



The Impact of Race on the Prognosis of Preclinical Diastolic Dysfunction: A Large Multiracial Urban Population Study

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ABSTRACT

BACKGROUND: This study was performed to assess the impact of race on the incidence of heart failure and survival in patients with preclinical diastolic dysfunction.

METHODS: All adults during a 5-year period with grade 1 diastolic dysfunction on echocardiogram, left ventricular ejection fraction $\geq 50\%$, and no diagnosis of heart failure were included in this study. Clinical endpoints were new diagnosis of heart failure (International Classification of Diseases-Ninth Revision code 428.0) and all-cause mortality. A total of 7878 patients: 20.8% non-Hispanic White, 35.8% non-Hispanic Black, and 31.0% Hispanic individuals (mean age was 68 ± 12 years, 37% men) were included in the study. Non-Hispanic Whites were older, more frequently male, and had a higher mean socioeconomic status and more antecedent myocardial infarction.

RESULTS: Non-Hispanic Blacks and Hispanics had more hypertension, diabetes, renal disease, and cerebrovascular disease. After a median follow-up time of 6 years, 1356 patients developed heart failure and 2078 patients died. The 10-year cumulative probabilities of heart failure and all-cause mortality were 23.9% and 32.6%, respectively. Time to incident heart failure was similar among the 3 racial groups. However, non-Hispanic Blacks (hazard ratio 0.80, $P = .002$) and Hispanics (hazard ratio 0.67, $P < .001$) experienced lower mortality compared with non-Hispanic Whites, which was confirmed on a propensity-scored sensitivity analysis.

CONCLUSIONS: Time to heart failure was similar among the 3 racial groups, however, non-Hispanic Whites experienced worse survival compared with non-Hispanic Blacks and Hispanics, despite their higher burden of risk factors. The reasons for worse survival in the non-Hispanic white population need to be further explored.

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There is a heart failure epidemic in the US, with 825,000 new cases diagnosed each year and 5.1 million Americans living with the disease in 2014.^{1,2} Treatment for heart failure continues to advance, but heart failure is still listed on death certificates as frequently in 2010 as it was in 1995.³ Prevention of heart failure remains an important issue, and a better understanding of its natural history and risk factors is needed.

A well-known but poorly understood risk factor for the development of heart failure is preclinical diastolic dysfunction, defined as impaired relaxation of the left ventricle during diastole without signs or symptoms of heart failure.⁴⁻⁶ Diastolic dysfunction is found in most patients with heart failure, irrespective of systolic function,^{5,7} and roughly half of all heart

failure patients have heart failure with preserved ejection fraction.^{8,9} Although the introduction of beta-blockers and renin-angiotensin aldosterone modulators in the past 2 decades has significantly improved the outcomes of heart failure with reduced ejection fraction, no treatment has yet been demonstrated to reduce morbidity and mortality in patients with heart failure with preserved ejection fraction.¹⁰ Therefore, identifying which patient factors affect the progression of preclinical diastolic dysfunction to heart failure is needed.

The impact of race on the progression of preclinical diastolic dysfunction to heart failure and overall survival has been understudied. Previous studies were in mainly small, non-Hispanic White cohorts with European ancestry.^{4,5,11-13} Race is known to play a key role in outcomes in patients who already have heart failure, but its role on outcomes in patients with preclinical diastolic dysfunction is unknown.¹⁴ Therefore, this study was undertaken in a large, racially diverse urban population with preclinical diastolic dysfunction to assess the impact of race on the incidence of heart failure and overall survival.

METHODS

Patient Population

The catchment area of the authors' institution represents one of the most diverse populations in the US. According to the US Census Bureau, in 2013 the Bronx County, New York, population consisted of 10.5% non-Hispanic White, 43.3% non-Hispanic Black, and 54.6% Hispanic or Latino (Hispanic) individuals, compared with national statistics, 62.6% non-Hispanic White, 13.2% non-Hispanic Black, and 17.1% Hispanic individuals. We retrospectively reviewed our institution's electronic medical record using Clinical Looking Glass (Ver. 3.3; Montefiore Medical Center, Bronx, NY), a patented software tool that collates medical records from multiple sources for research purposes. All patients between 18 and 90 years of age who were referred for echocardiography during the period of 2003 to 2008 were screened for inclusion based on the presence of preclinical diastolic dysfunction. Patients were excluded if they had a preexisting diagnosis of heart failure, valvulopathy of any type, or atrial fibrillation. If a patient had multiple echocardiograms (echos), the first echo meeting the definition of grade 1 diastolic dysfunction was considered the index echo at time "zero" for that patient. Socioeconomic status, self-reported race, preexisting comorbidities, serologic data, and medications were gathered using Clinical Looking Glass. Socioeconomic status was measured using a summary score combined from 6 variables representing

wealth and income (1. log of the median household income; 2. log of the median value of housing units; 3. the percentage of households receiving interest, dividend, or net rental income; 4. the percentage of adults 25 years of age or older who had completed high school; 5. the percentage of adults 25 years of age or older who had completed college; 6. the percentage of employed individuals 16 years of age or older in executive, managerial, or professional specialty occupations). A Z-score is computed that reflects the deviation below (negative) or above (positive) the mean socioeconomic status of the population in the state of New York.¹⁵ This method is used by Clinical Looking Glass and has been previously validated against the US Census Bureau geocoding database.¹⁶ Patient information was de-identified in accordance with the Health Insurance Portability and Accountability Act. The Institutional Review Board of Montefiore Medical Center and Albert Einstein College of Medicine approved this study.^{15,16}

CLINICAL SIGNIFICANCE

- In patients with preclinical diastolic dysfunction (PDD), the 10-year cumulative probability for heart failure is 23.9%. The 10-year cumulative probability for death is 32.6%.
- Men and women have similar risk of developing heart failure, but men die sooner.
- Non-Hispanic (NH) Whites, NH Blacks, and Hispanics with PDD develop heart failure at similar rates, yet NH Whites with PDD have significantly poorer survival than NH Blacks and Hispanics.

Echocardiography

Echocardiography was performed according to the guidelines of the American Society of Echocardiography using Sonos 5500, Sonos 7500, or IE-33 ultrasound systems (Philips Healthcare, Andover, MA).¹⁷ Left ventricular ejection fractions were calculated using either biplane Simpson's method or Teichholz formula.¹⁸ Diastolic function was measured by pulsed-wave Doppler examination of mitral inflow velocities before and during Valsalva maneuver. Preclinical diastolic dysfunction was defined as the presence of grade 1 diastolic dysfunction without a clinical diagnosis of heart failure based on the International Classification of Diseases, Ninth Revision (ICD-9) code 428.0, putting patients into stage B of the American College of Cardiology/American Heart Association stage of heart failure.¹⁹ We measured diastolic dysfunction based on the ratio of early (E) to late (A) mitral inflow velocity and ratio of E to the lateral mitral annual velocity (E') measured by tissue Doppler in accordance with current guidelines.²⁰ Grade 1 diastolic dysfunction (ie, impaired relaxation) was defined as $E/A \leq 0.75$.²¹ Increased volume status is a known confounder of diastolic function measurement. To ensure patients were euvolemic at the time of echocardiography, they must have had an $E/E' < 10$ and estimated pulmonary capillary wedge pressure < 10 mm Hg based on the Nagueh formula.²²

Clinical Endpoints

The primary endpoint of this study was the new diagnosis of heart failure and all-cause mortality. The new diagnosis of heart

failure was ascertained by ICD-9 code 428.0 from follow-up medical records. All-cause mortality data were ascertained from both the Social Security Death Index database and in-house death records through Clinical Looking Glass.

Statistical Analysis

Continuous variables are defined as mean and standard deviation. Categorical variables are defined as percentage. Comparison of variables among racial groups (non-Hispanic White, non-Hispanic Black, and Hispanic) was performed using a one-way analysis of variance for continuous variables and Pearson's chi-squared test for categorical variables. Cumulative incidence of heart failure and all-cause death were estimated using the Kaplan-Meier method. Univariate and multivariable adjusted Cox proportional hazard models were utilized to evaluate potential risk factors for heart failure and death. All variables collected in **Table 1** were adjusted in the multivariable models. Log-rank test was performed to compare the incident heart failure and patient survival by race. Due to the difference in patient characteristics among the racial groups, we performed a

sensitivity analysis to confirm our results by matching the groups using a propensity score-matched data set. All demographic and clinical variables in **Table 1** were utilized to construct the propensity scores. Multivariable adjusted Cox proportional hazards analysis was performed and log-rank test was utilized to compare the survival based on race. A *P*-value <.05 was considered significant. Analyses were performed with Stata Ver. 12 (StataCorp LP, College Station, TX).

RESULTS

Study Population

A total of 8483 patients who underwent echocardiography during the study period were found to have grade 1 diastolic dysfunction and left ventricular ejection fraction $\geq 50\%$. After removing patients with preexisting diagnosis of heart failure (*n* = 272), valvulopathy (*n* = 211), and atrial fibrillation (*n* = 133), 7878 patients were eligible for inclusion in the study. The population was highly diverse, with 20.8% (1636) non-Hispanic White; 35.8% (2824) non-Hispanic Black; 31.0%

Table 1 Characteristics of Study Population in Total and Between Races

Characteristics	Total	NH White	NH Black	Hispanic	<i>P</i> -Value	Missing Rate
<i>n</i>	7878	1636	2824	2443		
Age, y	68.0 ± 12.0	72.4 ± 11.6	66.9 ± 12.0	66.7 ± 11.6	<.001	0%
Men, %	37.3	44.5	32.8	35.3	<.001	0%
Social economic status, Z-score	-3.0 ± 2.9	-1.3 ± 2.5	-3.1 ± 2.7	-4.0 ± 2.7	<.001	3.5%
Comorbidities, %						
Hypertension	46.8	36.7	54.7	49.8	<.001	0%
Type 2 diabetes	37.5	27.2	40.5	40.9	<.001	0%
Myocardial infarction	12.0	15.2	9.1	12.1	<.001	0%
Peripheral vascular disease	10.4	10.9	11.4	9.2	.027	0%
Cerebral vascular disease	20.1	19.6	21.7	18.8	.028	0%
Pulmonary disease	25.7	25.5	25.4	27.8	.105	0%
Renal disease	12.9	9.5	17.4	11.0	<.001	0%
Malignancy	13.8	16.6	14.9	11.8	<.001	0%
Medications, %						
Beta-blocker	51.5	51.8	50.8	53.3	.189	0%
ACEI or ARB	54.5	54.8	54.8	55.1	.963	0%
Calcium channel blocker	40.4	41.4	39.7	40.6	.507	0%
Statins	50.7	50.3	50.9	52.3	.422	0%
Laboratory data, mean ± SD						
Hemoglobin, g/dL	12.3 ± 1.8	12.3 ± 1.8	12.3 ± 1.8	12.4 ± 1.8	.354	6.2%
Sodium, mEq/L	139.6 ± 2.9	139.5 ± 2.8	139.6 ± 2.8	139.6 ± 2.9	.139	4.8%
Potassium, mEq/L	4.2 ± 0.4	4.2 ± 0.4	4.2 ± 0.4	4.2 ± 0.4	.575	5.0%
BUN, mg/dL	20.5 ± 11.5	20.5 ± 11.5	20.6 ± 11.6	20.7 ± 11.6	.782	4.7%
Creatinine, mg/dL	1.3 ± 1.3	1.3 ± 1.4	1.3 ± 1.3	1.3 ± 1.3	.981	4.7%
Echocardiographic data						
LVEF, %	63.0 ± 6.0	62.2 ± 6.0	63.2 ± 6.5	62.4 ± 5.9	<.001	0%
Follow-up time to heart failure						
Median years	5.9	5.7	6.0	6.0		
Median person-years	42,193	8119	15,218	13,499		
Follow-up time to mortality						
Median years	6.3	6.1	6.3	6.3		
Median person-years	46,207	8914	16,635	14,928		

ACEI = angiotensin-converting enzymes inhibitor; ARB = angiotensin receptor blocker; BUN = blood urea nitrogen; LVEF = left ventricle ejection fraction; NH = non-Hispanic.

(2443) Hispanic; 1.5% (121) Asian; 8.6% (678) multiracial, native Hawaiian, or other Pacific Islander; and 2.2% (176) declined to respond (Table 1). Mean age was 68.0 ± 12.0 years and 37.3% patients were male. Hypertension was present in 46.8% of the population, 37.5% had diabetes mellitus, 12.0% had a history of myocardial infarction, 10.4% had peripheral vascular disease (PVD), 20.1% had known cerebral vascular disease, 25.7% had pulmonary disease, 12.9% had renal disease, and 13.8% had a history of malignancy. Mean left ventricular ejection fraction was $63.0 \pm 6.0\%$. The missingness rate for all variables was between 0% and 6.2%.

Differences Among Racial Groups at Baseline

We focused on 3 groups: non-Hispanic White, non-Hispanic Black, and Hispanic, in assessing differences among races (Table 1). Non-Hispanic White individuals were significantly older than non-Hispanic Blacks and Hispanics (mean age 72.4 years vs 66.9 and 66.7 years, respectively, $P < .001$). Only 32.8% and 35.3% patients were men in the non-Hispanic Black and Hispanic groups, respectively, whereas 44.5% of non-Hispanic Whites were men ($P < .001$). Non-Hispanic White individuals had a higher mean socioeconomic status (-1.3 ± 2.5) compared with non-Hispanic Blacks and Hispanics (-3.1 ± 2.7 and -4.0 ± 2.7 , respectively, $P < .001$). Hypertension, diabetes, and renal disease were more prevalent in non-Hispanic Blacks and Hispanics ($P < .001$ for all), however, non-Hispanic Whites had more antecedent myocardial infarction ($P < .001$). Non-Hispanic Blacks had greater left ventricular ejection fraction than non-Hispanic Whites and Hispanics (63.2 vs 62.2 and 62.4, $P < .001$).

Medication use and serological data were similar among the 3 racial groups.

Incident Heart Failure and Overall Survival

The median follow-up time of all patients in the time-to-heart-failure analysis was 5.9 years. The median follow-up time in the survival analysis was 6.3 years. The median follow-up time and person-years of each racial group are presented in Table 1. In total, 1356 patients had developed heart failure and 2078 patients died during the follow-up period. The 1-, 2-, 3-, 5-, and 10-year cumulative probabilities for heart failure were 5.9%, 8.8%, 11.3%, 15.7%, and 23.9%, respectively (Figure 1). The 1-, 2-, 3-, 5-, and 10-year cumulative probabilities for death were 9.3%, 12.9%, 16.2%, 21.8%, and 32.6%, respectively (Figure 2). Men and women had similar time to heart failure (Figure 2), but men died sooner than women ($P < .001$). Based on the log-rank test, non-Hispanic Whites developed heart failure slightly sooner than non-Hispanic Blacks and Hispanics ($P = .04$). Non-Hispanic Whites had the poorest survival compared with non-Hispanic Blacks or Hispanics ($P < .001$) (Figure 3).

Risk Factors for Heart Failure and Death

Results from the univariate analyses of the Cox proportional hazard models can be found in Supplementary Table 1 (Appendix, available online). On the adjusted regression analysis for incident heart failure, older age, diabetes, myocardial infarction, peripheral vascular disease, cerebral vascular disease, lung disease, renal disease, and malignancy

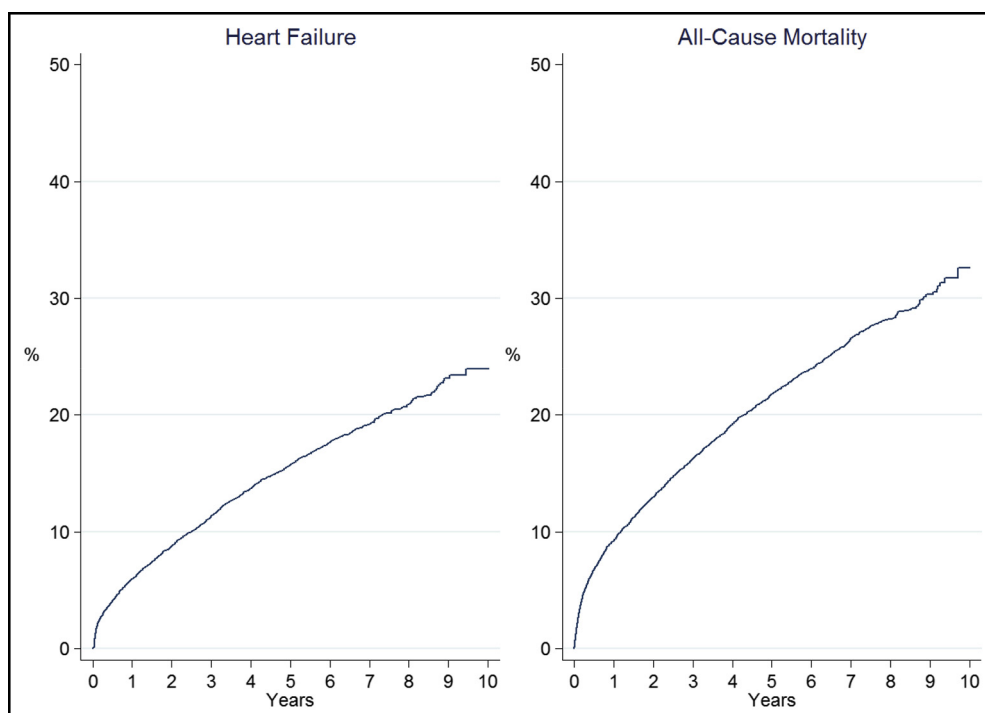


Figure 1 Cumulative probability of heart failure and all-cause death by Kaplan-Meier.

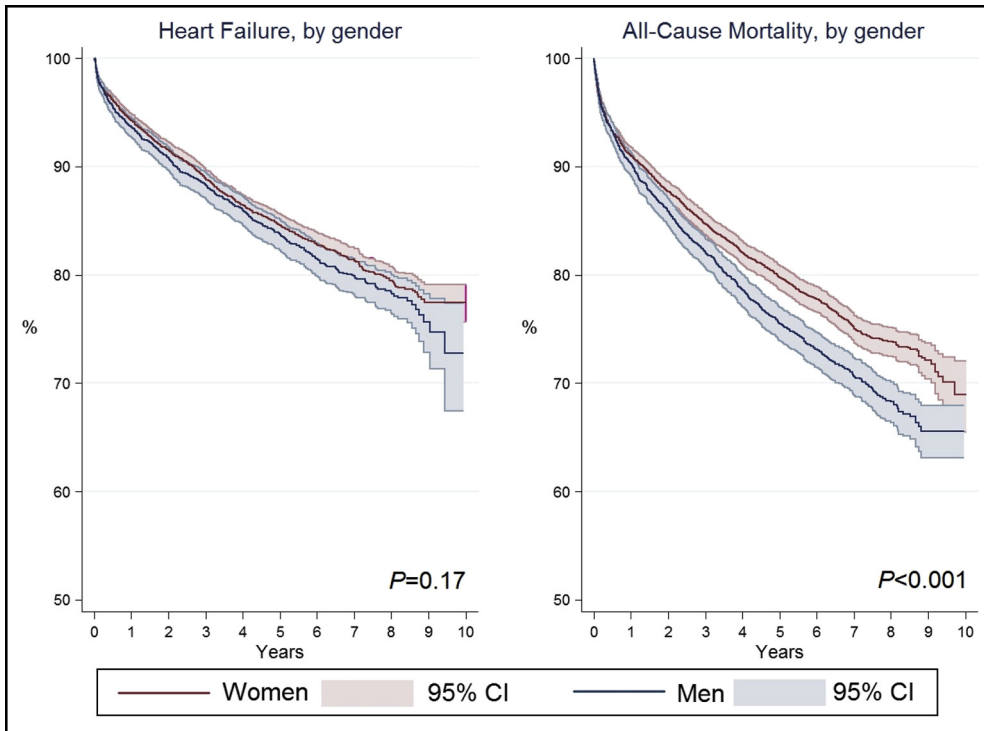


Figure 2 Survival curves of heart failure and all-cause death, by sex.

were independent predictors of heart failure (Table 2). Lower socioeconomic status (hazard ratio [HR] 1.02, per 1 SD below NY state mean; 95% confidence interval, 1.01-1.05; $P = .043$),

anemia (HR 1.30, per 1-mg/dL decrease, $P < .001$), hyponatremia (HR 1.04, per 1-mg/dL decrease, $P = .003$), and increased blood urea nitrogen levels (HR 1.01, per 1-mg/dL

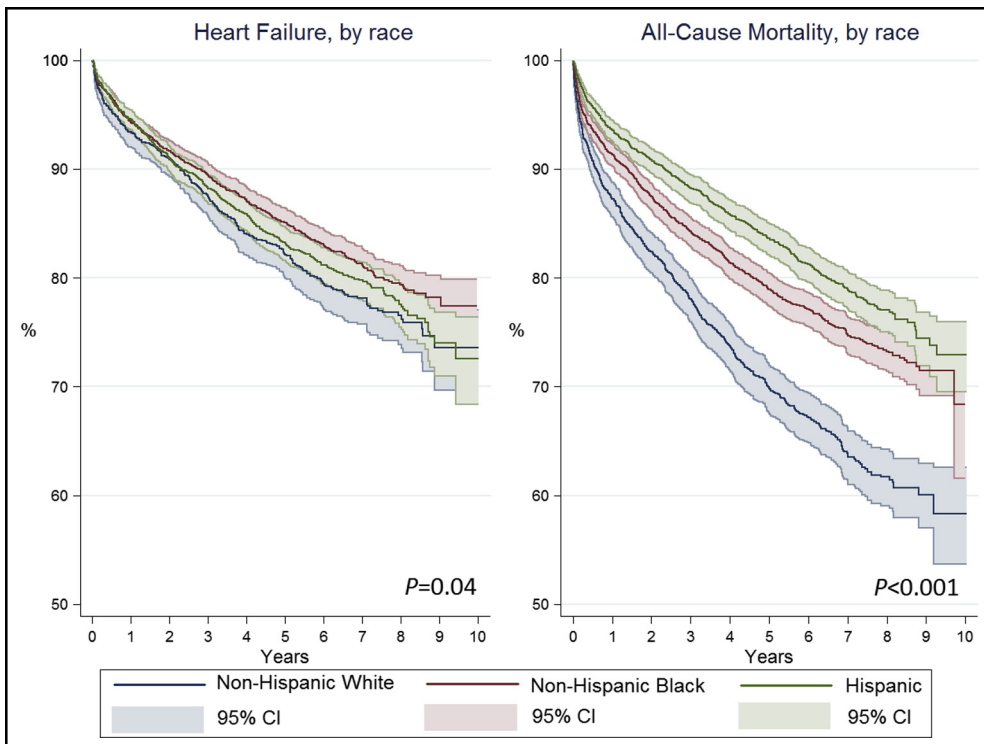


Figure 3 Survival curves of heart failure and all-cause death, by race.

Table 2 Multivariable Adjusted Cox Proportional Hazards Analysis for Heart Failure and All-Cause Death

Outcomes	Risk Factors	HR	95% CI	P Value	
Heart failure	Age, per 1 year increase	1.03	1.03-1.04	<.001	
	Lower SES, per 1 score decrease	1.02	1.01-1.05	.043	
	Diabetes	1.84	1.62-2.10	<.001	
	Myocardial infarction	1.64	1.39-1.94	<.001	
	Peripheral vascular disease	1.77	1.51-2.08	<.001	
	Cerebral vascular disease	1.24	1.07-1.43	.005	
	Lung disease	1.76	1.54-2.01	<.001	
	Renal disease	2.21	1.90-2.58	<.001	
	Any malignancy	1.43	1.20-1.70	<.001	
	Anemia, per 1g/dL decrease	1.30	1.12-1.52	<.001	
	Hyponatremia, per 1mEq/L decrease	1.04	1.01-1.03	.003	
	BUN, per 1mg/dL increase	1.01	1.00-1.02	.001	
	Death	Age, per 1 year increase	1.05	1.04-1.05	<.001
		Male	1.22	1.09-1.36	<.001
		Non Hispanic Black	0.80	0.69-0.92	.002
Hispanic		0.67	0.58-0.79	<.001	
Diabetes		1.41	1.26-1.57	<.001	
Myocardial infarction		1.19	1.03-1.38	.019	
Peripheral vascular disease		1.21	1.04-1.40	.014	
Cerebral vascular disease		1.39	1.23-1.57	<.001	
Lung disease		1.65	1.47-1.85	<.001	
Renal disease		1.71	1.49-1.95	<.001	
Any malignancy		2.57	2.28-2.91	<.001	
Anemia, per 1g/dL decrease		1.19	1.05-1.35	.004	

BUN = blood urea nitrogen; CI = confidence interval; HR = hazard ratio; SES = socioeconomic status.

increase, $P = .001$) were all independent predictors of heart failure (Table 2). No race was a significant predictor of heart failure.

On adjusted Cox regression analysis for all-cause mortality, older age, male sex, diabetes mellitus, myocardial infarction, peripheral vascular disease, cerebral vascular disease, lung disease, renal disease, malignancy, and anemia were independent predictors (Table 2). Compared with non-Hispanic White, non-Hispanic Black and Hispanic race were found to be protective (HR 0.80, $P = .002$; HR 0.67, $P < .001$, respectively).

Sensitivity Analysis

Due to the difference in patient characteristics among the 3 racial groups (Table 1), we performed a sensitivity analysis to

confirm our results by matching the 3 groups based on propensity scores (Supplementary Table 1; Appendix, available online). The time to heart failure was no longer significantly different among the 3 racial groups (log-rank $P = .24$). However, non-Hispanic Whites still experienced more all-cause mortality (log-rank $P = .009$) (Supplementary Figure 1; Appendix, available online). On adjusted regression analysis, no race conferred a higher risk of developing heart failure, but non-Hispanic Black and Hispanic race remained protective against mortality (HR 0.80, $P = .020$; HR = 0.65, $P < .001$, respectively).

DISCUSSION

Our study observed 7878 racially diverse patients with preclinical diastolic dysfunction for over 5 years and is the largest report on the impact of race on the progression of preclinical diastolic dysfunction to heart failure and overall survival. We found that race had little impact on the time to developing heart failure; however, non-Hispanic Whites with preclinical diastolic dysfunction had poorer overall survival compared with non-Hispanic Black and Hispanic individuals. Women with preclinical diastolic dysfunction had significantly better survival compared with men. We also identified multiple risk factors for the progression of preclinical diastolic dysfunction to heart failure and death, including: age, male sex, low socioeconomic status, anemia, hyponatremia, and malignancy.

Despite multiple reports on the prognostic value of preclinical diastolic dysfunction,^{5,23-25} the progression of preclinical diastolic dysfunction to heart failure and other clinical outcomes is not fully understood. Previous studies have been small and mainly populated with non-Hispanic White patients. The large, urban study population and longer follow-up time of the present study allowed for examination of various patient characteristics, comorbidities, and laboratory data. Consistent with a previous report by Vogel et al,²⁶ we found that individuals with preclinical diastolic dysfunction are commonly female, and the 3-year cumulative incidence of heart failure is approximately 11%. The 3-year mortality was much higher in the present study, 16.2%, vs 10.1% in Vogel's report,²⁶ but this is likely due to our population being older, having a lower mean socioeconomic status, and being hospital-based.²⁴⁻²⁹

Limited data exist on the difference of incident heart failure among non-Hispanic White, non-Hispanic Black, and Hispanic individuals. Previous large cohort studies, such as the Framingham study²⁷ and the Rotterdam study,²⁸ were composed of almost exclusively non-Hispanic White individuals with European ancestry. However, 3 large multi-racial population studies performed in the Chicago, Illinois area did allow for comparison of risk of heart failure across race. The Chicago Heart Association Detection Project In Industry (CHA)²⁹ cohort, The Atherosclerosis Risk In Communities (ARIC)³⁰ cohort, and the Cardiovascular Heart Study (CHS)³¹ cohorts examined a total of 39,578 adults, 5926 (15%) of whom were non-Hispanic Black. All 3 studies

used the same ICD-9 code (428.0) to define the endpoint of clinical heart failure, which allowed for a meta-analysis to be performed by Huffman et al.³² In this analysis, lifetime risk of heart failure was found to be similar between non-Hispanic White women and non-Hispanic Black women (32%-39% vs 24%-46%, respectively), and slightly higher in non-Hispanic White men compared with non-Hispanic Black men (32%-39% vs 20%-29%, respectively). In the present study, conducted in a hospital-based population with pre-clinical diastolic dysfunction, non-Hispanic White, non-Hispanic Black, and Hispanic individuals progress to heart failure at a similar rate. However, significantly worse survival was observed in non-Hispanic Whites. This difference in survival might be explained by the fact that non-Hispanic Blacks and Hispanics have been shown to have worse baseline indices of diastolic function than non-Hispanic Whites.³³ Therefore, it is possible that how we currently define grade I diastolic dysfunction may have different prognostic meaning across racial groups. Indeed, the normal values of diastolic function were developed based on data almost exclusively from non-Hispanic White populations, and non-Hispanic Black and Hispanic patients might require their own unique reference ranges.^{20,34,35}

Progression of Preclinical Diastolic Dysfunction is Influenced by Patient Comorbidities

In the general population, many comorbidities have been reported as risk factors for the development of heart failure, including: diabetes mellitus,³⁶ hypertension,⁴ peripheral vascular disease,³⁷ coronary heart disease,³⁸ renal dysfunction,²⁶ anemia,¹¹ and lung disease.¹¹ In a population of individuals with preclinical diastolic dysfunction, we confirmed the aforementioned comorbidities and we also observed a previously undescribed risk factor: hyponatremia. The association between hyponatremia at baseline with increased risk of heart failure later in life may indicate early inappropriate neurohormonal activation of the renin-angiotensin-aldosterone system and vasopressin system already occurring in these patients. It is well described that heart failure itself can lead to hyponatremia, however, the lack of clinical heart failure in our study population at the time of enrollment makes heart failure an unlikely cause. It may be a reflection of overall health and disease burden in our population that further supports the concept that heart failure is a systemic syndrome caused by many cardiac and noncardiac risk factors.³⁸

Limitations

Results of the present study should be interpreted with some limitations in mind. First, it was difficult to determine if patients continued following up in the same medical system after the initial echo. However, because the authors' institution is a part of a larger health network that serves the entire Bronx County, that does not discriminate based on ability to pay, it is reasonable to assume that the number of loss of follow-up was minimal and likely equal across racial

groups. Moreover, we ascertained the mortality data from the Social Security Death Index, which should not be affected by the location of follow-up. Second, the diagnosis of heart failure was ascertained through ICD-9 code 428.0, which potentially caused underestimation of the total cases of heart failure. However, this bias is evenly distributed among all patient groups, so it would not affect the comparison between groups. In addition, the ICD-9 code has been validated against the Framingham criteria for heart failure and it accurately identified 90% of cases.³⁹ Lastly, due to the retrospective nature of our study, some important information is missing, such as body mass index and indication for echo.

CONCLUSION

In this large, hospital-based, multiracial population with preclinical diastolic dysfunction, we observed a similar incidence of heart failure in non-Hispanic White, non-Hispanic Black, and Hispanic individuals, and a significantly worse survival in non-Hispanic Whites compared with non-Hispanic Black and Hispanic individuals. This suggests that an intrinsic heterogeneity in diastolic dysfunction, or the grading of diastolic dysfunction, exists across racial groups. In addition to race, preclinical diastolic dysfunction is more likely to progress to clinical heart failure in patients who are older, have lower socioeconomic status, hyponatremia, and multiple comorbidities. This highlights the profound impact of systemic illness on the progression of preclinical diastolic dysfunction to heart failure. Further study is warranted to fully describe the impact of patient comorbidities on the progression of preclinical diastolic dysfunction to heart failure and to confirm if the current grading system for diastolic dysfunction is applicable to non-Hispanic Black and Hispanic individuals.

References

- Loehr LR, Rosamond WD, Chang PP, Folsom AR, Chambless LE. Heart failure incidence and survival (from the Atherosclerosis Risk in Communities study). *Am J Cardiol*. 2008;101:1016-1022.
- Heidenreich PA, Albert NM, Allen LA, et al; American Heart Association Advocacy Coordinating Committee; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular Radiology and Intervention; Council on Clinical Cardiology; Council on Epidemiology and Prevention; Stroke Council. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. *Circ Heart Fail*. 2013;6(3):606-619.
- Go AS, Mozaffarian D, Roger VL, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2014 update: a report from the American Heart Association. *Circulation*. 2014;129:e28-e292.
- Kane GC, Karon BL, Mahoney DW, et al. Progression of left ventricular diastolic dysfunction and risk of heart failure. *JAMA*. 2011;306:856-863.
- Redfield MM, Jacobsen SJ, Burnett JC Jr, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. *JAMA*. 2003;289:194-202.
- Wan SH, Vogel MW, Chen HH. Pre-clinical diastolic dysfunction. *J Am Coll Cardiol*. 2014;63:407-416.

7. Bursi F, Weston SA, Redfield MM, et al. Systolic and diastolic heart failure in the community. *JAMA*. 2006;296:2209-2216.
8. Vasan RS, Larson MG, Benjamin EJ, Evans JC, Reiss CK, Levy D. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: prevalence and mortality in a population-based cohort. *J Am Coll Cardiol*. 1999;33:1948-1955.
9. Zile MR, Nappi J. Diastolic heart failure. *Curr Treat Options Cardiovasc Med*. 2000;2:439-450.
10. Yancy CW, Jessup M, Bozkurt B; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;62(16):e147-e239.
11. Lam CS, Lyass A, Kraigher-Krainer E, et al. Cardiac dysfunction and noncardiac dysfunction as precursors of heart failure with reduced and preserved ejection fraction in the community. *Circulation*. 2011;124:24-30.
12. Mureddu GF, Agabiti N, Rizzello V, et al; PREDICTOR Study Group. Prevalence of preclinical and clinical heart failure in the elderly. A population-based study in Central Italy. *Eur J Heart Fail*. 2012;14(7):718-729.
13. Abhayaratna WP, Marwick TH, Smith WT, Becker NG. Characteristics of left ventricular diastolic dysfunction in the community: an echocardiographic survey. *Heart*. 2006;92:1259-1264.
14. Bekwelem W, Lutsey PL, Loehr LR, et al. White blood cell count, C-reactive protein, and incident heart failure in the Atherosclerosis Risk in Communities (ARIC) Study. *Ann Epidemiol*. 2011;21:739-748.
15. Krieger N, Chen JT, Waterman PD, Rehkopf DH, Subramanian SV. Painting a truer picture of US socioeconomic and racial/ethnic health inequalities: the Public Health Disparities Geocoding Project. *Am J Public Health*. 2005;95:312-323.
16. Freeman K, Strauchler D, Miller TS. Impact of socioeconomic status on ionizing radiation exposure from medical imaging in children. *J Am Coll Radiol*. 2012;9:799-807.
17. Vegas A, Meineri M. Core review: three-dimensional transesophageal echocardiography is a major advance for intraoperative clinical management of patients undergoing cardiac surgery: a core review. *Anesth Analg*. 2010;110:1548-1573.
18. Teichholz LE, Kreulen T, Herman MV, Gorlin R. Problems in echocardiographic volume determinations: echocardiographic-angiographic correlations in the presence of absence of asynergy. *Am J Cardiol*. 1976;37(1):7-11.
19. Jessup M, Abraham WT, Casey DE, et al. 2009 focused update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation*. 2009;119:1977-2016.
20. Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *J Am Soc Echocardiogr*. 2009;22:107-133.
21. Daneshvar D, Wei J, Tolstrup K, Thomson LE, Shufelt C, Merz CN. Diastolic dysfunction: improved understanding using emerging imaging techniques. *Am Heart J*. 2010;160:394-404.
22. Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quinones MA. Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. *J Am Coll Cardiol*. 1997;30:1527-1533.
23. Desai CS, Colangelo LA, Liu K, et al. Prevalence, prospective risk markers, and prognosis associated with the presence of left ventricular diastolic dysfunction in young adults: the coronary artery risk development in young adults study. *Am J Epidemiol*. 2013;177:20-32.
24. Bella JN, Palmieri V, Roman MJ, et al. Mitral ratio of peak early to late diastolic filling velocity as a predictor of mortality in middle-aged and elderly adults: the Strong Heart Study. *Circulation*. 2002;105:1928-1933.
25. Carerj S, La Carrubba S, Antonini-Canterin F. Research Group of the Italian Society of Cardiovascular Echography. The incremental prognostic value of echocardiography in asymptomatic stage a heart failure. *J Am Soc Echocardiogr*. 2010;23(10):1025-1034.
26. Vogel MW, Slusser JP, Hodge DO, Chen HH. The natural history of preclinical diastolic dysfunction: a population-based study. *Circ Heart Fail*. 2012;5:144-151.
27. Lloyd-Jones DM, Larson MG, Leip EP, et al; Framingham Heart Study. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. *Circulation*. 2002;106:3068-3072.
28. Bleumink GS, Knetsch AM, Sturkenboom MC, et al. Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure The Rotterdam Study. *Eur Heart J*. 2004;25(18):1614-1619.
29. Stamler J, Dyer AR, Shekelle RB, Neaton J, Stamler R. Relationship of baseline major risk factors to coronary and all-cause mortality, and to longevity: findings from long-term follow-up of Chicago cohorts. *Cardiology*. 1993;82:191-222.
30. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. *Am J Epidemiol*. 1989;129:687-702.
31. Fried LP, Borhani NO, Enright P, et al. The Cardiovascular Health Study: design and rationale. *Ann Epidemiol*. 1991;1(3):263-276.
32. Huffman MD, Berry JD, Ning H, et al. Lifetime risk for heart failure among white and black Americans: cardiovascular lifetime risk pooling project. *J Am Coll Cardiol*. 2013;61:1510-1517.
33. Russo C, Jin Z, Homma S, et al. Race/ethnic disparities in left ventricular diastolic function in a triethnic community cohort. *Am Heart J*. 2010;160:152-158.
34. Evangelista A, Flachskampf F, Lancellotti P, et al; European Association of Echocardiography. European Association of Echocardiography recommendations for standardization of performance, digital storage and reporting of echocardiographic studies. *Eur J Echocardiogr*. 2008;9(4):438-448.
35. Klein AL, Burstow DJ, Tajik AJ, Zachariah PK, Bailey KR, Seward JB. Effects of age on left ventricular dimensions and filling dynamics in 117 normal persons. *Mayo Clin Proc*. 1994;69:212-224.
36. From AM, Scott CG, Chen HH. The development of heart failure in patients with diabetes mellitus and pre-clinical diastolic dysfunction a population-based study. *J Am Coll Cardiol*. 2010;55:300-305.
37. Correa de Sa DD, Hodge DO, Slusser JP, et al. Progression of preclinical diastolic dysfunction to the development of symptoms. *Heart*. 2010;96(7):528-532.
38. Ren X, Ristow B, Na B, Ali S, Schiller NB, Whooley MA. Prevalence and prognosis of asymptomatic left ventricular diastolic dysfunction in ambulatory patients with coronary heart disease. *Am J Cardiol*. 2007;99:1643-1647.
39. Roger VL, Weston SA, Redfield MM, et al. Trends in heart failure incidence and survival in a community-based population. *JAMA*. 2004;292:344-350.

APPENDIX

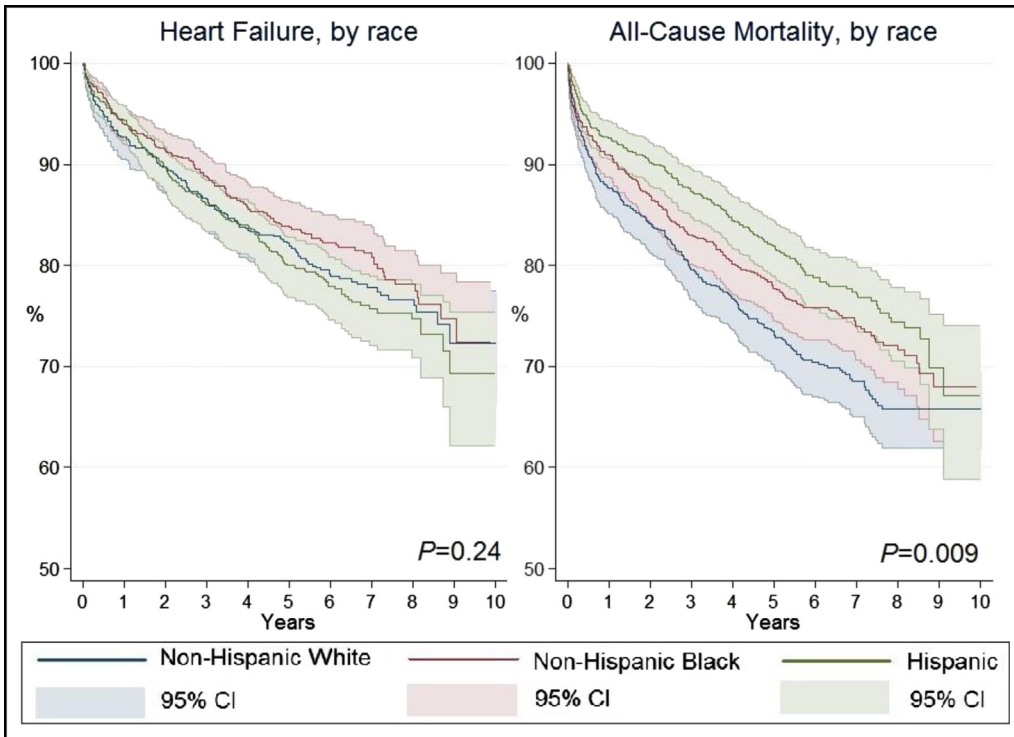
Supplementary table and figure accompanying this article can be found in the online version at <http://dx.doi.org/10.1016/j.amjmed.2015.08.036>.

APPENDIX

Supplementary Table 1 Characteristic of Propensity Score Matched Study Population, By Race

Characteristics	NH White n = 766	NH Black n = 766	Hispanic n = 766	P-Value
Age, y	69.8 ± 12.0	70.1 ± 10.8	70.1 ± 10.6	.780
Male sex, %	38.1	38.0	40.9	.429
Social economic status, Z score	-2.1 ± 2.5	-2.0 ± 2.1	-2.3 ± 2.2	.053
Comorbidities, %				
Hypertension	45.4	47.7	44.3	.400
Type 2 diabetes	34.2	34.6	35.4	.886
Myocardial infarction	12.7	12.4	13.6	.771
Peripheral vascular disease	8.4	11.1	11.2	.111
Cerebral vascular disease	19.1	19.7	19.8	.918
Pulmonary disease	26.0	24.8	26.1	.812
Renal disease	10.1	13.3	11.4	.133
Malignancy	14.4	15.9	14.6	.654
Laboratory data, mean ± SD				
BUN, mg/dL	20.3 ± 11.0	20.2 ± 10.6	20.4 ± 10.9	.945
Creatinine, mg/dL	1.3 ± 1.3	1.3 ± 1.2	1.3 ± 1.3	.968
Hemoglobin, g/dL	12.5 ± 1.7	12.6 ± 1.8	12.4 ± 1.7	.215
Sodium, mEq/L	139.7 ± 2.6	139.7 ± 2.7	139.7 ± 2.7	.874
Potassium, mEq/L	4.2 ± 0.4	4.2 ± 0.4	4.2 ± 0.4	.930
Medications, %				
Beta blocker	55.1	53.9	56.4	.621
ACEI or ARB	60.1	59.5	61.0	.845
Calcium channel blocker	44.3	44.8	43.7	.919
Statins	57.6	58.1	60.3	.512
Echocardiography data				
Ejection fraction, %	62.5 ± 5.9	62.6 ± 6.1	62.3 ± 5.8	.623

ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; BUN = blood urea nitrogen.



Supplementary Figure 1 Survival curves of heart failure, and all-cause death, by race in propensity score-matched population.