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

EDITORIAL COMMENT

Understanding Race, Genotype, and Socioeconomic Status in Transthyretin Amyloid Cardiomyopathy

An Area of Deprivation*

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In this issue of *JACC: CardioOncology*, the study by Shankar et al[1] addresses an important knowledge gap with regard to how race interacts with socioeconomic status to influence patient presentation and outcomes in transthyretin amyloid cardiomyopathy (ATTR-CM). We applaud the authors on a carefully constructed retrospective study that adds a layer of welcomed nuance to prior studies that have examined race and genotype ATTR-CM without examining socioeconomic status as a contributing factor to longitudinal outcomes.

The authors use a well-validated marker of socioeconomic status at the neighborhood level, the national Area Deprivation Index, in addition to work, insurance, and marital status to study how socioeconomic status impacts outcomes in ATTR-CM. Importantly, Black patients with a high Area Deprivation Index had lower event-free survival overall and a higher hazard of heart failure (HF) hospitalization or death compared to White patients across income classes even when adjusting for disease stage. Despite equitable initiation of disease-specific treatment with tafamidis, Black patients from deprived neighborhoods suffered increased morbidity, predominantly driven by hospitalization during the 5-year follow-up period. This raises the important question of how HF management in this vulnerable population can be improved in patients who are historically underserved, including the need for frequent volume optimization, management of comorbid disease, the use of guideline-directed medical therapy, and access to specialized cardiovascular care.

Importantly, the authors analyzed a diverse cohort (46% self-identified Black race) from a high-volume urban center and have added to a body of literature that has challenged the long-held belief that lower median survival in patients with Val122Ile variant disease compared with wild-type disease is driven exclusively or even predominantly by a more "malignant" pathobiology intrinsic to this common variant.[2,3] The Val122Ile variant is present in approximately 3% to 4% of self-identified Black individuals in the United States; however, this variant comprises the significant majority of ATTR-CM in Black patients across multiple registries including 79% of those in the present study.[3,4] We now understand that ATTR-CM prognosis is a complex interplay between racial inequities including burden of comorbidities, genotype, access to specialized cardiovascular care, and socioeconomic status. Unfortunately, most retrospective analyses including the present study have been limited by the relatively small numbers of Black patients with wild-type disease, a logical "control" to compare the impact of genotype on outcomes without race as a confounding factor.

Prior work has shown worse outcomes in Black patients regardless of genotype. A recent analysis from a large cohort showed that Black patients were

*Editorials published in *JACC: CardioOncology* reflect the views of the authors and do not necessarily represent the views of *JACC: CardioOncology* or the American College of Cardiology.

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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.

ISSN 2666-0873 https://doi.org/10.1016/j.jaccao.2024.05.006

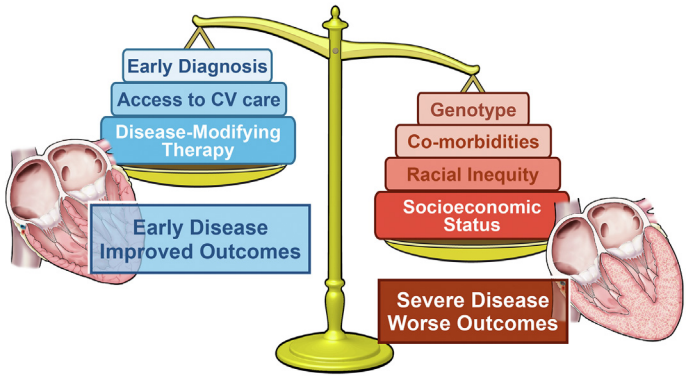
more likely to present with HF with reduced ejection fraction at the time of diagnosis regardless of genotype (wild-type transthyretin amyloid cardiomyopathy [ATTRwt-CM] or variant transthyretin amyloid cardiomyopathy [ATTRv-CM]) compared with White patients.[5] Additional work by Khedraki et al[6] showed that Black patients (ATTRv and ATTRwt) had worse longitudinal survival than White patients with wild-type disease. The increased risk of hospitalization and mortality as a composite outcome in Black Americans observed in the present study are, unfortunately, not unique to amyloidosis and reflect disturbing and persistent inequalities in HF outcomes.[7-9] Black patients in the current analysis were more likely to have prior HF hospitalizations, were on higher doses of loop diuretic, had worse renal function, and were more likely to be NYHA functional class III than White patients at their index visit. The possible reasons for this more severe presentation merit discussion.

Given that ATTR-CM is a progressive infiltrative cardiomyopathy that mimics hypertensive, diabetic, and chronic kidney disease-associated heart disease, we posit that late presentation that is seen in both ATTRwt and ATTRv Black patients could be caused by diagnostic biases around what constitutes "typical" cardiomyopathy in Black patients with comorbid disease.[10] Even experienced clinicians may attribute wall thickening on echocardiography to other common pathologies. Broader application of multimodal imaging techniques and measures such as global longitudinal strain may help us move beyond wall thickness as a crude marker of ATTR-CM risk.

Notably, differing diagnostic patterns were observed in the current study in which Black patients were more likely to undergo endomyocardial biopsy compared with White patients who were more commonly diagnosed noninvasively with technetium-99m pyrophosphate scanning. Consistent with the broader HF population, prior studies have shown that Black patients have more comorbid diabetes and hypertension than White patients with ATTR-CM.[5,6] Given that these comorbidities are well-established HF risk factors, they could contribute to more severe disease presentation with lower ejection fraction as the result of a "multihit" phenomenon wherein there is both amyloid and conventional cardiomyopathy contributions to HF risk.

With multiple exciting disease-modifying therapies on the horizon, understanding the full phenotypic spectrum of amyloidosis presentation across subgroups is critical to scaling efforts to better diagnose and optimally treat ATTR-CM. This includes the differing symptomology, imaging, biomarkers, and diagnostic clues (ie, carpal tunnel and lumbar stenosis) across different subgroups. Otherwise, patients from the most vulnerable and historically underserved groups could be left behind and deprived of optimal HF management and potentially lifesaving therapies.[8,10]

FIGURE 1 **Race, Genotype, and Socioeconomic Status in Transthyretin Amyloid Cardiomyopathy**



There are multiple modifiable and inherited factors that influence patient outcomes in transthyretin amyloid cardiomyopathy. The degree to which each risk factor contributes to patient outcomes is not well understood. Understanding how to mitigate the impact of racial and socioeconomic inequities should be a priority in future research.
CV = cardiovascular.

A recent publication by Davies et al[11] developed and validated a useful and easily transferable "simple risk score for ATTR-CM" for patients with left ventricular ejection fraction >40%. The score was built to risk stratify patients with suspected ATTR-CM and identify patients with high pretest risk for ATTR-CM who would warrant diagnostic evaluation. It is important to note that Black patients made up only 3% of the derivation cohort, and HF with reduced ejection fraction patients were excluded. The simple risk score represents an important contribution that will certainly aid nonexpert clinicians in identifying those who need further evaluation. Importantly, Davies et al[11] took effort to validate their findings in more diverse and multicenter cohorts to avoid replicating diagnostic bias that could be propagated from a cohort lacking diversity.

Worse cardiovascular outcomes in Black patients are likely multifactorial, including decreased health care literacy, poor access to care, mistrust in health care providers, and systemic biases in the U.S. health care system.[10] Unfortunately, ATTR-CM is no exception, and proactive strategies are needed to

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address these ongoing disparities that are not attributable to genotype alone. Again, we applaud the authors in helping us progress toward a more nuanced understanding of ATTR-CM and the multiple factors, including racial inequities, socioeconomic status, comorbid disease, and genotypic variation, that contribute to the varied and complex presentation of an increasingly treatable disease (**Figure 1**).

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Martyn serves as an advisor or has received consulting fees from Fire1, Cleveland Clinic/American Well Joint Venture, NirSense, Boehringer Ingelheim/Eli Lilly, Novo Nordisk, and Apricity Robotics; and has received grant support from Ionis Therapeutics, AstraZeneca related to amyloidosis, and the Heart Failure Society of America. Dr Hanna has served on Advisory Boards for Alnylam, Eidos, Ionis, Alexion pharmaceuticals and Pfizer. Dr Simkowski has reported that she has no relationships relevant to the contents of this paper to disclose.

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KEY WORDS genotype, race, racial inequity, socioeconomic status, transthyretin amyloid cardiomyopathy