acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2018;39:119–177.
3. Fleddermann AM, Hayes CH, Magalski A, Main ML. Efficacy of Direct Acting Oral Anticoagulants in Treatment of Left Ventricular Thrombus. *Am J Cardiol* 2019;124:367–372. Available at: https://pubmed.ncbi.nlm.nih.gov/31126539/. Accessed August 17, 2020.
4. Verma B, Singh A, Kumar M. Use of dabigatran for treatment of left ventricular thrombus: A tertiary care center experience. *J Fam Med Prim care* 2019;8:2656–2660. Available at: /pmc/articles/PMC6753807/?report=abstract. Accessed August 17, 2020.
5. Cochran J, Jia X, Hamzeh I, Circulation YB-, 2018 undefined. Direct oral anticoagulant use for left ventricular thrombus: a single center experience. *Am Hear Assoc* 2020. Available at: https://www.ahajournals.org/doi/abs/10.1161/circ.138.suppl_1.16411. Accessed August 17.
6. McCarthy CP, Murphy S, Venkateswaran RV, Singh A, Chang LL, Joice MG, Rivero JM, Vaduganathan M, Januzzi JL, Bhatt DL. Left Ventricular Thrombus: Contemporary Etiologies, Treatment Strategies, and Outcomes. *J Am Coll Cardiol* 2019;73:2007–2009.
7. Lattuca B, Bouziri N, Kerneis M, Portal JJ, Zhou J, Hauguel-Moreau M, Mameri A, Zeitouni M, Guedeney P, Hammoudi N, Isnard R, Pousset F, Collet JP, Vicaut E, Montalescot G, Silvain J. Antithrombotic Therapy for Patients With Left Ventricular Mural Thrombus. *J Am Coll Cardiol* 2020;75:1676–1685.
8. Robinson AA, Trankle CR, Eubanks G, Schumann C, Thompson P, Wallace RL, Gottiparthi S, Ruth B, Kramer CM, Salerno M, Bilchick KC, Deen C, Kontos MC, Dent J. Off-label Use of Direct Oral Anticoagulants Compared With Warfarin for Left Ventricular Thrombi. *JAMA Cardiol* 2020;5:685–692. Available at: https://jamanetwork.com/. Accessed August 29, 2020.
9. Yunis A, Seese L, Stearns B, MG-J of the, 2020 U. Direct oral anticoagulants are effective therapy in treating left ventricular thrombi. *JACC* 2020. Available at: https://www.onlinejacc.org/content/75/11_Supplement_1/948.abstract. Accessed August 29, 2020.
10. Iqbal H, Straw S, Craven TP, Stirling K, Wheatcroft SB, Witte KK. Direct oral anticoagulants compared to vitamin K antagonist for the management of left ventricular thrombus. *ESC Hear Fail* 2020. Available at: https://onlinelibrary.wiley.com/doi/abs/10.1002/ehf2.12718. Accessed August 29, 2020.
11. Guddeti R, Anwar M, Walters R, … DA-TAJ of, 2020 U. Treatment of Left Ventricular Thrombus With Direct Oral Anticoagulants: A Retrospective Observational Study. *Am J Med* 2020. Available at: https://www.sciencedirect.com/science/article/pii/S0002934320305234. Accessed August 29, 2020.
12. Jones DA, Wright P, Alizadeh MA, Fhadil S, Rathod KS, Guttmann O, Knight C, Timmis A, Baumbach A, Wragg A, Mathur A, Antoniou S, Jones DA. Bartholomew's Hospital S. The Use of Novel Oral Anti-Coagulant's (NOAC) compared to Vitamin K Antagonists (Warfarin) in patients with Left Ventricular thrombus after Acute Myocardial Infarction. *Eur Hear J - Cardiovasc Pharmacother* 2020. Available at: https://academic.oup.com/ehjcvp/advance-article/doi/10.1093/ehjcvp/pvaa096/5878958. Accessed August 29, 2020.
13. Daher J, Da Costa A, Hilaire C, … TF-CD, 2020 U. Management of Left Ventricular Thrombi with Direct Oral Anticoagulants: Retrospective Comparative Study with Vitamin K Antagonists. *Clin Drug Investig* 2020;40:343–353. Available at: https://link.springer.com/content/pdf/10.1007/s40261-020-00898-3.pdf. Accessed August 29, 2020.
14. Bass M, Page II RL, Kiser TH, McIlvennan CK, Allen LA, Wright G, Shakowski C. Comparative Effectiveness of Direct Oral Anticoagulants and Warfarin for the Treatment of Left Ventricular Thrombus. *J Card Fail* 2019;25:S26–S27. Available at: https://www.onlinejcf.com/article/S1071-9164(19)30848-6/abstract. Accessed August 29, 2020.
15. Gama F, Freitas P, Trabulo M, … AF-EH, 2019 U. Direct oral anticoagulants are an effective therapy for left ventricular thrombus formation. *Eur Heart J* 2019;40. Available at: https://academic.oup.com/eurheartj/article-abstract/40/Supplement_1/ehz747.0118/5594706. Accessed August 29, 2020.
16. Jaidka A, Zhu T, Lavi S, Johri A. Treatment of left ventricular thrombus using warfarin versus direct oral anticoagulants following anterior myocardial infarction. *Can J Cardiol* 2018;34:S143.. Available at http://www.onlinecjc.ca/article/S0828282X18307104/fulltext. Accessed August 29, 2020.
17. Robinson A, Ruth B, Dent J. Direct oral anticoagulants compared to warfarin for left ventricular thrombi: a singel center experience. *J Am Coll Cardiol* 2018;71:A981. Available at: https://www.onlinejacc.org/content/71/11_Supplement/A981. Accessed August 29, 2020.
18. Leow AST, Sia CH, Tan BYQ, Loh JPY. A meta-summary of case reports of non-vitamin K antagonist oral anticoagulant use in patients with left ventricular thrombus. *J Thromb Thrombolysis* 2018;46:68–73. Available at: https://pubmed.ncbi.nlm.nih.gov/29616407/. Accessed August 29, 2020.

https://doi.org/10.1016/j.amjcard.2020.12.014

Prediction of Incident Heart Failure in *TTR* Val122Ile Carriers One Year Ahead of Diagnosis in a Multiethnic Biobank

Hereditary transthyretin (*TTR*) amyloid cardiomyopathy (hATTR-CM) due to the *TTR* Val122Ile variant is associated with increased heart failure (HF) risk in both African-Americans and Hispanic Americans.[1] However, this variant has incomplete and age dependent penetrance, as not all carriers develop clinical heart failure.[2] Thus, early risk stratification of carriers can potentially inform medical management, especially with widespread genetic testing and available therapies. Here, we use electronic health records on a machine learning framework to predict HF 1-year ahead of diagnosis in African and Hispanic American Val122Ile carriers.

We obtained whole exome sequencing data of *TTR* Val122Ile for self-reported 213 (14% cases) African-Americans & 114 (15% cases) Hispanic Americans from a multiethnic quaternary care biobank (Bio*Me*).[1] 46 HF cases identified by diagnostic codes were stratified in 3 timeframes before diagnosis: <6, 6 to 12, and >12 months. We removed continuous (labs/vitals) features with more than 60% of missing values, then imputed using a random forest-based algorithm. Between all 2 highly correlated features (>0.8 in Pearson's correlation coefficient), the feature with the highest overall correlation was removed; the remaining were normalized. Medications and diagnostic codes were treated as binary data.

We ensured robustness by splitting cases and controls in train and test sets (60:40). The 40% test set was kept blind to feature selection, normalization, and fitting the model. We performed feature selection 100 times using a random subset of the train set for each iteration. To do so, a random forest model is trained using all features in the train set. Discarded features will be those who do not impact on the models' performance when removed. The union of all selected features, including age, gender, and ethnicity, were then used to fit 100 models using support vector machine.[3] For each iteration, a random subset of controls was sampled from the train set to generate a balanced dataset (Figure 1). A subset of the test set was used to evaluate predictive power 1 year before HF diagnosis. Standard performance metrics, namely sensitivity (recall), specificity, accuracy, and area under receiver operating characteristic (AUROC) curve were used to assess the performance of each model. Results are reported as the

Dr Do is supported by the National Institute of General Medical Sciences of the National Institutes of Health (NIH) (R35-GM124836) and the National Heart, Lung, and Blood Institute of the NIH (R01-HL139865). Dr Nadkarni is supported by a career development award from the NIH (K23-DK107908) and by NIH grants R01-DK108803, U01-HG007278, U01-HG009610, and U01-DK116100.

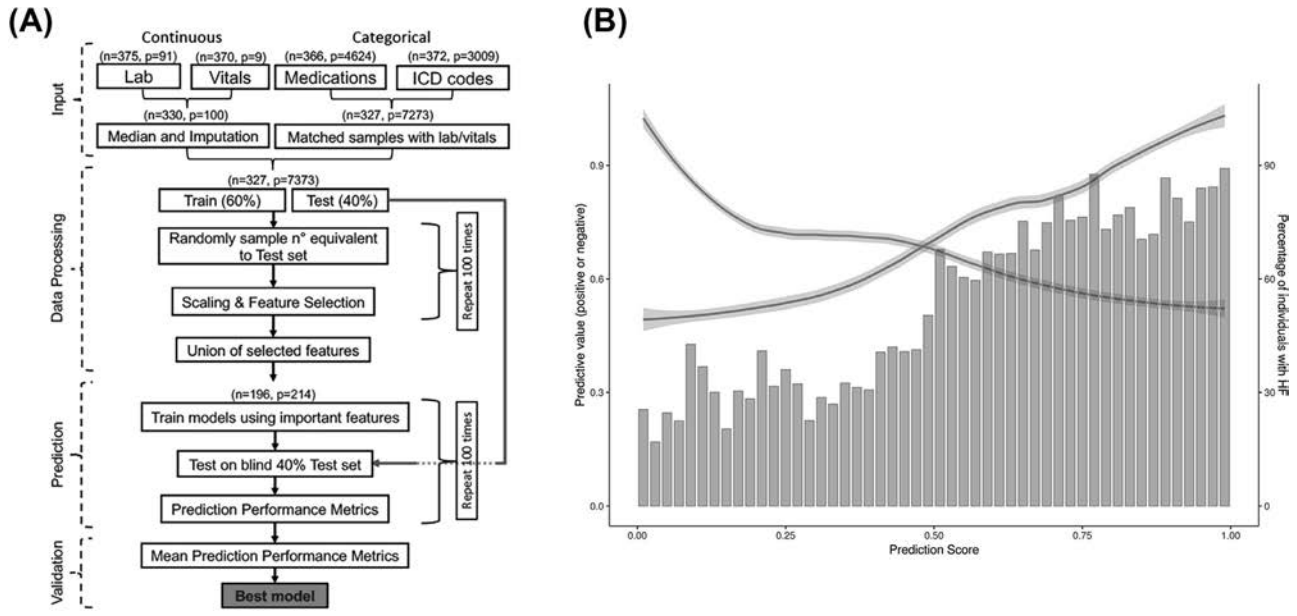

Figure 1. (A) Diagram describing the employed workflow (n = N of patients, p = N of features). (B) Probability distribution of heart failure cases 1 year before diagnosis. The X-axis indicates the prediction, the Y-axis (left) indicates positive predicted value for HF (red line) and negative value for non-HF (blue line); and the Y-axis (right) indicates percentage of individuals with hearth failure (grey bars).

median of each metric across 100 iterations. Wilcoxon rank-sum, Chi-squared, and Fisher's exact tests were performed on highly contributing features to identify significant differences between HF cases and controls. Highly contributing features are determined by their weight in fitting the model.

The distribution of HF patients within the 3 specified timeframes was 9 (19%), 4 (9%), and 33 (72%), respectively, using 91 laboratory results, 9 vitals, 3,009 diagnostic codes, and 4,624 medications. Feature selection resulted in 87, 7, 56 and 61 features from each data type respectively, accounting for 214 features (including gender, age and ethnicity) used to fit the model. We observed a 0.74 AUROC (78% recall) on the full test set. A similar performance of 0.70 AUROC (69% recall) was observed on cases 1 year before HF, at a 0.40 threshold of the predicted score. Importantly, the model correctly predicted 82% of cases (positive predictive value = 0.82) 1 year before HF in high-risk patients (prediction score > 0.65) (Figure 1). A baseline linear model on the same dataset showed considerably lower performance with 0.52 AUROC (54% recall) at the same threshold. We identified 18 features enriched in the HF class with a significant difference between HF and non-HF participants. These are diagnostic codes for history of pulmonary embolism, angina pectoris, primary hypertension, and shortness of breath, laboratory results for corrected QT interval, prothrombin time, hemoglobin A1c, lactate dehydrogenase, lipase, glucose, creatinine and vitals for systolic, and diastolic blood pressure. Of note, some of these features are clinically relevant to heart disease.[4,5] Moreover, the 30 most important features to fit the model drive 22% of the prediction. These include the above-mentioned features in addition to diagnostic codes for hypercholesterolemia, presence of cardiac defibrillator, atrial fibrillation, chest pain and laboratory results for red cell distribution width, neutrophil (count), alkaline phosphatase, activated partial thromboplastin time, atrial rate, HDL cholesterol, potassium and nitrogen in blood, in others.

We note the following limitations. First, the relatively small sample size in the number of carriers of the TTR Val122Ile mutation means we have reduced statistical power in our predictions. However, we observe good prediction performance in our test set and additionally this could be considered a robust sample size for a rare disease. Second, we lack external validation; however, we perform 100 iterations of cross-validation on independent datasets to minimize bias in our model performance. Finally, we predict heart failure using a 1-year prediction interval only. A future direction is to extend our approach to longer time intervals. Importantly, this study shows electronic health records implemented on a machine learning model can predict HF in 82% of high-risk subjects 1 year before diagnosis (Figure 1). Thus, notwithstanding limitations, this represents a first effort to address this important unmet need. In conjunction with now available hATTR-CM therapies, such an approach holds potential for HF risk prediction and early therapeutic intervention in Val122Ile carriers of African ancestry.

Author Contributions

Dr. Chaudhary and B.Sc. Ben O. Petrazzini contributed equally to this work. Drs. Nadkarni and Do jointly supervised this work.

Declaration of Interests

The authors declare that they have no known competing financial interests or personal relations that could have appeared to influence the work reported in this report.

Disclosures

Dr Do reported receiving grants from AstraZeneca, grants and nonfinancial support from Goldfinch Bio, being a scientific co-founder and equity holder for Pensieve Health and being a consultant for Variant Bio. Dr Nadkarni reported being a scientific co-founder, consultant, advisory board member, and equity owner of Renalytix AI, is a scientific co-founder and equity holder for Pensieve Health, being a consultant for Variant Bio and receiving grants from Goldfinch Bio and receiving personal fees from Renalytix AI, BioVie, Reata, AstraZeneca and GLG Consulting. No other disclosures were reported.

Acknowledgments

Genotyping of Bio*Me* was performed in collaboration with Regeneron Genetics Center. Aayushee Jain, MS, Arden Moscati, PHD, Gillian Belbin, PHD, Lisheng Zhou, PHD, Michael Preuss, PHD, Quingbin Song, PHD, Stephane Wenric, PHD, and Steve Ellis, MS, all of whom are/were affiliated with the Icahn School of Medicine at Mount Sinai, assisted with quality control and/or file handling for the Bio*Me* genome-wide genotyping data.

Kumardeep Chaudhary, PhD[abc1]
Ben O. Petrazzini, B.Sc.[ac1]
Jagat Narula, MD, PhD[a]
Girish N. Nadkarni, MD[abd]
Ron Do, PhD[abc*]

[a] The Charles Bronfman Institute for Personalized Medicine, Icahn School of Medicine at Mount Sinai, New York, New York, USA
[b] Bio*Me* Phenomics Center, Icahn School of Medicine at Mount Sinai, New York, New York, USA
[c] Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, New York, USA
[d] Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, New York, USA
[1] Dr. Chaudhary and B.Sc. Petrazzini contributed equally to this work.
27 November 2020

1. Damrauer SM, Chaudhary K, Cho JH, et al. Association of the V122I hereditary transthyretin amyloidosis genetic variant with heart failure among individuals of african or hispanic/latino ancestry. *JAMA* 2019;322:2191–2202.
2. Buxbaum JN, Ruberg FL. Transthyretin V122I (pV142I)* cardiac amyloidosis: an age-dependent autosomal dominant cardiomyopathy too common to be overlooked as a cause of significant heart disease in elderly African Americans. *Genet Med* 2017;19:733–742.
3. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2014 http://www.R-project.org/.
4. Filippatos G, Farmakis D, Parissis J. Renal dysfunction and heart failure: things are seldom what they seem. *Eur Heart J* 2013;35:416–418. https://doi.org/10.1093/eurheartj/eht515.
5. Watson R. ABC of heart failure: clinical features and complications. *BMJ* 2000; 320:236–239. https://doi.org/10.1136/bmj.320.7229.236.

https://doi.org/10.1016/j.amjcard.2020.12.015

Major Depression and Anxiety Among Patients Hospitalized With Heart Failure

Several studies have shown that major depression and anxiety are prevalent among heart failure (HF) patients and are associated with reduced quality of life and increased mortality.[1] In this study, we sought to assess the temporal trends and the sex differences in the prevalence of major depression and anxiety among patients hospitalized for HF.

The National Inpatient Sample (NIS) database was queried between 2008 to 2017 to identify primary HF hospitalizations using International Classification of Disease (ICD-9 and ICD-10) codes. NIS is the largest all-payer US inpatient database containing data from about 8 million hospital stays per year and covering more than 95% of the United States population. The ICD-9 and 10 codes used for major depression were 2962x, 2,963x,311, F32x and F33x and the codes utilized for anxiety disorder were 3,000x and F41x. These codes have been used previously by policymakers and researchers for estimates.[2] Mood disorders and anxiety disorders due to specific fears or known physiological conditions were excluded. Multiple logistic regression analysis for yearly trends was conducted. The annual percent change in the odds was estimated as equal to (odds ratio-1) x 100 and was reported along with p- *trend* to provide quantitative estimation of trends. Stata v14.2 MP (college station, Texas) was used to perform all the statistical analysis.

During the 10-year analysis period, there were 9,206,283 hospitalizations with primary diagnosis codes for HF, among which 690,471 (7.5%) had major depression and 533,964 (5.8%) had anxiety documented. A temporal increase in both major depression and anxiety was observed in the overall cohort (major depression: 6.2% in 2008 vs 9.1% in 2017, p-trend <0.001; anxiety: 3.3% in 2008 vs 8.4% in 2017, p-trend <0.001) (Figure 1). The temporal increase was observed in both men and women (major depression: 4.8% vs 7.5% in 2008; 6.9% vs 11.4% in 2017 respectively, p-trend <0.001; anxiety: 2.2% vs 4.3% in 2008; 6.0% vs 11.0% in 2017 respectively, p-trend <0.001). Both major depression (9.3% vs 5.8%, $p < 0.001$) and anxiety (7.6% vs 4.1%, $p < 0.001$) were more prevalent in women compared with men, and the temporal trend in major depression was more pronounced in women compared with men (p-interaction <0.001).

Among a contemporary cohort of hospitalized HF patients in the US from 2008 through 2017, prevalence of anxiety has approximately tripled, with major depression also steadily increasing. The majority of HF research has focused on pharmacological drugs/devices development and implementation with little emphasis on mental health interventions targeting the psychological needs of HF patients. While selective serotonin reuptake inhibitors have not shown to improve outcomes in HF patients, several knowledge gaps exist.[3] Thus, there is an urgent need for a paradigm shift to a comprehensive assessment of HF patients which includes addressing their psychological and social health, in addition traditional medical endpoints.

In contrast to the hospitalized HF cohort, the crude prevalence of anxiety disorders in the US general population aged >50 years has not changed significantly in the same time period (3.60% in 2008, and 3.70% in 2017). As of 2017, the prevalence of anxiety amongst hospitalized HF patients is considerably higher compared with the general population.[4] Similarly, there has been no significant change in the crude prevalence of depression from 2005 (4.2%) to 2015 (4.8%) in the US general population aged >50 years.[5] This suggests that the increase in