

1 **Development and Multinational Validation of an Ensemble Deep Learning**
2 **Algorithm for Detecting and Predicting Structural Heart Disease Using Noisy**
3 **Single-lead Electrocardiograms**
4

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1 **ABSTRACT**

2 **Background and Aims:** AI-enhanced 12-lead ECG can detect a range of structural
3 heart diseases (SHDs) but has a limited role in community-based screening. We
4 developed and externally validated a noise-resilient single-lead AI-ECG algorithm that
5 can detect SHD and predict the risk of their development using wearable/portable
6 devices.

7 **Methods:** Using 266,740 ECGs from 99,205 patients with paired echocardiographic
8 data at Yale New Haven Hospital, we developed ADAPT-HEART, a noise-resilient,
9 deep-learning algorithm, to detect SHD using lead I ECG. SHD was defined as a
10 composite of LVEF<40%, moderate or severe left-sided valvular disease, and severe
11 LVH. ADAPT-HEART was validated in four community hospitals in the US, and the
12 population-based cohort of ELSA-Brasil. We assessed the model's performance as a
13 predictive biomarker among those without baseline SHD across hospital-based sites
14 and the UK Biobank.

15 **Results:** The development population had a median age of 66 [IQR, 54-77] years and
16 included 49,947 (50.3%) women, with 18,896 (19.0%) having any SHD. ADAPT-HEART
17 had an AUROC of 0.879 (95% CI, 0.870-0.888) with good calibration for detecting SHD
18 in the test set, and consistent performance in hospital-based external sites (AUROC:
19 0.852-0.891) and ELSA-Brasil (AUROC: 0.859). Among those without baseline SHD,
20 high vs. low ADAPT-HEART probability conferred a 2.8- to 5.7-fold increase in the risk
21 of future SHD across data sources (all $P<0.05$).

1 **Conclusions:** We propose a novel model that detects and predicts a range of SHDs
2 from noisy single-lead ECGs obtainable on portable/wearable devices, providing a
3 scalable strategy for community-based screening and risk stratification for SHD.

4

5 **Keywords:** Structural Heart Disease; Mass Screening; Wearable Electronic Devices;
6 Electrocardiography; Public Health

1 INTRODUCTION

2 Early diagnosis of structural heart disease (SHD) enables the timely initiation of
3 therapies that can improve disease trajectory and patient outcomes.¹⁻⁶ While a majority
4 of SHDs are characterized by a long presymptomatic phase,⁵⁻⁸ there is currently no
5 systematic approach for detecting SHD before symptom onset. This challenge arises
6 from the lack of feasible screening strategies that can be deployed at scale without
7 requiring advanced imaging or detailed healthcare evaluation.^{9,10} Currently, the
8 diagnosis of SHD requires referral for an echocardiogram or other advanced cardiac
9 imaging, with no specific guidance on which asymptomatic patients should be
10 referred.¹¹ The increasing availability of wearable and portable devices, many of which
11 can capture single-lead ECGs, provides a low-cost cardiac diagnostic modality for a
12 broad population.^{12,13} Nonetheless, there are no discernible signatures for detecting
13 SHD from portable single-lead ECGs.

14 The advent of artificial intelligence (AI) algorithms has enabled the detection of
15 subtle, human-unreadable digital signatures of distinct SHDs using 12-lead
16 electrocardiograms (ECG).^{14,15} While such advances in AI enable a new role for ECGs
17 as a modality for SHD screening, reliance on 12-lead ECGs obtained in clinical settings
18 limits the scale and impact of such a screening strategy.^{14,16} Specifically, this strategy
19 excludes individuals who have not undergone such testing, either due to the absence of
20 clinical indications or lack of access. Conversely, portable and wearable devices enable
21 the acquisition of single-lead ECGs from a broader population.^{12,13} We have previously
22 demonstrated that left ventricular systolic dysfunction (LVSD), a key SHD, can be
23 accurately identified on a noisy lead I ECG obtainable on wearable and portable

1 devices.¹⁷ Nevertheless, detecting individual conditions in a community setting is
2 challenging due to their low prevalence, with a high rate of false positives, even with
3 high-performing models.¹⁶ This obstacle can be addressed by using single-lead ECGs
4 to detect a composite of multiple SHDs, which would result in fewer false positives due
5 to the higher overall prevalence of the composite SHD. This approach could represent
6 an objective and scalable strategy for referral for cardiac imaging to detect SHD.

7 To fully leverage the promise of AI-ECG for transforming community-level ECG
8 screening for SHD, we sought to develop and externally validate a noise-resilient deep
9 learning algorithm to identify a range of clinically actionable SHDs spanning LVSD,
10 moderate or severe left-sided valvular disease, and severe left ventricular hypertrophy
11 (sLVH), using single-lead ECGs. We also explored the predictive role of this algorithm
12 for the risk of incident SHD.

13

14 **METHODS**

15 **Data Sources**

16 We developed the model using ECG paired with echocardiographic data from the Yale
17 New Haven Hospital (YNHH) during 2015-2023 (**Figure S1**). YNHH serves a large and
18 diverse population in New Haven, one of the most representative counties in the US,
19 and across Connecticut.¹⁸ We accessed 2.0 million ECG waveforms containing raw
20 voltage data from all 12 leads of a standard clinical ECG. The echocardiographic data
21 consisted of 335,184 transthoracic echocardiograms (TTE) with structured reports. For
22 external validation, we obtained data from four geographically distinct community
23 hospitals in the Yale New Haven Health System, covering other towns and regions in

1 Southern Connecticut and Rhode Island. These include the Bridgeport Hospital,
2 Greenwich Hospital, Lawrence + Memorial Hospital, and Westerly Hospital. To prevent
3 any representation of the same patients across development and external validation
4 datasets, we excluded patients from the external validation sites whose data had been
5 used for model development. In addition to the hospital-based cohorts, we assessed the
6 external validity of the model in the Brazilian Longitudinal Study of Adult Health (ELSA-
7 Brasil), the largest prospective population-based cohort in Brazil with protocolized ECG
8 and TTEs.¹⁹

9 To evaluate the predictive significance of the model, in addition to hospital-based
10 cohorts, we included participants from the UK Biobank (UKB). UKB is the largest
11 population-based cohort from the UK where participants underwent protocolized ECGs
12 during 2014-2020 with linked data from the national death registry as well as the
13 comprehensive electronic health records (EHR) data from the National Health Service
14 England.²⁰

15

16 **Study Population**

17 To develop the model and assess its external validity, we included individuals from the
18 clinical sites and ELSA-Brasil. From the clinical sites, we identified patients with at least
19 one pair of ECG-TTE occurring within a 30-day window. Each ECG was paired with at
20 most one TTE, while each TTE could have been paired with multiple ECGs. In cases
21 where multiple TTEs were obtained within 30 days of an ECG, only the TTE closest to
22 the ECG was included. Conversely, if multiple ECGs were recorded within 30 days of a
23 TTE, we included up to five ECGs per patient in the development set to avoid over-

1 representation of patients with frequent health encounters. We excluded information
2 from patients who had a history of cardiac procedures at the time of ECG, including
3 coronary artery bypass grafting, aortic or mitral valve procedures, left ventricular assist
4 device implantation, heart transplant, alcohol septal ablation, and ventricular myectomy
5 (**Figure S1**). From ELSA-Brasil, we included all participants who underwent a
6 simultaneous ECG and TTE at their baseline visit during 2008-2010.

7 To assess the predictive role of the algorithm in predicting incident SHD, we
8 included individuals from the clinical sites and the UKB. From the clinical sites, we
9 identified patients with an ECG during 2013-2023 at YNHH and the four community
10 hospitals. We excluded those with SHD based on TTE, heart failure based on diagnosis
11 codes, or left-sided valve replacement or repair based on procedure codes before the
12 index date (**Table S1**). In the clinical sites, diagnosis codes were recorded as the
13 International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-
14 CM), and procedure codes were recorded as the International Classification of
15 Diseases, Tenth Revision, Procedure Coding System (ICD-10-PCS) or Current
16 Procedural Terminology 4 (CPT4). The index date was defined as the date of the first
17 ECG acquisition at any time after one year from their first health encounter. This one-
18 year blanking period was included to ensure prevalent SHD was not misclassified as
19 incident SHD. We also excluded those from YNHH whose data were used for model
20 development.

21 For predictive assessment in the UKB, we identified participants who received
22 protocolized ECG during 2014-2021. We excluded those with a history of heart failure or
23 left-sided valvular disease based on diagnosis codes, as well as those who had

1 undergone left-sided valve replacement or repair based on procedure codes, before
2 their ECG acquisition (**Table S1**). Diagnoses were coded in the International
3 Classification of Diseases, Ninth and Tenth Revisions (ICD-9 and ICD-10), and
4 procedures were coded in the Office of Population Censuses and Surveys Classification
5 of Interventions and Procedures, versions 3 and 4 (OPCS-3 and OPCS-4). This
6 information was obtained from the linkage of the UKB with the national EHR, predating
7 the UKB enrollment in 2006, to ensure complete capture of baseline SHD status.

8

9 **Study Covariates**

10 We defined SHD as the TTE-defined presence of a composite of LVSD, moderate or
11 severe left-sided valvular disease, and/or sLVH. LVSD was defined as a left ventricular
12 ejection fraction (LVEF) <40%. Moderate or severe left-sided valvular diseases were
13 identified by the presence of any moderate or severe aortic regurgitation (AR), aortic
14 stenosis (AS), mitral regurgitation (MR), or mitral stenosis (MS). We characterized sLVH
15 by an interventricular septal diameter at end-diastole (IVSd) greater than 15 mm with
16 concomitant moderate or severe left ventricular diastolic dysfunction (LVDD). All
17 echocardiographic indices were measured according to the American Society of
18 Echocardiography guidelines.¹¹ IVSd and LVEF were measured objectively, while the
19 severity of LVDD and valvular disease were graded by the reading cardiologist, based
20 on the guidelines.¹¹ LVEF was defined using three-dimensional echo, Simpson's
21 biplane, or visual estimation methods. The valvular component of SHD entailed
22 moderate, moderate to severe, or severe stenotic or regurgitant disorders of aortic or
23 mitral valves. We also evaluated an alternative definition for SHD that consists of LVSD

1 and sLVH, but included severe, instead of moderate or severe, left-sided valvular
2 disease.

3

4 **Development of an Ensemble Noise-adapted Model**

5 We randomly split the included ECGs into training, internal validation, and held-out test
6 sets with a ratio of 85:5:10 at the patient level to avoid train-test contamination. In the
7 training set, we retained up to five random ECGs per patient to ensure the adequacy of
8 training data, as noted above. However, the validation and test sets included only one
9 random ECG per patient to avoid any artificial inflation or deflation of the model's
10 performance. Similarly, we included one random ECG per patient from the hospital-
11 based external validation sites.

12 We employed a standard signal preprocessing strategy to extract the signal data
13 from lead I - representing the standard lead captured by portable devices - of 12-lead
14 ECG recordings in the YNHH development set. However, the lead I isolated from
15 clinical 12-lead ECGs is often less noisy than real-world lead I ECGs acquired using
16 portable and wearable devices.²¹ To account for these differences, we adopted our
17 previously developed method to construct noise-resilient algorithms.¹⁷ Briefly, to
18 conform clinical ECGs with portable ECGs, we augmented ECGs in the training set
19 using random Gaussian noise, while we tested the model on clean ECGs that were not
20 noised (**Supplemental Methods**). Algorithms trained using this approach have retained
21 their performance when tested on lead I ECGs, even when augmented with real-world
22 noise from portable devices.¹⁷

1 The model development involved a two-step approach where we first trained
2 separate deep learning algorithms to detect individual SHD components, and then
3 combined their outputs with the patient's age and sex to detect the composite SHD
4 label. To train label-specific algorithms, we employed a convolutional neural network
5 (CNN) architecture with excellent discrimination for detecting LVSD from single-lead
6 ECG.¹⁷ Leveraging this architecture and transfer learning, we trained six distinct CNN
7 models to predict LVSD, moderate or severe left-sided valvular disease, moderate or
8 severe AR, moderate or severe AS, moderate or severe MR, and sLVH (**Supplemental**
9 **Methods**). All models were trained using all ECGs in the training set. However, given
10 the low prevalence of sLVH (<1%), we adopted a case-control training strategy with
11 age- and sex-matching for the sLVH model to ensure learning specific ECG signatures
12 of sLVH. For the sLVH training set, each ECG from patients with sLVH was matched
13 with 10 ECGs from patients without sLVH, ensuring that they had the same sex and
14 were within a 5-year age window. To further improve the model's ability to learn sLVH
15 ECG signatures, we trained the sLVH model on extreme phenotypes, excluding
16 intermediate ones. For training, positive cases were defined by the sLVH criteria (IVSd
17 >15 mm and moderate or severe LVDD), and negative cases were defined by an IVSd
18 <12 mm in the absence of moderate or severe LVDD. The model's performance was
19 then assessed based on the presence or absence of sLVH. Therefore, while the sLVH
20 model was trained on extreme phenotypes, it was tested against the full spectrum of
21 phenotypes in the internal validation and held-out test sets.

22 Leveraging an ensemble learning strategy, we developed ADAPT-HEART (AI
23 Deep learning for Adapting Portable Technology in HEART disease detection) using

1 extreme gradient boosting to predict the composite SHD based on the CNN models'
2 output probabilities, as well as the patient's age and sex as predictive features (**Figure**
3 **1**). The ensemble model's performance was evaluated in the held-out test set and
4 external validation sets. For the predictive assessment, we deployed the ensemble
5 algorithm to obtain the probability of concomitant SHD from corresponding ECGs.

6

7 **Study Outcome**

8 The primary study outcome was the model's discrimination for detecting the presence of
9 composite SHD, measured by the area under the receiver operating characteristics
10 curve (AUROC). The exploratory outcome was the model's performance for predicting
11 new-onset SHD in individuals without baseline SHD, measured by the hazard ratio (HR)
12 of high- vs. low-risk groups. We defined the risk groups by the model output probability
13 using the threshold for optimizing sensitivity at 90%. For the predictive assessment,
14 incident SHD was characterized as TTE-defined SHD, heart failure hospitalization
15 based on diagnosis codes, or left-sided valve replacement or repair based on procedure
16 codes in YNHH and hospital-based external validation sites. In the UKB, due to the
17 absence of serial imaging, incident SHD was characterized by hospitalization for heart
18 failure, or the first recorded diagnosis code of left-sided valvular disease or procedure
19 codes for left-sided valve replacement or repair (**Table S1**).

20

21 **Statistical Analysis**

22 Continuous and categorical variables were reported as medians and interquartile
23 ranges (IQRs) and numbers and percentages, respectively. The model's performance

1 was presented using AUROC, along with sensitivity, specificity, positive predictive value
2 (PPV), negative predictive value (NPV), and F1 score of the model across the
3 thresholds and specifically for the threshold corresponding to a sensitivity of 90% using
4 the internal validation set. The 95% confidence intervals (CI) for AUROC were
5 calculated using bootstrapping with 1000 iterations. We computed 95% CI for
6 sensitivity, specificity, PPV, and NPV using the standard error formula for proportion. To
7 quantify the model calibration, we calculated the Brier score, which is the mean squared
8 difference between the predicted probabilities and the actual outcomes, ranging from 0
9 to 1, with values closer to 0 representing good calibration.²²

10 For the predictive assessment, we fit age- and sex-adjusted Cox proportional
11 hazard models with incident SHD as the dependent variable and the risk groups defined
12 by the model output probability using the threshold for optimizing sensitivity at 90% as
13 the key independent variable. These risk groups comprised those with a high probability
14 of SHD but without SHD, false positives, compared with those with a low probability of
15 SHD and without SHD, true negatives. We further adjusted the Cox models for baseline
16 hypertension and diabetes mellitus. Additionally, we accounted for the competing risk of
17 death using the Fine-Gray subdistribution hazard model.²³

18 All statistical analyses were executed using Python 3.11.2, and R version 4.2.0.
19 Statistical tests were two-sided with the significance level set at 0.05. The Yale
20 Institutional Review Board approved the study protocol and waived the need for
21 informed consent as the study involves analyzing pre-existing data. Patients who opted
22 out of research studies were not included in the study. Participants from ELSA-Brasil

1 and the UKB provided informed consent, and their de-identified data were analyzed in
2 this study.^{19,20} We used the UK Biobank Resource under Application Number 71033.

3

4 **RESULTS**

5 **Study Population**

6 The model was developed in 266,740 ECGs with paired TTE data from 99,205 unique
7 patients with a median age of 66 [54-77] years. This included 49,947 (50.3%) women,
8 13,503 (14.0%) non-Hispanic Black, and 7,832 (8.1%) Hispanic individuals (**Table 1**). In
9 the development set, 60,096 (22.5%) ECGs were linked to a TTE with SHD, including
10 25,552 (9.6%) with LVSD, 42,989 (16.1%) with moderate or severe left-sided valvular
11 disease, and 1,004 (0.4%) with sLVH (**Table 1**). The training set included 261,228
12 ECGs from 93,693 unique patients, while the validation and held-out test sets included
13 5,512 and 11,023 ECGs, respectively, with one ECG drawn per person (**Figure S1**,
14 **Table S2**). For external validation, we included 65,988 patients from four community
15 hospitals and 3,014 participants from the ELSA-Brasil with diverse demographic
16 backgrounds (**Table 1, Figure S1**). The prevalence of SHD varied from 20.2%-27.1% in
17 hospital-based external validation sites compared with 2.9% in ELSA-Brasil (**Table 1**).

18

19 **Detection of Structural Heart Disease**

20 ADAPT-HEART demonstrated an AUROC of 0.879 (95% CI, 0.870-0.888) for detecting
21 SHD on a single-lead ECG in the YNHH held-out test set (**Figure 2A, Table S3**). The
22 model was well-calibrated for detecting the primary study outcome with a Brier score of
23 0.083. ADAPT-HEART had higher discrimination (AUROC, 0.910 [95% CI, 0.900-

1 0.920]) when the composite SHD label included severe, instead of moderate or severe,
2 left-sided valvular disease (**Figure 2B**). The model's probability threshold corresponding
3 to a sensitivity of 90% for predicting SHD in the internal validation set was 0.190. At this
4 probability threshold, in the held-out test set, ADAPT-HEART had a sensitivity of 90.9%
5 (95% CI, 90.2-91.6), specificity of 61.8% (95% CI, 60.6-63.0), PPV of 54.6% (95% CI,
6 53.4-55.9), and NPV of 93.1% (95% CI, 92.4-93.7) for detecting SHD. A higher
7 probability threshold, aimed at optimizing the F1 score, had higher specificity and PPV
8 (**Figure 3, Table S4**).

9 ADAPT-HEART performed consistently across external validation cohorts, with
10 the AUROC varying from 0.852 (95% CI, 0.845-0.859) at Bridgeport Hospital to 0.891
11 (95% CI, 0.877-0.904) with good calibration across clinical sites (**Figure 2, Table S3**). In
12 the prospective ELSA-Brasil that had protocolized paired ECGs and TTEs, ADAPT-
13 HEART retained high discrimination and good calibration with an AUROC of 0.859 (95%
14 CI, 0.816-0.895) (**Figure 2**). The model's performance was comparable across key
15 demographic subgroups of age, sex, and race and ethnicity in the held-out test set and
16 external validation sites (**Figure 4, Tables S5-10**). Individual label-specific models
17 demonstrated consistent performance in the YNHH held-out test set and external
18 validation sites (**Tables S11-16, Figure S2**)

19

20 **Predictive Performance of ADAPT-HEART**

21 For the predictive assessment, we identified 127,547 individuals from YNHH, 105,992
22 from hospital-based external validation sites, and 41,800 from the UKB (**Table S17**).
23 Over a median follow-up of 4.0 [1.7-6.4] years, 5,353 (4.2%) patients developed new-

1 onset SHD in YNHH compared with 5.6% to 8.1% across hospital-based external
2 validation sites with the median follow-up ranging from 2.4 to 4.7 years (**Table S17**). In
3 the UKB, 413 (1.0%) participants had new-onset SHD over a median follow-up of 3.0
4 [2.1-4.5] years. A screen-positive single-lead ECG defined by ADAPT-HEART was
5 associated with a 4-fold higher hazard of incident SHD in YNHH (adjusted HR, 4.03;
6 95% CI, 3.71-4.37), with a consistently elevated risk across hospital-based cohorts
7 (**Table 2**). In the UKB, a positive AI-ECG portended a nearly 3-fold hazard (HR: 2.82;
8 95% CI, 2.13-3.74) for incident SHD, with a modified definition that did not include serial
9 imaging. The risk of SHD was consistently observed with a positive AI-ECG screen,
10 independent of additional adjustment for cardiovascular risk factors of hypertension and
11 diabetes mellitus, and also the competing risk of death (**Table 2**).

12

13 **DISCUSSION**

14 We developed and externally validated ADAPT-HEART, a noise-adapted deep learning
15 algorithm that detects and predicts SHD from single-lead ECGs obtainable on portable
16 and wearable devices, using a large and diverse population. Our novel noise-adapted
17 strategy for single-lead ECGs demonstrates robust discrimination and calibration for
18 detecting a composite of multiple clinically significant SHDs, including LVSD, left-sided
19 valvular disease, and sLVH, using age, sex, and a single-lead ECG recording as the
20 only inputs. ADAPT-HEART performed comparably across external validation cohorts
21 and key demographic subgroups. Depending on the prevalence of SHD in the target
22 screening population, the screening strategy informed by ADAPT-HEART requires 2-12
23 individuals to undergo TTE to find one case with any SHD. Additionally, individuals

1 without baseline SHD but with high ADAPT-HEART probability were three to six times
2 more likely to develop SHD.

3 ADAPT-HEART builds upon the current literature by providing a scalable strategy
4 for SHD screening in the community using single-lead ECGs acquired on portable and
5 wearable devices.^{16,24–26} The advantages of using single-lead ECGs compared with 12-
6 lead ECGs for SHD screening are two-fold; first, the feasibility of obtaining single-lead
7 ECGs on portable devices expands the scale of screening from healthcare settings to
8 broader communities, and second, it allows targeting individuals regardless of their
9 access to healthcare. Additionally, ADAPT-HEART leverages our previous work to
10 retain robust performance despite the noisy acquisition of real-world portable
11 ECGs.^{14,15,17} We also employed an ensemble learning strategy that enables the learning
12 of granular ECG signatures for individual SHDs, resulting in superior performance
13 compared with a single multi-label CNN model for detecting the composite SHD label.¹⁶
14 Thus, the rapidly increasing number of portable and wearable device users, combined
15 with the ADAPT-HEART development, significantly enhances SHD screening strategies
16 in the communities.^{12,13,27}

17 In addition to the diagnostic value of ADAPT-HEART, we demonstrated its role
18 as a biomarker for predicting incident SHD using single-lead ECGs. Thus, ADAPT-
19 HEART not only enables the identification of individuals with asymptomatic SHD but
20 also enables risk stratification for those without SHD. This approach can be particularly
21 valuable to risk stratify asymptomatic individuals at risk for SHD, such as those with
22 hypertension and ischemic heart disease, and older adults.²⁸ The lack of an evidence-
23 based protocolized follow-up for such individuals underscores the need for precision

1 tools such as ADAPT-HEART to provide personalized care to at-risk people.
2 Additionally, the predictive significance of ADAPT-HEART for new-onset SHD may
3 serve as its clinical explainability, where a high model probability in those without
4 baseline SHD can indicate electrical signatures of SHD in the subclinical stages.

5 Leveraging ADAPT-HEART and single-lead ECGs for SHD screening in the
6 community can transform cardiovascular care by enabling early detection and timely
7 treatment. Beyond the use case of ADAPT-HEART for SHD screening among the
8 growing number of portable and wearable device users, it can also enhance screening
9 for individuals without such devices or those less likely to access healthcare settings.²⁹
10 Public health promotion programs, such as hypertension screening in barbershops and
11 pharmacies or cancer screening in churches, can be adapted to establish SHD
12 screening programs using portable ECGs.^{30,31} These community outreach efforts would
13 allow the screening of a large number of individuals for SHD using a limited number of
14 portable devices, offering an efficient strategy to identify individuals who may benefit
15 from advanced cardiac imaging.^{32,33} Furthermore, the proposed screening strategy can
16 help prioritize echocardiographic studies in underserved areas, including low- and
17 middle-income countries.^{34,35} Therefore, our study establishes new frameworks to
18 improve SHD diagnosis at scale and serves as a tool that has the potential to reduce
19 disparities in SHD care.

20 Our findings should be interpreted in the light of the following limitations. First,
21 ADAPT-HEART was developed using pairs of ECG-TTE among individuals who
22 underwent these tests within 30 days of each other, representing a selective population.
23 However, the model performed consistently across four hospitals and a population-

1 based cohort study, indicating generalizability to distinct settings. Second, hospitals in
2 the same health system as the development set were part of model validation sets.
3 Nonetheless, we excluded patients from the external validation sites whose data were
4 used for model development to ensure independence of development and external
5 validation populations. Furthermore, the model generalized well to the population-based
6 cohort of ELSA-Brasil, suggesting its robustness and external validity outside the Yale
7 New Haven Health System. Third, we developed the model using lead I extracted from
8 12-lead ECGs rather than portable-acquired ECGs. However, the lack of a large and
9 rigorous data source where portable ECGs are paired with advanced cardiac imaging
10 data precludes the development of such a model using portable ECGs. Additionally,
11 single-lead AI-ECG algorithms that were developed using clinical 12-lead ECGs have
12 been shown to retain performance while deployed to real-world smartwatch ECGs.³⁶ We
13 also adopted a noising strategy for model development to enhance the model's
14 resilience to noise in real-world settings.¹⁷

15

16 **CONCLUSION**

17 We propose a novel model that detects and predicts a range of SHDs from noisy single-
18 lead ECGs obtainable on portable/wearable devices, providing a scalable strategy for
19 community-based screening and risk stratification for SHD.

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3

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14

15 **Disclosure of Interest**

16 Mr. Khunte and Dr. Khera are the coinventors of U.S. Provisional Patent Application No.
17 63/428,569. Dr. Khera is the coinventor of U.S. Pending Patent Application No.
18 63/346,610, and is the co-founder of Ensignt-AI with Dr. Krumholz. Dr. Khera is the
19 coinventor of U.S. Provisional Pending Patent Applications WO2023230345A1,
20 US20220336048A1, 63/484,426, 63/508,315, 63/580,137, 63/606,203, 63/619,241, and
21 63/562,335 all unrelated to current work, and is a co-founder of Evidence2Health, a
22 precision health platform for evidence-based care. He is also an associate editor at
23 JAMA, and received support from the National Heart, Lung, and Blood Institute of the

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7 (18/813,882, 17/720,068, 63/619,241, 63/177,117, 63/580,137, 63/606,203, 63/562,335,
8 US11948230B2 , US20210374951A1), has been a consultant for Caristo Diagnostics
9 Ltd and Ensignt-AI Inc, and has received royalty fees from technology licensed through
10 the University of Oxford, outside the submitted work. Dr. Krumholz works under contract
11 with the Centers for Medicare & Medicaid Services to support quality measurement
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18 the Martin Baughman Law Firm for work related to the Cook Celect IVC filter litigation,
19 and from the Siegfried and Jensen Law Firm for work related to Vioxx litigation; chairs a
20 Cardiac Scientific Advisory Board for UnitedHealth; was a member of the IBM Watson
21 Health Life Sciences Board; is a member of the Advisory Board for Element Science,
22 the Advisory Board for Facebook, and the Physician Advisory Board for Aetna; and is
23 the co-founder of Hugo Health, a personal health information platform, and co-founder

1 of Refactor Health, a healthcare AI-augmented data management company, and
2 Ensight-AI, Inc. All other authors declare no relevant competing interests.

3

4 **Data Availability Statement**

5 The data from the Yale New Haven Health System represent protected health
6 information. To protect patient privacy, the Yale Institutional Review Board does not
7 allow sharing of these data. Data from the Brazilian Longitudinal Study of Adult Health
8 and the UK Biobank are available for research to licensed users.

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Table 1. Demographics and Prevalence of Structural Heart Disease in the Development and External Validation Set at Patient- and ECG-level

Characteristic*	Development Set		Held-out Test Set	External Validation Sets				
	ECG	Patients	Yale New Haven Hospital	Bridgeport Hospital	Greenwich Hospital	Lawrence + Memorial Hospital	Westerly Hospital	ELSA-Brasil
Number	266,740	99,205	11,023	18,222	4,720	17,867	3,782	3,014
Age (years)	67.8 [56.0-78.3]	66.4 [54.1-77.3]	66.3 [53.7-77.4]	68.5 [56.0-80.0]	74.0 [59.9-84.5]	68.7 [57.3-79.5]	73.3 [62.2-82.4]	62.0 [57.0-67.0]
Female Sex	128529 (48.2%)	49947 (50.3%)	5501 (49.9%)	9210 (50.5%)	2316 (49.1%)	8634 (48.3%)	1821 (48.1%)	1596 (53.0%)
Race and Ethnicity								
White	179193 (68.8%)	66132 (68.5%)	7264 (67.5%)	10420 (58.2%)	3110 (67.8%)	12944 (73.9%)	3181 (85.0%)	1661 (55.1%)
Black	40055 (15.4%)	13503 (14.0%)	1474 (13.7%)	3472 (19.4%)	182 (4.0%)	1184 (6.8%)	56 (1.5%)	455 (15.1%)
Asian	3878 (1.5%)	1648 (1.7%)	183 (1.7%)	218 (1.2%)	121 (2.6%)	221 (1.3%)	23 (0.6%)	74 (2.5%)
Hispanic	21572 (8.3%)	7832 (8.1%)	897 (8.3%)	2849 (15.9%)	504 (11.0%)	1271 (7.3%)	53 (1.4%)	0 (0%)
Pardo	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	753 (25.0%)
Others	15826 (6.1%)	7479 (7.7%)	937 (8.7%)	956 (5.3%)	671 (14.6%)	1887 (10.8%)	428 (11.4%)	71 (2.4%)
SHD†	60096 (22.5%)	18896 (19.0%)	2085 (18.9%)	4167 (22.9%)	1130 (23.9%)	3601 (20.2%)	1024 (27.1%)	88 (2.9%)
Indeterminate	122181 (45.8%)	43296 (43.6%)	4820 (43.7%)	9278 (50.9%)	2449 (51.9%)	6420 (35.9%)	1939 (51.3%)	26 (0.9%)
SHD with Severe Valvular Disease‡	31311 (11.7%)	9005 (9.1%)	1067 (9.7%)	2189 (12.0%)	442 (9.4%)	1731 (9.7%)	466 (12.3%)	88 (2.9%)
Indeterminate	143515 (53.8%)	50463 (50.9%)	5548 (50.3%)	10795 (59.2%)	3016 (63.9%)	7612 (42.6%)	2410 (63.7%)	26 (0.9%)
LVSD (LVEF <40%)	25552 (9.6%)	6991 (7.0%)	821 (7.4%)	1772 (9.7%)	368 (7.8%)	1466 (8.2%)	386 (10.2%)	37 (1.2%)
Indeterminate	4787 (1.8%)	1506 (1.5%)	163 (1.5%)	307 (1.7%)	414 (8.8%)	137 (0.8%)	168 (4.4%)	2 (0.1%)
Moderate or Severe Left-sided Valvular Disease	42989 (16.1%)	14216 (14.3%)	1569 (14.2%)	3053 (16.8%)	924 (19.6%)	2640 (14.8%)	818 (21.6%)	55 (1.8%)

Indeterminate	93282 (35.0%)	32255 (32.5%)	3597 (32.6%)	6979 (38.3%)	1243 (26.3%)	4537 (25.4%)	1611 (42.6%)	27 (0.9%)
Moderate or Severe AR	10485 (3.9%)	3660 (3.7%)	392 (3.6%)	688 (3.8%)	224 (4.7%)	694 (3.9%)	188 (5.0%)	24 (0.8%)
Indeterminate	28962 (10.9%)	9345 (9.4%)	997 (9.0%)	2436 (13.4%)	472 (10.0%)	1204 (6.7%)	277 (7.3%)	12 (0.4%)
Moderate or Severe AS	10472 (3.9%)	3591 (3.6%)	426 (3.9%)	714 (3.9%)	226 (4.8%)	607 (3.4%)	236 (6.2%)	4 (0.1%)
Indeterminate	86106 (32.3%)	29757 (30.0%)	3312 (30.0%)	5958 (32.7%)	1167 (24.7%)	4343 (24.3%)	1252 (33.1%)	9 (0.3%)
Moderate or Severe MR	27850 (10.4%)	8902 (9.0%)	958 (8.7%)	2104 (11.5%)	627 (13.3%)	1670 (9.3%)	537 (14.2%)	30 (1.0%)
Indeterminate	21474 (8.1%)	6815 (6.9%)	759 (6.9%)	1222 (6.7%)	310 (6.6%)	823 (4.6%)	170 (4.5%)	15 (0.5%)
Severe Left-sided Valvular Disease	6321 (2.4%)	2188 (2.2%)	279 (2.5%)	400 (2.2%)	81 (1.7%)	281 (1.6%)	81 (2.1%)	0 (0%)
Indeterminate	110298 (41.4%)	37722 (38.0%)	4166 (37.8%)	8318 (45.6%)	1560 (33.1%)	5407 (30.3%)	2054 (54.3%)	0 (0%)
Severe AR	358 (0.1%)	119 (0.1%)	15 (0.1%)	27 (0.1%)	7 (0.1%)	12 (0.1%)	1 (0.0%)	0 (0%)
Indeterminate	28962 (10.9%)	9345 (9.4%)	997 (9.0%)	2436 (13.4%)	472 (10.0%)	1204 (6.7%)	277 (7.3%)	0 (0%)
Severe AS	3193 (1.2%)	1202 (1.2%)	155 (1.4%)	220 (1.2%)	47 (1.0%)	167 (0.9%)	59 (1.6%)	0 (0%)
Indeterminate	86106 (32.3%)	29757 (30.0%)	3312 (30.0%)	5958 (32.7%)	1167 (24.7%)	4343 (24.3%)	1252 (33.1%)	0 (0%)
Severe MR	2716 (1.0%)	857 (0.9%)	104 (0.9%)	146 (0.8%)	28 (0.6%)	94 (0.5%)	19 (0.5%)	0 (0%)
Indeterminate	21474 (8.1%)	6815 (6.9%)	759 (6.9%)	1222 (6.7%)	310 (6.6%)	823 (4.6%)	170 (4.5%)	0 (0%)
sLVH	1004 (0.4%)	305 (0.3%)	33 (0.3%)	133 (0.7%)	15 (0.3%)	60 (0.3%)	20 (0.5%)	6 (0.2%)
Indeterminate	121139 (45.4%)	40185 (40.5%)	4446 (40.3%)	8814 (48.4%)	2979 (63.1%)	5991 (33.5%)	2152 (56.9%)	0 (0%)

*Data are presented as median [interquartile range], or number (percentage%).

†Includes a composite of LVEF <40%, moderate or severe left-sided valvular disease, and sLVH.

‡Includes a composite of LVEF <50%, severe left-sided valvular disease, and sLVH.

Abbreviations: AR, aortic regurgitation; AS, aortic stenosis; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; sLVH, severe left ventricular hypertrophy; MR, mitral regurgitation; YNH, Yale New Haven Hospital.

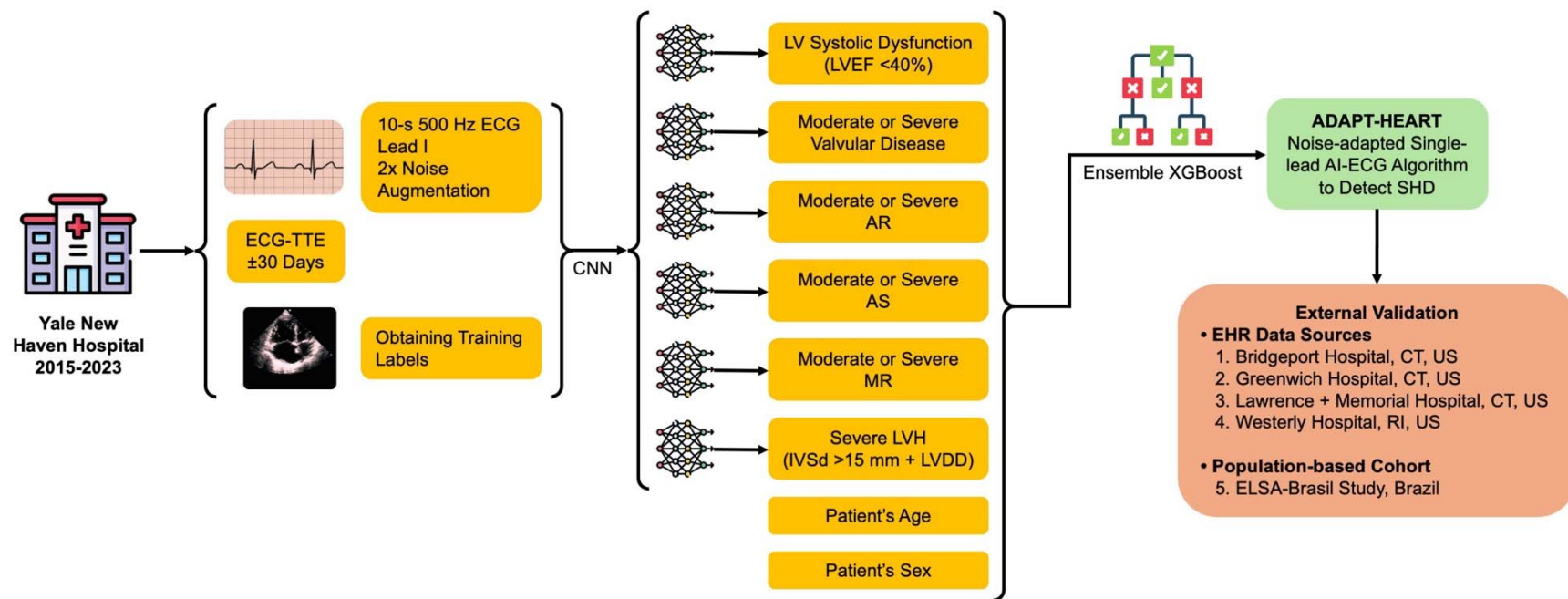
Table 2. Hazard Ratio of Screen-positive ECG Based on ADAPT-HEART for Predicting Incident Structural Heart Disease in Yale New Haven Hospital, Hospital-based External Validation Sites, and the UK Biobank

Model*	Covariates	Yale New Haven Hospital	Bridgeport Hospital	Greenwich Hospital	Lawrence + Memorial Hospital	Westerly Hospital	UK Biobank
Cox Proportional Hazard Model							
Model 1	Screen-positive, Age, and Sex	4.03 (3.71-4.37)	4.95 (4.45-5.5)	5.74 (4.64-7.11)	3.97 (3.45-4.58)	5.19 (3.42-7.88)	2.82 (2.13-3.74)
Model 2	Model 1, HTN, DM	3.74 (3.45-4.06)	4.52 (4.07-5.02)	5.06 (4.09-6.26)	3.52 (3.06-4.06)	4.83 (3.18-7.31)	2.75 (2.07-3.66)
Fine-Gray Subdistribution Hazard Model							
Model 3	Model 1, Competing Risk of Death	4.00 (3.65-4.38)	4.93 (4.39-5.54)	5.84 (4.62-7.39)	3.94 (3.38-4.59)	5.25 (3.46-7.97)	2.48 (1.89-3.26)
Model 4	Model 2, Competing Risk of Death	3.70 (3.39-4.05)	4.50 (4.01-5.05)	5.16 (4.08-6.52)	3.50 (3.01-4.07)	4.85 (3.21-7.34)	2.43 (1.85-3.20)

*Data are presented as HR (95% CI).

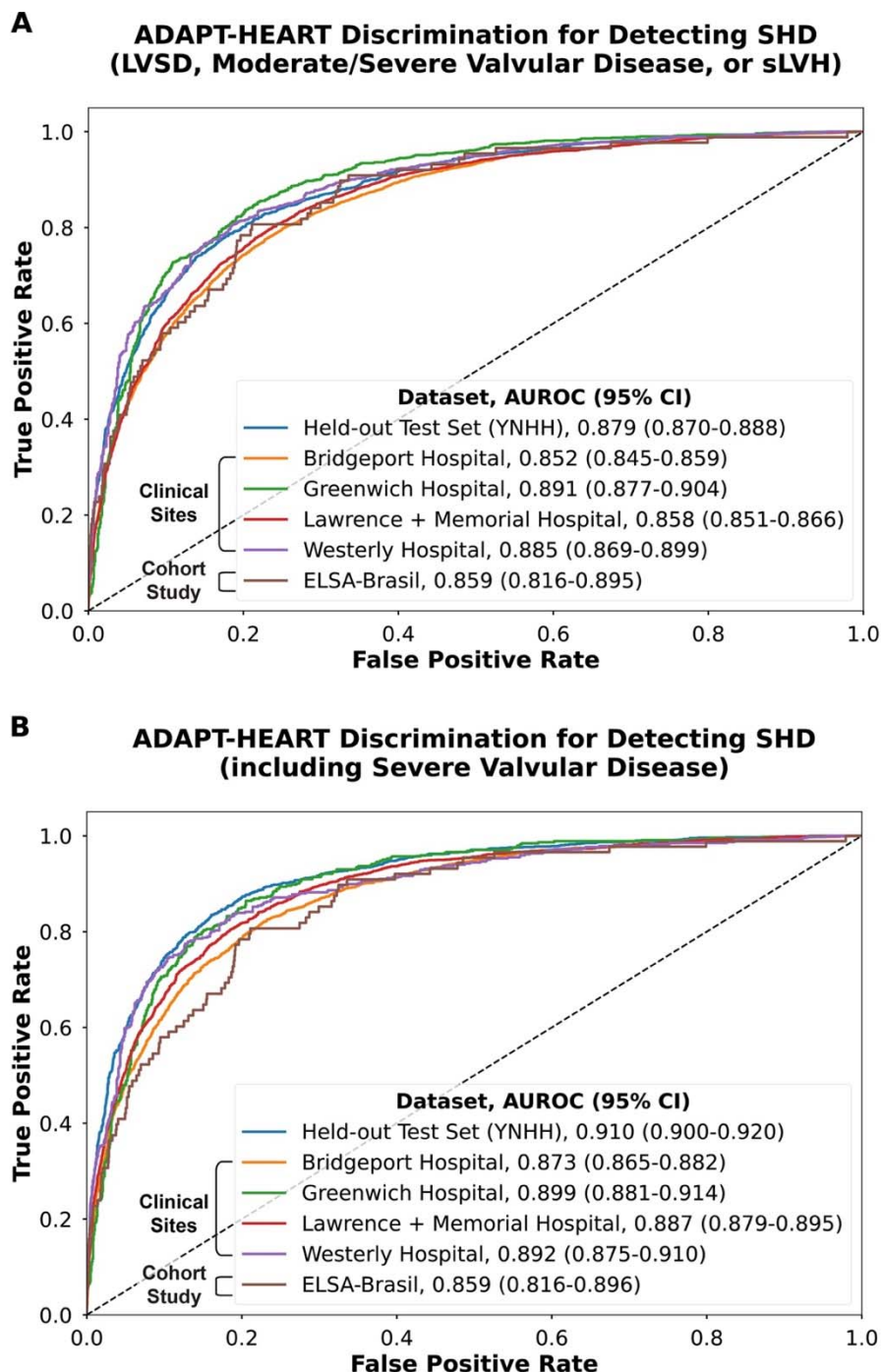
Abbreviations: DM, diabetes mellitus; HTN, hypertension.

Figure 1. Model Development for Detecting Multiple Structural Heart Diseases



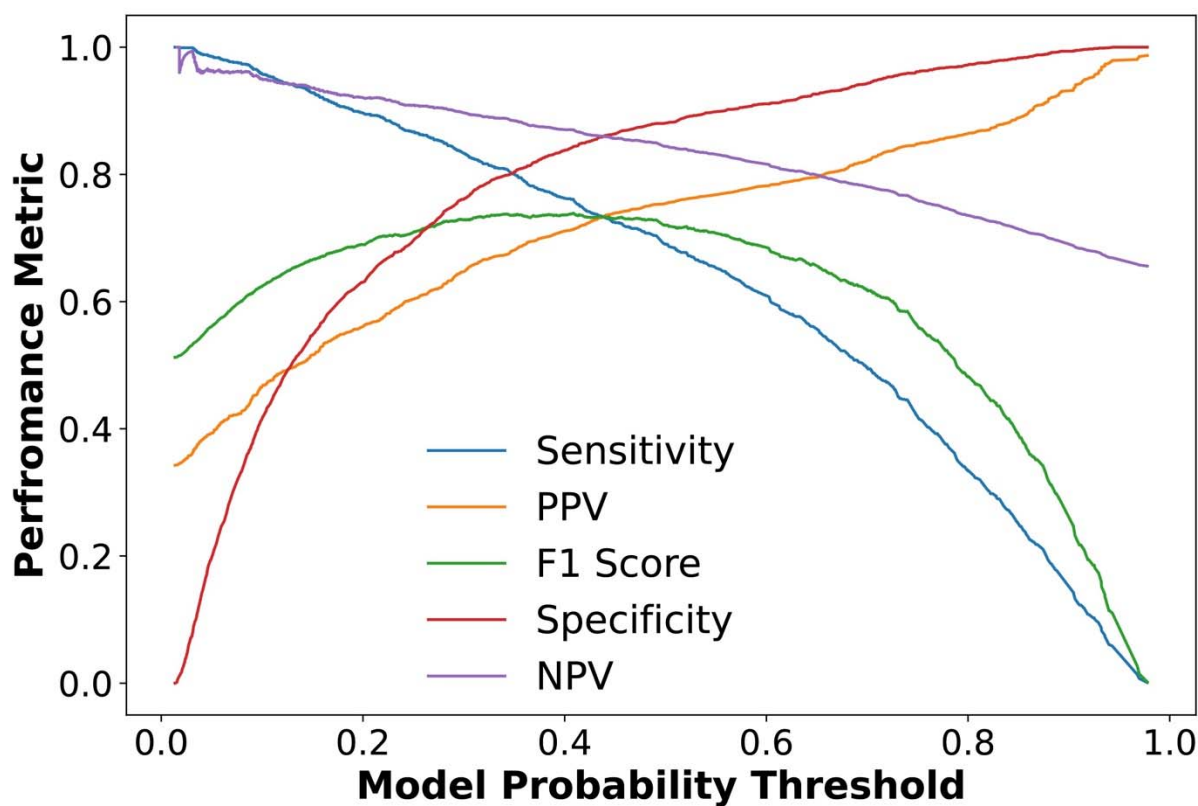
Abbreviations: ADAPT-HEART, AI Deep learning for Adapting Portable Technology in HEART disease detection; AR, aortic regurgitation; AS, aortic stenosis; CNN, convolutional neural network; ECG, electrocardiogram; LVH, left ventricular hypertrophy; IVSd, interventricular septal diameter at end-diastole; LVDD, left ventricular diastolic dysfunction; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; XGBoost, extreme gradient boosting.

Figure 2. Receiver Operating Characteristic Curves of the ADAPT-HEART for Detecting (A) the Primary and (B) the Secondary Outcome Structural Heart Disease in the Held-out Test Set and External Validation Cohorts



Abbreviations: ADAPT-HEART, AI Deep learning for Adapting Portable Technology in HEART disease detection; AUROC, area under the receiver operating characteristic curve; YNHH, Yale New Haven Hospital.

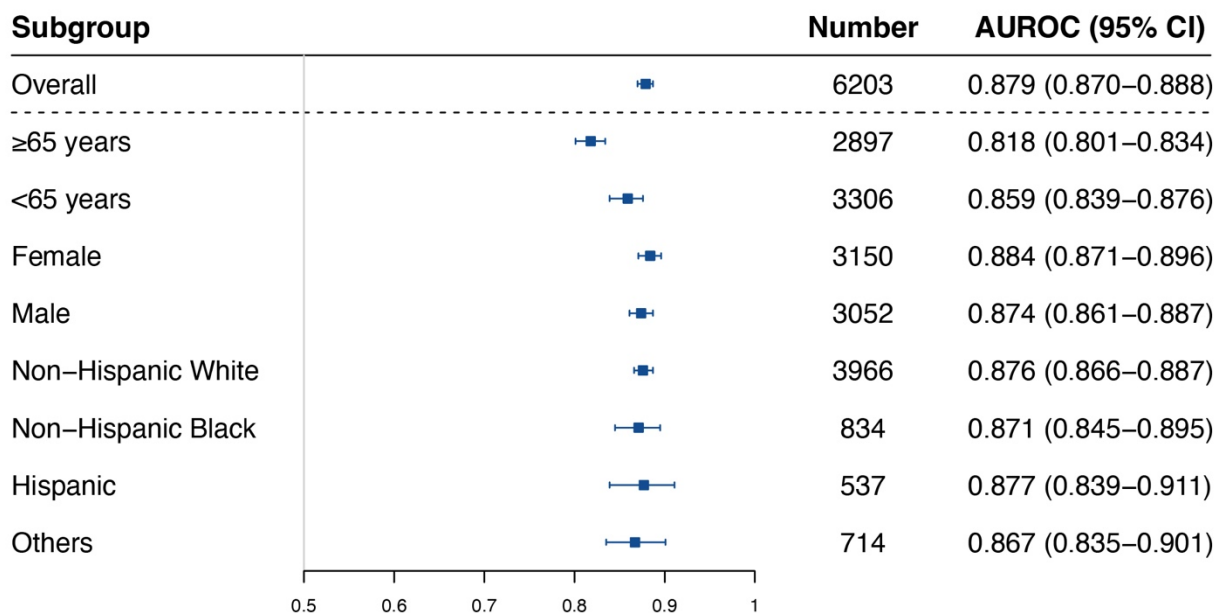
Figure 3. Model's Performance Measures Across Thresholds in the Held-out Test Set



Abbreviations: NPV, negative predictive value; PPV, positive predictive value.

Figure 4. Model’s Performance for Detecting Structural Heart Disease Across Key Demographic Subgroups in the Held-out Test Set

ADAPT–HEART Discrimination Across Demographic Subgroups



Abbreviations: AUROC, area under the receiver operating characteristic curve; CI, confidence interval.