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ORIGINAL RESEARCH ARTICLE

Development and Validation of Machine Learning–Based Race-Specific Models to Predict 10-Year Risk of Heart Failure

A Multicohort Analysis

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BACKGROUND: Heart failure (HF) risk and the underlying risk factors vary by race. Traditional models for HF risk prediction treat race as a covariate in risk prediction and do not account for significant parameters such as cardiac biomarkers. Machine learning (ML) may offer advantages over traditional modeling techniques to develop race-specific HF risk prediction models and to elucidate important contributors of HF development across races.

METHODS: We performed a retrospective analysis of 4 large, community cohort studies (ARIC [Atherosclerosis Risk in Communities], DHS [Dallas Heart Study], JHS [Jackson Heart Study], and MESA [Multi-Ethnic Study of Atherosclerosis]) with adjudicated HF events. The study included participants who were >40 years of age and free of HF at baseline. Race-specific ML models for HF risk prediction were developed in the JHS cohort (for Black race–specific model) and White adults from ARIC (for White race–specific model). The models included 39 candidate variables across demographic, anthropometric, medical history, laboratory, and electrocardiographic domains. The ML models were externally validated and compared with prior established traditional and non–race-specific ML models in race-specific subgroups of the pooled MESA/DHS cohort and Black participants of ARIC. The Harrell C-index and Greenwood-Nam-D'Agostino χ^2 tests were used to assess discrimination and calibration, respectively.

RESULTS: The ML models had excellent discrimination in the derivation cohorts for Black (n=4141 in JHS, C-index=0.88) and White (n=7858 in ARIC, C-index=0.89) participants. In the external validation cohorts, the race-specific ML model demonstrated adequate calibration and superior discrimination (Black individuals, C-index=0.80–0.83; White individuals, C-index=0.82) compared with established HF risk models or with non–race-specific ML models derived with race included as a covariate. Among the risk factors, natriuretic peptide levels were the most important predictor of HF risk across both races, followed by troponin levels in Black and ECG-based Cornell voltage in White individuals. Other key predictors of HF risk among Black individuals were glycemic parameters and socioeconomic factors. In contrast, prevalent cardiovascular disease and traditional cardiovascular risk factors were stronger predictors of HF risk in White adults.

CONCLUSIONS: Race-specific and ML-based HF risk models that integrate clinical, laboratory, and biomarker data demonstrated superior performance compared with traditional HF risk and non–race-specific ML models. This approach identifies distinct race-specific contributors of HF.

Key Words: epidemiology ■ heart failure ■ machine learning ■ risk

Clinical Perspective

What Is New?

- Race-specific, machine learning–based heart failure (HF) risk models that integrate clinical, laboratory, and biomarker data demonstrate superior performance compared with traditional HF risk and non–race-specific machine learning models.
- Among the risk factors, natriuretic peptide levels were the most important predictors of HF risk across both races, followed by troponin levels, glycemic parameters, and socioeconomic factors in Black adults.
- The ECG-based measure of Cornell voltage and left ventricular hypertrophy, prevalent cardiovascular disease, and traditional cardiovascular risk factors were stronger predictors of HF risk in White adults.

What Are the Clinical Implications?

- The race-specific machine learning models for HF risk prediction can identify high-risk individuals who are most likely to benefit from effective approaches to HF prevention.
- Implementation and integration of race-specific machine learning–based models for HF risk prediction with electronic health record systems can improve the accessibility and real-world application of these tools.

Nonstandard Abbreviations and Acronyms

ARIC	Atherosclerosis Risk in Communities
BNP	B-type natriuretic peptide
CVD	cardiovascular disease
DHS	Dallas Heart Study
FPG	fasting plasma glucose
HF	heart failure
hs-cTn	high-sensitivity cardiac troponin
JHS	Jackson Heart Study
MESA	Multi-Ethnic Study of Atherosclerosis
ML	machine learning
NP	natriuretic peptide
NT-proBNP	N-terminal pro-B-type
oRSF	oblique random survival forest
PARP	population attributable risk percentage
PCP-HF	Pooled Cohort Equation to Prevent HF
VIMP	variable importance

Heart failure (HF) affects >64 million adults worldwide and accounts for nearly 6% of the total health care expenditure in North America and Europe.[1,2] As a result of the growing burden of cardiovascular risk factors such as obesity and diabetes and more prolonged survival after myocardial infarction and incident HF, the prevalence is expected to increase.[3] The lifetime risk of developing HF is 20% to 46% and varies substantially by race.[4,5] Race is a social construct and Black adults are more likely to develop HF compared with White individuals in large part because of structural racism, social inequality, poor health care access, and a greater downstream burden of cardiovascular risk factors such as hypertension and diabetes.[6–8] In addition, Black adults have a higher prevalence of subclinical phenotypes such as left ventricular hypertrophy and chronic myocardial injury assessed by high-sensitivity cardiac troponin (hs-cTn), which are associated with higher risk of HF.[9] In contrast, natriuretic peptide (NP) levels are lower among Black adults, further suggesting potential differences in the determinants of HF risk across racial groups.[10,11] After the development of HF, prognosis is poor and Black adults appear to have significantly higher risk of adverse events, particularly HF hospitalization, compared with other racial groups.[12] Thus, there is a global need for effective approaches to the prevention of HF, but the optimal strategies may differ by race.[13]

Risk stratification tools to identify individuals at higher risk for developing HF are available and can help target those at high risk with appropriate preventive strategies.[14–19] However, most existing HF risk prediction models do not include key prognostic markers such as hs-cTn and NP levels.[14,15,19] Furthermore, most existing HF risk prediction models, with the exception of the recently developed Pooled Cohort Equation to Prevent Heart Failure (PCP-HF) risk score,[19] are not race specific, have been developed in biracial or mixed ethnic cohorts, and incorporate race only as a covariate. Self-reported race as a covariate in such risk models may not completely capture the social and biological pathways that might predispose Black individuals to a higher risk of HF. In addition, current HF risk prediction tools were developed with classic statistical modeling techniques constrained by assumptions such as distribution normality, noninformative or random censoring, and hazard risk linearity.[20] Machine learning (ML) methods use large, multidimensional data efficiently and may improve HF risk prediction.

In the present study, we developed HF risk prediction models separately in Black participants and White participants as a strategy to better elucidate the importance of risk factors that may be most relevant to the development of HF across races. Specifically, using ML techniques incorporating clinical parameters, including biomarker data, we developed and externally validated race-specific risk models to predict the 10-year risk of incident HF in Black adults and White adults. We compared the performance of ML-based race-specific models to the established HF risk prediction models and non–race-specific ML model derived with race used as a covariate. We further identified the distinct associations

of several risk factors and clinical characteristics with HF development in Black adults and White adults.

METHODS

Requests to access the ARIC (Atherosclerosis Risk in Communities Study), DHS (Dallas Heart Study), JHS (Jackson Heart Study), and MESA (Multi-Ethnic Study of Atherosclerosis) data sets can be obtained by the respective study coordinating institutions. Details on the software code used in this study are provided in the Data Supplement and available from the corresponding author on reasonable request.

Study Population

The present study included individual-level data from 4 cohort studies: ARIC, DHS, JHS, and MESA. The study design, enrollment criteria, participant characteristics, and event adjudication for each cohort have been described previously and are discussed briefly in the Data Supplement.[21–25] For the present analysis, the initial (visit 1) phases of JHS (2000–2004), DHS (2000–2002), and MESA (2000–2004) and visit 4 for the ARIC cohort (1996–1998) are considered the baseline visits to allow similar follow-up time and consistent availability of biomarkers across cohorts. Adults <40 years of age or those with a history of HF at study baseline were excluded from each cohort (Figure I in the Data Supplement).

Race-specific HF risk prediction models were developed in a derivation cohort and subsequently externally validated (Figure 1). Data from JHS were used to derive the HF risk prediction model for Black participants. The HF risk prediction model for Black adults was validated in 2 separate cohorts of (1) a subset of Black participants from ARIC, excluding participants who were also enrolled from Jackson, MS, and were included in JHS; and (2) a pooled cohort of Black participants from MESA and DHS. The HF risk prediction model for White participants was developed using data from ARIC and externally validated among White participants from the pooled MESA/DHS data set. Written informed consent was obtained from all study participants, and local institutional review boards approved the study protocols. The present analysis was approved by the coordinating centers for each cohort and was considered exempt from institutional review board approval at the University of Texas Southwestern Medical Center, Dallas. The study followed the TRIPOD (Transparent Reporting of the Multivariable Prediction Model for Individual Prognosis or Diagnosis) and PROBAST (Prediction Model Risk of Bias Assessment Tool) reporting guidelines.[26,27]

Candidate Clinical Covariates

Participants from all 4 cohorts underwent comprehensive evaluations at the study baseline, including self-reported history, assessment of clinical and anthropometric characteristics by examination, and laboratory tests using standardized protocols as detailed in the Data Supplement. In the present analysis, 54 demographic, anthropometric, clinic, electrocardiographic, and laboratory variables assessed at the study baseline were considered candidate covariates. Categorical candidate variables were harmonized across study cohorts. Troponin was measured as hs-cTnT in MESA and DHS and as hs-cTnI in JHS and

ARIC cohorts with commercially available assays as reported previously.[28–31] NP levels were measured as BNP (B-type NP) in JHS and NT-proBNP (N-terminal pro-B-type NP) in ARIC, MESA, and DHS studies as reported previously.[29,30,32,33] NP and hs-cTn levels were each transformed into z scores as previously described to facilitate comparison across different assays.[34] In total, 39 predictor variables were included in the present analysis after the exclusion of 12 covariates for >20% missingness and 3 for correlation coefficient >0.70 (Table I in the Data Supplement).

Outcome of Interest

The primary outcome of interest for the present study was incident HF. Each cohort follow-up was landmarked at 1 year from baseline visit to account for reverse causation secondary to potential subclinical HF at study baseline. Each cohort had at least 10 years of follow-up for outcome assessment and HF end points were censored at 10 years. Incident HF events were identified by the first hospitalization event with HF in each of the study cohorts and adjudicated according to standardized protocols as described in the Data Supplement.

Model Development and Evaluation

HF risk prediction models were developed separately for Black (JHS cohort) and White participants (ARIC cohort). The derivation cohorts were randomly split into a training (50%) and testing (50%) data set. Imputation was performed on each data set separately using random forest imputation to prevent data leakage across cohorts.[35] The performance of the best-performing ML-based algorithms was further compared with that of models derived with a similar approach: (1) with only routine clinical covariates (age, sex, systolic blood pressure, diastolic blood pressure, heart rate, body mass index, smoking history, history of cardiovascular disease [CVD], history of diabetes); (2) clinical plus routine laboratory covariates (hemoglobin A1c, total cholesterol, high-density lipoprotein cholesterol); (3) with only NP levels and only hs-cTn levels as covariates; (4) model that was not race-specific and was developed using the overall cohort (ie, not derived separately for Black adults and White adults) with race as a covariate; and (5) model that was developed among individuals without any missing data on all the parameters. The analysis overview is shown in Figure 1.

ML-Based Methods

In the training data set, HF prediction models were developed incorporating the 39 covariates identified previously using the following 6 candidate ML-based and traditional Cox algorithms: (1) oblique random survival forest (oRSF), (2) forward stepwise Cox regression, (3) lasso Cox regression, (4) ridge Cox regression, (5) boosted Cox regression, and (6) gradient boosted trees. A brief description of each method is provided in the Data Supplement.

Variable Selection

Variable selection was performed to optimize the number of covariates included in the HF risk prediction model. While oRSF can be used for risk prediction, random forest methods can also be used in variable selection.[36] Permutation-based selection was performed to quantify variable importance (VIMP). Briefly, the values of a predictor variable were randomly
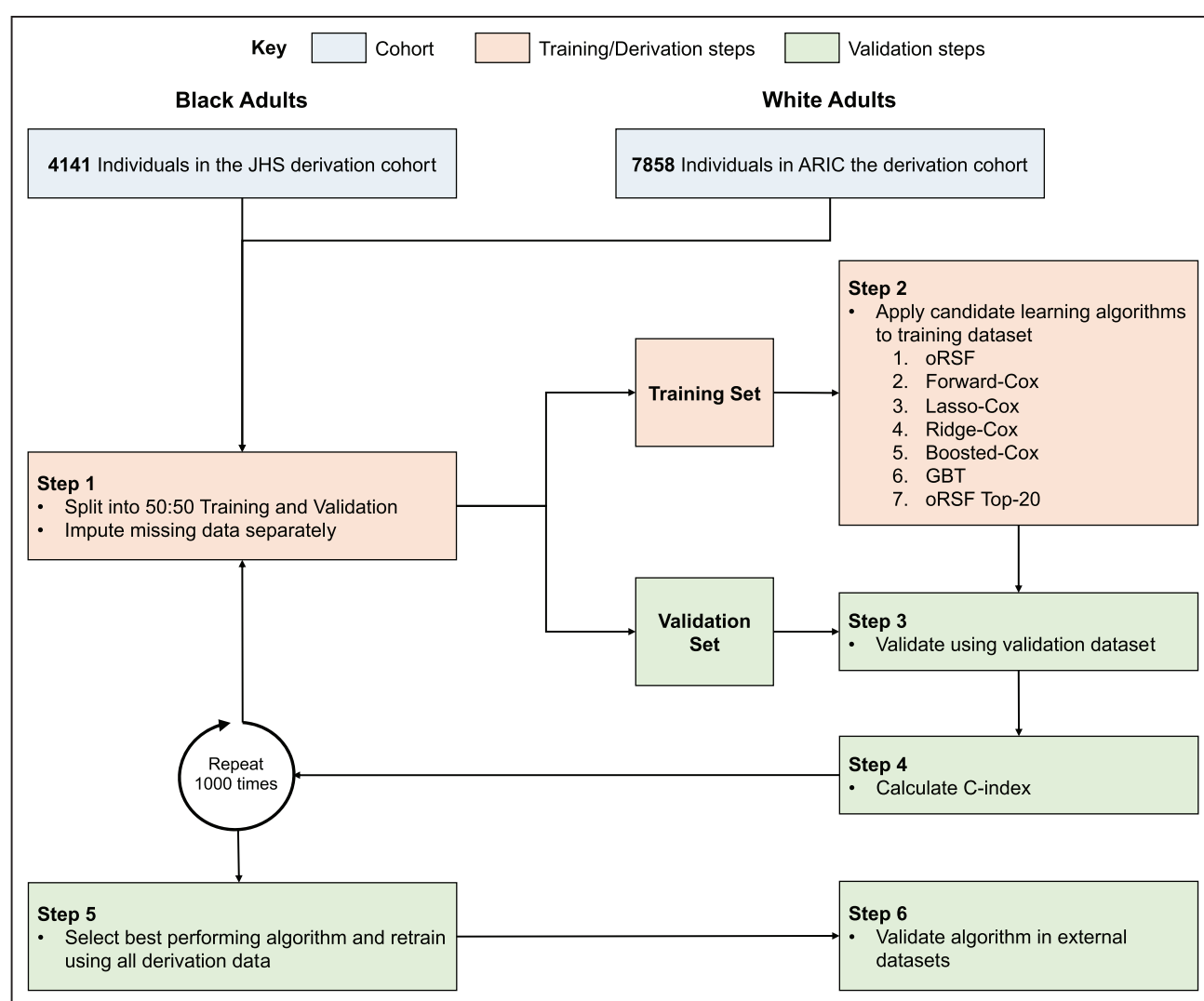
Figure 1. Analysis overview for identifying best-performing risk prediction model.
ARIC indicates Atherosclerosis Risk in Communities; GBT, gradient boosted trees; JHS, Jackson Heart Study; and oRSF, oblique random survival forest.

permuted and the importance of that variable was quantified by the resulting degradation in model prediction accuracy.[20] A high VIMP suggests that permutation of the variable worsens predictive accuracy and thus the variable is important in model prediction. Given the diminishing returns of model performance with additional covariates, the top 20 variables in Black adults and White adults separately with the highest VIMP metrics were included in the ML-based algorithm with the highest discrimination.[37]

Statistical Analysis

Internal validation in the development cohort was assessed with Monte Carlo cross-validation. The discriminatory performance of each model was evaluated in the validation data set (50% of the derivation cohort) by calculating the Harrell concordance index (C-index).[38] The data transformation, imputation, training, and testing steps were repeated 1000 times, with the final C-index reported as mean (95% CI). The DeLong test was used to evaluate for differences between C-indices.[39] Calibration of the HF risk prediction model with

the best discrimination was assessed with the Greenwood-Nam-D'Agostino (GND) statistic, with a value of $P>0.05$ indicating adequate calibration.[40]

External Validation

The best-performing HF risk prediction model in the internal validation data set was evaluated in external data sets. The ML model for Black adults was externally validated in 2 separate cohorts of Black participants from (1) ARIC (excluding Black individuals enrolled in JHS) and (2) pooled MESA/DHS data sets. The ML model for White adults was externally validated in White participants from the pooled MESA/DHS cohort. The performance of ML-based models was further compared with the following well-established traditional Cox regression–based HF risk prediction models: the ARIC-HF biomarker, the PCP-HF, and MESA-HF risk scores, each of which were developed in one of the external validation cohorts.[17–19] Last, decision curves, a measure of the clinical net benefit, were compared between the ML, ARIC-HF, PCP-HF, and MESA-HF models.[41] Decision curves measure the number of true-positive

cases identified without increasing the false-positive rate at a specific risk threshold.

Sensitivity Analysis

Several sensitivity and subgroup analyses were performed to assess the robustness of the ML-based race-specific HF risk prediction models. First, we compared the performance of the ML-based race-specific models in the other race (ie, White race–specific model in Black participants and vice versa) using discrimination, calibration metrics, and decision curve analysis. Second, to assess generalizability of the ML-based models in cohorts without biomarker data, we evaluated their performance in the validation cohorts with missing biomarker (NP and hs-cTn levels) data (ie, setting the biomarker values to missing). Third, sensitivity analyses were performed to assess the performance of the ML-based model in a primary prevention population, excluding individuals with baseline atherosclerotic CVD. Fourth, subgroup analyses were performed to evaluate the performance of the ML-based race-specific model in sex-based (men and women) subgroups. Last, the performance of the ML-based race-specific model was assessed to predict the risk of incident HF subtypes (HF with reduced ejection fraction and HF with preserved ejection fraction). For the HF subtype prediction analysis, the other HF subtype and mortality were considered as censoring events.

Contribution of Specific Risk Factors to Overall Risk Across Races

To determine the proportion of HF incidence attributable to specific HF risk factor burden across races, we used a Monte Carlo simulation of 1 million patients with risk factor burden similar to the that of the ARIC cohort in both Black adults and White adults. A detailed description is provided in the Data Supplement. The predicted risk of each patient in the simulated cohorts was calculated with the best-performing HF risk prediction model. The population attributable risk percentage (PARP) for each specific risk factor was estimated as the difference between the average risk in the unexposed group and the average risk in the overall population. For the PARP estimation, continuous variables were dichotomized into clinically meaningful categories using previously established cutoffs (BNP ≥30 pg/mL, NT-proBNP ≥125 pg/mL, hs-cTn ≥14 ng/L). Analyses were performed with R version 3.6.3, with a value of $P<0.05$ indicating statistical significance.

RESULTS

Study Cohort and Baseline Characteristics

The derivation cohort for Black adults and White adults consisted of 4141 participants from JHS and 7858 participants from ARIC, respectively (Figure I in the Data Supplement). MESA and the DHS contributed 1848 and 973 participants to the external validation cohort for Black adults (n=2821), respectively, and ARIC contributed 1024 participants. The external validation cohort for White adults (n=3236) consisted of 2595 participants from MESA and 641 participants from DHS. Dur-

ing a maximum follow-up of 10 years, there were 288 (7.0%; male, 99 [6.7%], female, 189 [7.1%]) and 634 (8.1%; male, 340 [9.4%], female, 294 [7.0%]) HF events among Black adults and White adults in the derivation cohorts, respectively. In the external validation cohort, 284 (7.4%; ARIC cohort, 169 [16.5%] and MESA/DHS, 115 [4.1%]) Black and 100 (3.1%) White participants developed HF over a maximum of 10 years of follow-up (Figure II in the Data Supplement).

Table 1 shows the baseline characteristics of Black participants and White participants across the derivation and validation cohorts. Black adults had a greater burden of cardiovascular risk factors, including a higher prevalence of hypertension and diabetes; higher body mass index, blood pressure, and fasting plasma glucose (FPG); and greater chronic myocardial injury burden than White adults (Table 1). Conversely, White adults were more likely to be male and had higher rates of renal dysfunction and smoking than Black adults.

Derivation of Prediction Models

The 39 predictor covariates incorporated into the risk prediction models included demographics, anthropometrics, vital signs, social history, clinical history, medications, laboratory, and electrocardiographic parameters (Table I in the Data Supplement). The C-indices for the ML-based race-specific HF risk prediction models are displayed in Table 2. Across both race groups, the oRSF model had the highest C-index of 0.88 (95% CI, 0.86–0.91) among Black adults and 0.89 (95% CI, 0.86–0.91) among White adults. Across both races, the forward stepwise Cox regression model had the lowest C-index (Black adults, 0.76 [95% CI, 0.71–0.80]; White adults, 0.77 [95% CI, 0.73–0.80]).

To improve clinical usability, we further constructed a model using the top 20 covariates identified by the VIMP metric in oRSF (Figure 2). Among Black adults, the C-index for the oRSF top 20 model was 0.88 (95% CI, 0.85–0.90) and was not significantly different from the oRSF model that included all 39 variables (DeLong $P=0.38$). Similarly, among White participants, discrimination of the oRSF model incorporating all covariates was not different from that of the model that included only the top 20 variables with the highest VIMP metrics (0.88 [95% CI, 0.85–0.90]; DeLong $P=0.22$). Thus, the oRSF top 20 model was identified as the best-performing model among Black adults and White adults (hereby referred to as the ML model).

The oRSF models derived using only routine clinical variables or clinical and laboratory parameters had a lower overall C index than the oRSF top 20 model (C-indices, 0.75–0.76; Table 3). In addition, oRSF models with biomarkers only (NP alone or hs-cTn alone) also had a lower overall C index than the oRSF top 20 (Table 3). Performance of the oRSF top-20 model was also superior to

Table 1. Baseline Characteristics of Black Adults and White Adults, by Derivation and Validation Cohorts

Variable	Black adults			White adults	
	Derivation cohort	Validation cohorts		Derivation cohort	Validation cohort
	JHS (n=4141)	ARIC (n=1024)	MESA/DHS (n=2821)	ARIC (n=7858)	MESA/DHS (n=3236)
Age, y	58.1 (10.5)	62.4 (5.9)	58.3 (10.4)	63.0 (5.6)	60.2 (10.8)
Male, n (%)	1468 (35.5)	412 (40.2)	1219 (43.2)	3633 (46.2)	1540 (47.6)
Heart rate, bpm	64.2 (10.5)	65.3 (11.5)	67.5 (12.2)	61.8 (9.7)	64.9 (10.5)
SBP, mm Hg	128.6 (16.7)	135.3 (20.4)	132.8 (21.2)	125.6 (18.1)	123.5 (19.3)
BMI, kg/m²	31.6 (6.9)	30.2 (6.6)	30.4 (6.3)	28.1 (5.1)	27.9 (5.4)
Hypertension, n (%)	2498 (60.3)	604 (59.4)	1277 (45.9)	2416 (30.9)	1001 (31.2)
Diabetes, n (%)	929 (22.7)	301 (30.7)	492 (17.5)	996 (12.7)	198 (6.1)
Cardiovascular disease, n (%)	397 (9.6)	65 (6.6)	132 (4.7)	542 (6.9)	34 (1.1)
Current smoker, n (%)	506 (12.3)	212 (21.4)	652 (23.2)	1093 (13.9)	448 (13.9)
Ever smoker, n (%)	1374 (33.2)	555 (55.9)	1502 (53.5)	4655 (59.3)	1761 (54.6)
Education level, n (%)					
Less than high school	880 (21.3)	366 (35.8)	399 (14.2)	1080 (13.8)	167 (5.2)
High school graduate/GED	750 (18.2)	246 (24.1)	871 (31.0)	2873 (36.6)	742 (23.0)
College/vocational	2492 (60.5)	409 (40.1)	1539 (54.8)	3897 (49.6)	2318 (71.8)
Income, n (%)					
<$25 000	1308 (31.6)	568 (55.5)	872 (35.4)	1751 (22.3)	485 (15.6)
$25 000–$49 999	962 (23.2)	216 (21.1)	802 (32.6)	2948 (37.5)	852 (27.4)
≥$50 000	1871 (45.2)	240 (23.4)	789 (32.0)	3159 (40.2)	1773 (57.0)
eGFR, mL·min⁻¹·1.73 m⁻²	92.1 (20.2)	91.6 (21.1)	90.7 (21.5)	84.9 (14.0)	78.3 (7.5)
FPG, mg/dL	100.6 (32.3)	114.5 (46.2)	103.5 (39.1)	106.5 (29.3)	92.6 (22.3)
HDL-c, mg/dL	52.4 (14.8)	53.7 (18.2)	52.4 (15.2)	49.3 (16.3)	51.8 (15.8)
Total cholesterol, mg/dL	201.7 (39.8)	199.4 (37.7)	187.4 (38.2)	201.6 (36.2)	194.2 (35.8)
BNP, pg/mL*	16.7 (2.7–19.9)	N/A	N/A	N/A	N/A
NT-proBNP, pg/mL*	N/A	49.1 (20.7–107.5)	43.5 (19.2–94.1)	69.5 (34.9–131.8)	99.1 (25.3–110.2)
Troponin, ng/L*†	6.0 (2.2–4.7)	6.1 (2.2–7.8)	6.9 (3.0–7.6)	6.5 (2.7–8.6)	5.7 (3–7)
QRS duration, ms	93.9 (14.2)	93.2 (15.5)	92.5 (12.2)	93.5 (14.1)	92.5 (12.2)
QTc duration, ms	426.8 (26.8)	423.2 (25.7)	427.1 (22.7)	419.9 (20.1)	427.1 (22.7)
Cornell voltage, microVolts	1502.4 (647.8)	1537.8 (656.2)	1193.4 (501.0)	1216.0 (506.1)	1193.4 (501.0)

Values are before imputation and displayed as mean (SD) when appropriate.

ARIC indicates Atherosclerosis Risk in Communities Study; BMI, body mass index; BNP, B-type natriuretic peptide; DHS, Dallas Heart Study; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; GED, General Educational Development; HDL-c, high-density lipoprotein cholesterol; JHS, Jackson Heart Study; MESA, Multi-Ethnic Study of Atherosclerosis; N/A, not applicable; NT-proBNP, N-terminal pro-B type natriuretic peptide; and SBP, systolic blood pressure.

*Displayed as median (quartile 1–quartile 3).

†Troponin was recorded as high-sensitivity cardiac troponin-I in JHS and ARIC and high-sensitivity troponin-T in MESA and DHS.

that of the non–race-specific model derived in the overall cohort including race as a covariate (Table 2). Last, in a cohort of participants with no missing data (n=10 053, 83.8% of the derivation cohort), the complete data oRSF top 20 model performed similarly to the oRSF top 20 model with missing data (Table 3).

External Validation of Prediction Models Among Black Adults

Among Black adults, the overall C-index for the ML risk score was high in both external validation cohorts (ARIC,

0.80 [95% CI, 0.75–0.84]; MESA/DHS, 0.83 [95% CI, 0.77–0.87]; Table 4). Discrimination and calibration were acceptable in a cohort with missing biomarker data (Table II in the Data Supplement). The ML risk score performance was also superior to other HF risk scores (ARIC-HF, MESA-HF, and PCP-HF) in external cohorts, including those that were used to derive these models (Table 4). Calibration was adequate for the ML model in both the ARIC and MESA/DHS validation cohorts. In contrast, the ARIC-HF and PCP-HF risk scores demonstrated good calibration among Black participants from the ARIC cohort but not in the pooled cohort of MESA/

Table 2. Discrimination of the Models for Predicting 10-Year Risk of Developing Heart Failure in the Derivation Cohort Among Black Adults and White Adults

	Race specific							Not race specific
	oRSF	oRSF with top 20 most important variables	Forward stepwise Cox regression	Lasso Cox regression	Ridge Cox regression	Boosted Cox regression	GBT	oRSF*
Black adults	0.88 (0.86–0.91)	0.88 (0.85–0.90)	0.76 (0.71–0.80)	0.80 (0.75–0.84)	0.81 (0.50–0.85)	0.81 (0.74–0.87)	0.86 (0.84–0.89)	0.81 (0.78–0.83)
White adults	0.89 (0.86–0.91)	0.88 (0.85–0.90)	0.77 (0.73–0.80)	0.78 (0.55–0.84)	0.78 (0.50–0.82)	0.82 (0.71–0.87)	0.87 (0.85–0.90)	0.80 (0.76–0.85)

Data presented are C-index values (95% CIs). CIs are the 95% ranges among 1000 bootstrapped replicates. orSF indicates oblique random survival forest; and GBT, gradient boosted trees.

*Race was included as a covariate in the model.

DHS (Figure 3A and 3B). The MESA-HF risk score demonstrated adequate calibration in Black participants from both external validation cohorts (Figure 3A and 3B). In decision curve analysis, the ML model increased the number of HF events detected by 12, 17, and 19 per 1000 patients compared with the ARIC-HF, PCP-HF, and MESA-HF risk scores in the ARIC validation cohort (Figure III in the Data Supplement). Similarly, in the pooled MESA/DHS validation cohort, the ML model detected an additional 6, 2, and 5 HF events per 1000 patients compared with the ARIC-HF, PCP-HF, and MESA-HF risk scores (Figure III in the Data Supplement). In a primary prevention cohort of individuals without CVD, the ML model demonstrated improved discrimination and calibration compared with the other established risk scores (Table III in the Data Supplement).
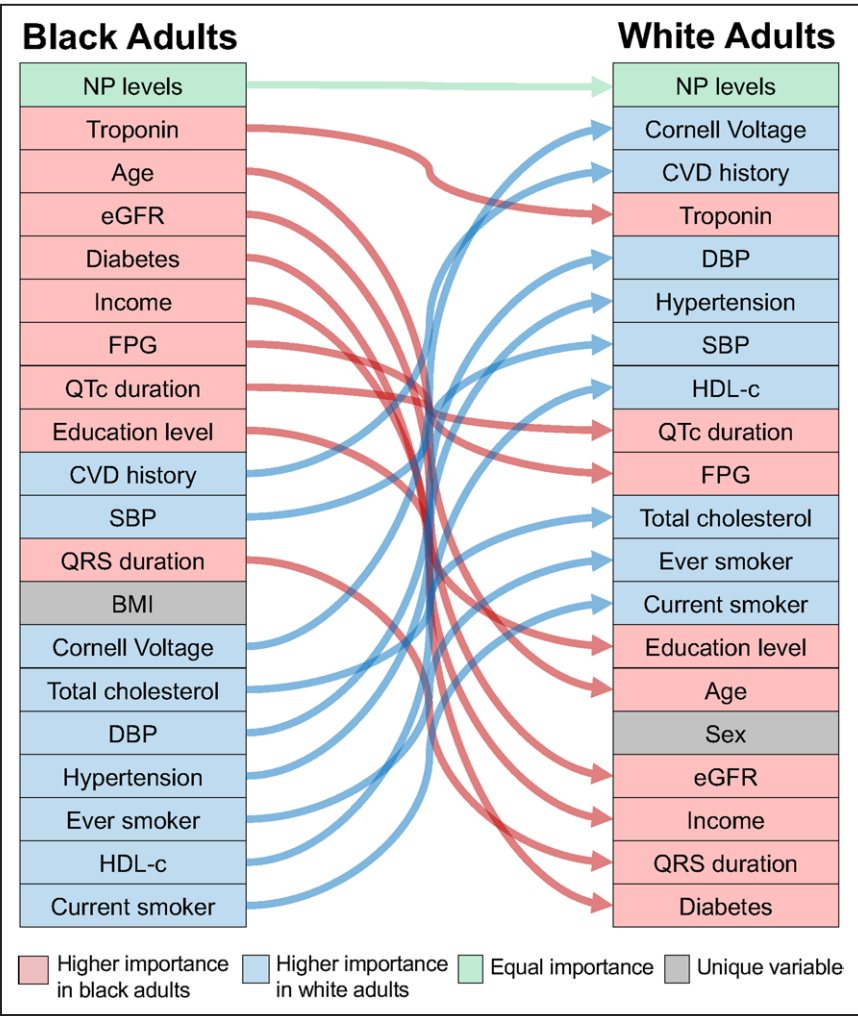
Figure 2. Alluvial plot of the 20 most important parameters for HF risk prediction identified by the variable importance metric in the oblique random survival forest model in the derivation cohort.
BMI indicates body mass index; CVD, cardiovascular disease; DPB, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HDL-c, high-density lipoprotein cholesterol; HF, heart failure; NP, natriuretic peptide; and SBP, systolic blood pressure.

Table 3. Discrimination of the Reference Machine Learning Clinical Variables, Natriuretic Peptide Only, Troponin Only, and Complete Data Models for Predicting 10-Year Risk of Developing Heart Failure in the Derivation Cohort Among Black Adults and White Adults

	Top 20 (reference)	Clinical variables	Clinical+laboratory variables	NP only	Troponin only	Complete data
Black adults	0.88 (0.85–0.90)	0.75 (0.73–0.78)	0.75 (0.73–0.78)	0.70 (0.66–0.74)	0.70 (0.66–0.72)	0.88 (0.85–0.90)
White adults	0.88 (0.85–0.90)	0.76 (0.71–0.80)	0.76 (0.71–0.81)	0.64 (0.61–0.66)	0.69 (0.66–0.71)	0.88 (0.85–0.90)

Data presented are C-index values (95% CIs). The following models were analyzed: race-specific oblique random survival forests (oRSF) with the top 20 most important variables (reference), oRSF with only clinical variables (age, sex, systolic blood pressure, diastolic blood pressure, heart rate, body mass index, smoking history, history cardiovascular disease, history of diabetes), oRSF with clinical and laboratory variables (clinical variables+hemoglobin A1c, total cholesterol, high-density lipoprotein cholesterol), oRSF with natriuretic peptide levels only, oRSF with troponin levels only, and oRSF with complete data (ie, no missing data). Of the 11 999 participants in the derivation cohort, 10 053 (83.8%) had no missing data. CIs are the 95% ranges among 1000 bootstrapped replicates.

External Validation of Prediction Models Among White Adults

In the external validation cohort of pooled White participants from DHS and MESA, the ML risk score had the greatest discrimination as assessed by the C index of 0.82 (95% CI, 0.78–0.86), followed by the MESA-HF, ARIC-HF, and PCP-HF risk scores (Table 4). Only the ML and MESA-HF risk scores had adequate calibration with similar predicted and observed risk of HF (*P*>0.05; Figure 3C). In decision curve analysis, the ML model detected an additional 3, 6, and 4 HF events per 1000 patients compared with the ARIC-HF, PCP-HF, and MESA-HF risk scores (Figure III in the Data Supplement). Discrimination and calibration were also acceptable in a cohort with missing biomarker data (Table II in the Data Supplement). In a primary prevention cohort of individuals without CVD, the ML model demonstrated improved discrimination and calibration compared with the other established risk scores (Table III in the Data Supplement).

Performance of Black Race–Specific and White Race–Specific Models in the Validation Cohort of the Other Race

We evaluated the performance of the race-specific models in the other race (ie, White model in Black participants and vice versa) in the MESA/DHS external validation cohort. The discriminatory performance (C-index) of race-specific models was superior in race-concordant versus race-discordant cohorts (C-index of the Black model in Black versus White participants, 0.83 versus 0.80; C-index of the White model in White versus Black participants, 0.82 versus 0.78). Similarly, validation in race-discordant cohorts resulted in significant miscalibration (Greenwood-Nam-D'Agostino *P*<0.05 for all; Table IV in the Data Supplement). In decision curve analysis, Black race–specific models detected an additional 6 cases per 1000 participants in the Black versus White cohort. Similarly, the White race–specific model detected an additional 4 cases per 1000 participants in the White versus Black cohort (Figure IV in the Data Supplement).

Performance of ML-Based Race-Specific Models in Sex- and HF Subtype–Based Groups

In sex-based subgroup analysis, the race-specific models demonstrated good and comparable performance in men and women across both races in the validation cohorts (Table V in the Data Supplement). For the HF subtype outcomes, the Black race–specific model performed well in predicting risk of HF with reduced ejection fraction (C index, 0.84 [95% CI, 0.79–0.90]) and HF with preserved ejection fraction (C index, 0.82 [95% CI, 0.76–0.87]) in the MESA/DHS validation cohort (Table V in the Data Supplement). Similarly, the White race–specific model demonstrated good performance in predicting the risk of HF with reduced ejection fraction (C-index, 0.83 [95% CI, 0.77–0.89]) and HF with preserved ejection fraction (C-index, 0.79 [95% CI, 0.74–0.85]) in the MESA/DHS cohort.

Differences in Predictors of HF Risk in Black Versus White Adults

The variables identified as the top 20 most important parameters for HF risk prediction according to VIMP in Black adults and White adults are displayed in an alluvial plot in Figure 2. The key variables for predicting HF risk were mostly the same for both race groups except for body mass index, which was included only in the Black race model, and sex, which was part of only the White race model. NP level was the most important parameter in HF risk prediction for both race groups, followed by hs-cTn levels in Black individuals and electrocardiographic left ventricular mass measure (Cornell voltage) in White individuals. Estimated glomerular filtration rate, cardio-metabolic parameters (presence of diabetes, FPG), and socioeconomic characteristics (education and income levels) were more important predictors of HF risk in Black versus White adults. The other important predictors of HF risk in White adults included prevalent CVD, traditional CVD risk factors (hypertension, blood pressure levels, high-density lipoprotein cholesterol), and hs-cTn levels.

Among Black individuals, the highest PARP for incident HF was noted for elevated NP levels (NT-proBNP ≥125 pg/mL; PARP, 21.1%), followed by cardiac troponin (hs-TnI ≥14 ng/L; PARP, 12.2%), annual income (upper

Table 4. Discrimination and Calibration of the Models for Predicting 10-Year Risk of Developing Heart Failure in the Validation Cohorts Among Black Adults and White Adults

	ARIC			MESA/DHS		
	C-index (95% CIs)	GND χ² (*P* value)	DeLong test (*P* value)*	C-index (95% CIs)	GND χ² (*P* value)	DeLong test (*P* value)*
Black adults						
ML risk score	0.80 (0.75–0.84)	10.1 (0.26)	Ref	0.83 (0.77–0.87)	11.7 (0.17)	Ref
ARIC-HF risk score	0.77 (0.73–0.80)	8.9 (0.35)	<0.001	0.80 (0.76–0.84)	29.8 (<0.001)	0.01
PCP-HF risk score	0.73 (0.69–0.77)	14.4 (0.07)	<0.001	0.75 (0.71–0.79)	16.1 (0.04)	<0.001
MESA-HF risk score	0.72 (0.67–0.75)	6.9 (0.55)	<0.001	0.78 (0.74–0.82)	6.0 (0.54)	0.006
White adults						
ML risk score	N/A			0.82 (0.78–0.86)	9.9 (0.27)	Ref
ARIC-HF risk score				0.79 (0.76–0.81)	25.5 (0.001)	0.008
PCP-HF risk score				0.75 (0.71–0.79)	19.1 (0.01)	<0.001
MESA-HF risk score				0.80 (0.76–0.83)	8.33 (0.40)	0.044

ARIC indicates Atherosclerosis Risk in Communities; DHS, Dallas Heart Study; GND, Greenwood-Nam-D'Agostino; HF, heart failure; JHS, Jackson Heart Study; MESA, Multi-Ethnic Study of Atherosclerosis; ML, machine learning; N/A, not applicable; PCP-HF, Pooled Cohort Equations-Heart Failure; and Ref, reference.

*The DeLong test of C-index compared with the ML risk score model.

middle or above, 11.7%), and cardiometabolic parameters (FPG ≥140 mg/dL, 9.5%; presence of diabetes, 8.6%; Figure 4). Among White individuals (versus Black individuals), the PARP for incident HF associated with cardiac biomarkers was more modest (NT-proBNP ≥125, 17.9%; hs-cTn ≥14 ng/L, 6.8%), lower than that associated with other risk factors such as FPG ≥140 mg/dL (4.3%) and annual income (7.4%), and higher among current smoking (9.1%) and left ventricular hypertrophy (8.0%; Figure 4).

DISCUSSION

In this individual-level analysis of 4 prospective cohort studies, we developed and validated race-specific ML-based models to predict the 10-year risk of incident HF. We evaluated 6 unique ML-based algorithms and identified the oRSF model as the best-performing HF risk prediction tool with excellent discrimination and calibration in external validation cohorts and improved performance compared to previously developed risk scores. We similarly observed that ML models derived with race used as a covariate have inferior performance compared with race-specific models. Using ML to identify the most important predictors of HF risk across racial groups, we noted differences in the risk factor profiles and relative importance and contribution of key predictors to the overall risk among Black adults and White adults. The present study supports the use of the ML model to identify Black individuals and White individuals at higher risk for developing HF who may benefit from effective preventive strategies. To improve the clinical utility of our study, we implemented the ML model on a publicly available website[42] (Figure V in the Data Supplement).

HF Risk Prediction and Use of ML

A critical component of population-based strategies for preventing HF is identifying the highest-risk individuals
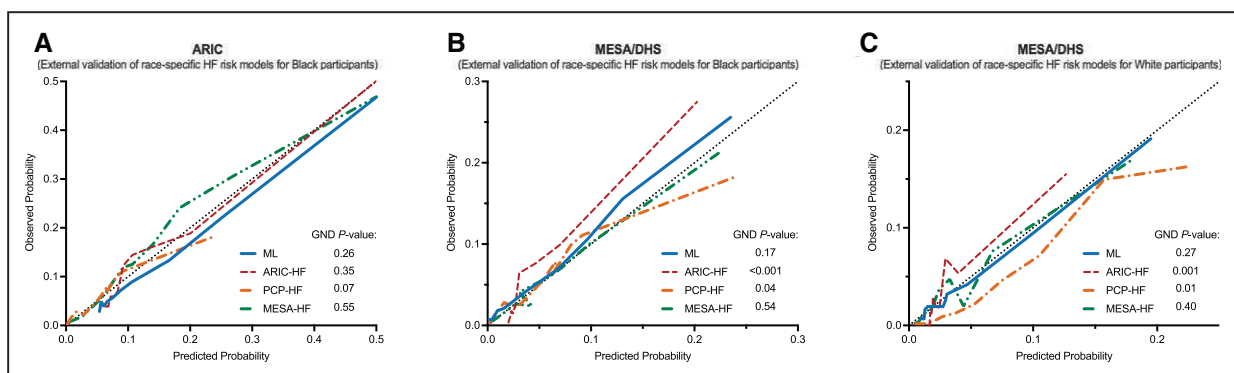
Figure 3. Calibration of the models for predicting 10-year risk of developing HF in Black adult and White adult cohorts.
A, Black participants in the ARIC cohort, Black participants in the pooled MESA/DHS cohort (**B**), and White participants in the pooled MESA/DHS validation cohort (**C**). ARIC indicates Atherosclerosis Risk in Communities; DHS, Dallas Heart Study; GND, Greenwood-Nam-D'Agostino; HF, heart failure; MESA, Multi-Ethnic Study of Atherosclerosis; ML, machine learning; and PCP, Pooled Cohort Equations.
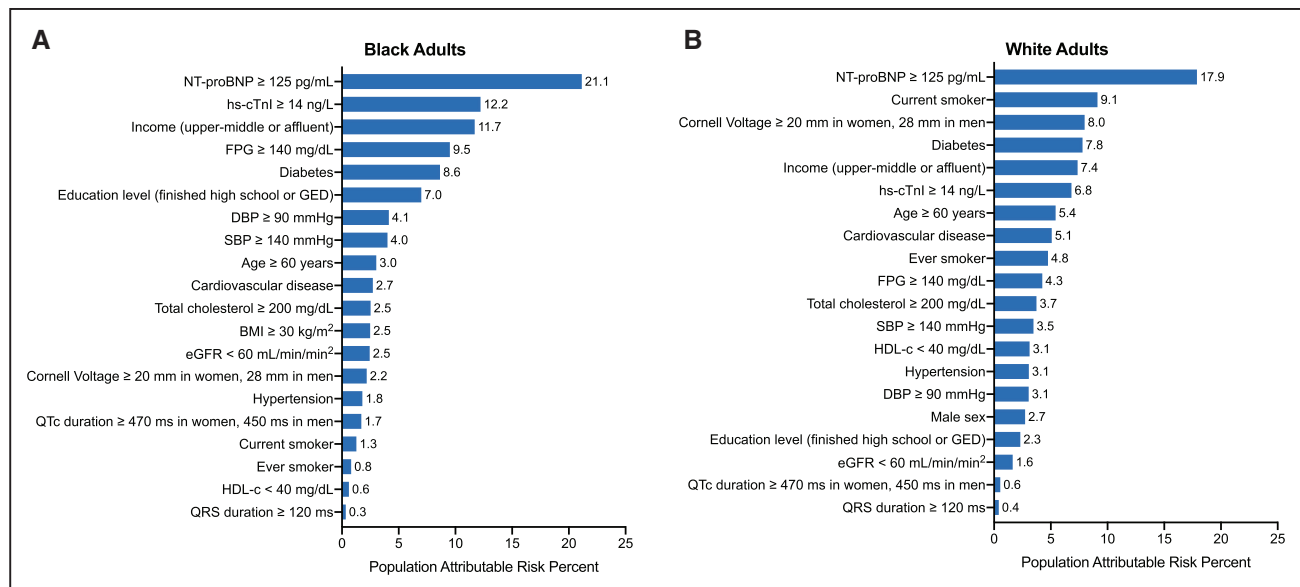
Figure 4. Results of the Monte Carlo simulation to calculate the population attributable risk percent of each covariate among Black adults and White adults.
Simulation values were obtained on the basis of patient characteristics from Black adults (**A**) and White adults (**B**) from the ARIC cohort. The referent group was the group opposite the listed cutoff. ARIC indicates Atherosclerosis Risk in Communities Study; BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; GED, General Educational Development; HDL-c, high density lipoprotein cholesterol; hs-cTnI, high-sensitivity cardiac troponin I; NT-proBNP, N-terminal pro-B type natriuretic peptide; and SBP, systolic blood pressure.

who may be targeted with effective preventive approaches. HF risk scores were previously developed in selected populations, including predominantly White adults in the Framingham Heart Study, older individuals in the Health ABC study (Health, Aging, and Body Composition), and more recently among adults with no history of CVD in the PCP-HF study.[14,15,19] Recent studies included more diverse populations and incorporated traditional risk factors into Cox models to estimate HF risk.[16,18] Model performance has improved with the inclusion of biomarkers, specifically NT-proBNP in the ARIC-HF and MESA-HF models.[16–18] However, traditional statistical modeling with Cox proportional hazard regression is unable to include nonlinear outcomes or missing or correlated variables.

ML uses less stringent techniques that allow for the inclusion of large amounts of multidimensional data and has been shown to predict adverse events in population-based cohort studies.[43] Furthermore, ML models are better equipped to handle missing data on covariates and nonlinear interactions between covariates compared with traditional Cox models. In the current study, of 54 candidate covariates, 39 variables were incorporated into risk prediction models. Although all 6 ML-based algorithms had excellent discrimination for HF risk prediction, the oRSF model had the best performance. The oRSF model incorporating the top 20 most important predictors of HF risk, which included clinical parameters and cardiac biomarkers, outperformed previously established risk prediction tools. The oRSF top 20 model outperformed traditional models, including those developed in

the external validation cohorts, and included biomarkers as covariates (ARIC and MESA HF risk score).

Need for Race-Specific HF Risk Scores

Despite differences in HF epidemiology across races, most traditional HF risk prediction tools are not race specific and incorporate self-reported race as a covariate adjustment in the risk prediction equation.[16] Self-reported Black race is a heterogeneous entity and a surrogate marker for several factors, including but not limited to genetics, socioeconomic status, cultural elements, and often unmeasured societal experiences related to structured racism.[44,45] The disproportionately higher risk of HF and other adverse outcomes in Black individuals is related to the downstream effects of all these components, which may not be adequately accounted for by adjusting for race in the risk models. Accordingly, there is a growing consensus to move away from race as a risk predictor approach.[46] In the present study, we developed and validated HF risk prediction models in Black participants and White participants separately as a strategy to better elucidate the importance of risk factors that may be most relevant to development of HF in Black individuals. The ML-based race-specific HF risk models developed in this study included individuals with and without baseline CVD and complement the existing race- and sex-specific Cox-model based PCP-HF risk score, which is focused on the primary prevention population.[19] The ML-based race-specific models demonstrated superior performance in

the race-concordant validation cohorts compared with validation in the other race. Furthermore, the race-specific ML model for HF risk demonstrated superior performance than non–race-specific ML models that included race as a covariate. Overall, these findings highlight the prognostic utility of race-specific risk assessment for HF.

HF Risk Factors and Relative Differences Among Black Adults and White Adults

In addition to providing a race-specific HF risk stratification tool, our study provides key insights into the differences in the risk factors for HF development among Black versus White adults. Across both races, we observed that NP levels were the most important predictor of HF risk. Biomarkers of chronic myocardial injury were a more important risk predictor in Black versus White individuals. Furthermore, the PARP associated with cardiac biomarkers for HF risk was higher in Black than in White individuals. This is particularly noteworthy because among Black individuals chronic myocardial injury is more prevalent and has been associated with a disproportionately higher risk of HF.[28] Socioeconomic factors such as income and cardiometabolic parameters (FPG, presence of diabetes) were also of higher importance and associated with higher PARP for incident HF among Black versus White individuals.

Besides differences in relative importance of predictor variables shared across both race-specific models, there were unique variables identified as key predictors of HF risk in Black versus White adults. Sex was identified as a significant predictor variable only in White individuals, and body mass index was a significant for incident HF only in Black individuals. These differences may be related to differences in the epidemiology of HF development in Black versus White adults. For example, as noted in our study and by others,[6] sex differences in risk of HF in Black adults are more modest compared with those noted among White adults, likely because of high baseline risk of HF among Black women.[9] This may explain why sex is one of the top predictors of HF risk only in the White race model.[6] It is also plausible that the contribution of certain factors to HF risk may be accounted for by other covariates and the interactions between covariates. For example, the contribution of female sex to HF risk in Black individuals may be accounted for by body mass index and other cardiometabolic parameters, which are already in the model.[47,48]

Role of Biomarkers in Risk Prediction Using ML-Based Models

Our ML-based models also highlight the role of biomarker assessment, in addition to routinely captured clinical risk factors, for improved risk stratification. Across both race groups, NP levels were identified as the single most important predictor of HF risk. In addition, hs-cTn was a significant predictor of HF risk, but more so in Black versus

White adults. We observed improved discrimination with the oRSF top 20 model compared with the ML models with clinical parameters only and those with biomarkers only. This is particularly important because high-sensitivity assays for troponin are currently available and can be routinely assessed in outpatient setting. In addition, the 2017 American College of Cardiology/American Heart Association HF focused update recommends NP screening as part of an HF prevention strategy.[49] Complementing our study findings, previous studies have also demonstrated the utility of cardiac biomarkers in identifying individuals with risk factors such as hypertension, diabetes, and prediabetes who may be at a higher risk of developing HF and may benefit from targeted preventive strategies.[50,51] However, cardiac biomarkers may not be routinely available among all at-risk participants, particularly those without existing CVD. The ML models demonstrated robust performance in subgroups with missing biomarker data and among individuals without CVD at baseline, highlighting their generalizability across different clinical settings. A pragmatic application of the ML-based models for HF risk prediction in the real world may involve a multistep approach tailored to the population under consideration. For example, in the general primary prevention population without biomarker data, clinical risk factors can be used to predict risk as the first step, followed by selective biomarker testing to refine risk prediction by capturing residual risk of HF.

Clinical Implications and Future Directions

The ML model for HF risk prediction developed in the present study can identify high-risk individuals who are most likely to benefit from effective preventive therapies. These strategies may include lifestyle interventions to improve cardiorespiratory fitness and weight loss,[52,53] intensive blood pressure control,[54] and initiation of pharmacotherapies such as sodium-glucose cotransporter-2 inhibitors among individuals with type 2 diabetes.[55]

A key next step for the practical implementation of the ML-based race-specific model in the clinical setting is its integration with electronic health records. This will not only improve accessibility and real-world application of these ML-based models but also allow better and automated capture of data on the risk prediction variables. To this end, continued improvements in electronic health record software will allow ML models to be developed and stored on a secure cloud server and implemented in the electronic health record through the use of an application programming interface (Figure VI in the Data Supplement). The next steps to facilitate integration of the ML-based race-specific models with the electronic health record include storing the models on a secure cloud-computing server, developing an application programming interface to access our race-specific models, and scaling the platform to provide real-time estimates of a patient's HF risk.

Limitations

Our study has several limitations. First, we included only risk factors that were consistently available across all cohorts at the baseline visit in the derivation cohorts. Data on important predictors of HF risk such as echocardiographic characteristics were not included in the derivation of the risk prediction model. However, the ML model included a wide range of clinical variables such as traditional risk factors and biomarkers with established prognostic importance that have not been included in other HF risk prediction tools.[19] Although echocardiographic parameters are able to accurately risk-stratify HF prognosis, echocardiograms are not routinely obtained in patients without suspected HF. It is thus possible that the ML models can improve resource allocation of echocardiograms for individuals at highest risk for HF. Second, we could not account for several social risk factors, including structural racism, access to care, and racial disparities in management of cardiovascular risk factors, which may influence the risk of HF among Black participants or individuals who identify as neither White nor Black. Future cohort studies that better capture the effects of long-standing societal racism and disparities may improve our HF risk model performance by incorporating objective measures of these microaggressions and allopathic load. Similarly, data on relevant lifestyle factors such as physical activity, cardiorespiratory fitness, and adiposity measures, which may differ across races and are associated with risk of HF, were not available.[52,56,57] However, the ML-based models demonstrate robust performance even in the absence of data on key parameters and across different subgroups and sensitivity analysis. Furthermore, through the use of an application programming interface, the ML-based models can be continuously updated as these data become available in additional cohorts. Last, HF event adjudication differed slightly across all cohorts, and HF subtypes were not systematically captured. However, each cohort study has its own well-established, prespecified criteria for HF event ascertainment, and the model performance was tested separately in each specific cohort and demonstrated good discrimination and calibration.

Conclusions

We used ML to develop race-specific models to predict the 10-year risk of incident HF and externally validated these findings in large population-based cohorts. The ML models displayed excellent discrimination and calibration among Black adults and White adults. Last, using ML to identify the most important predictors of HF risk across racial groups, we found a similar profile of risk factors with substantial differences in the relative importance and contribution to the overall risk of specific parameters among Black adults and White adults.

Supplemental Materials

Expanded Methods
Data Supplement Tables I–V
Data Supplement Figures I–VI
References 58–67

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