower SES have worse outcomes compared with those with higher SES and White patients and thus provides groundwork for ongoing health care disparities research in ATTR-CM. Going forward, it will be important to prioritize enrollment of Black patients in ATTR-CM clinical trials to better identify effective therapies for this vulnerable population.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Hereditary ATTR-CM related to the Val122Ile genetic variant is a highly morbid cause of HF in Black individuals and leads to worse outcomes compared with wild-type ATTR-CM disease. Black patients from the most socioeconomically deprived areas had the poorest event-free survival compared with other groups. Among patients with ADI $>$ 25, the hazard of HF hospitalization or mortality was significantly higher in Black compared with White patients, even when adjusting for disease severity at diagnosis.

TRANSLATIONAL OUTLOOK: Black patients are underrepresented in contemporary ATTR-CM clinical trials. Future trial designs need to focus on increasing representation of Black patients as well as those with Val122Ile disease to identify effective therapies for patients at risk for worse outcomes to patients with wild-type disease. Moreover, a greater understanding of the more aggressive pathobiology of Val122Ile is needed in this vulnerable patient subset.

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KEY WORDS cardiac amyloidosis, health care disparities, outcomes, transthyretin

APPENDIX For supplemental tables and a figure, please see the online version of this paper.