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EDITORIAL COMMENT

A Glimpse Into the Black Box

Using Machine Learning to Prioritize Predictors of Vascular Disease*

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Peripheral arterial disease (PAD) is a massively underdiagnosed condition estimated to affect over 200 million people worldwide.[1] Unfortunately, the disease is insidious with roughly 50% patients being asymptomatic.[2] In addition to the presence of comorbid coronary and cerebrovascular disease, patients with PAD have increased risk of composite myocardial infarction, stroke, vascular mortality, and rehospitalization compared to patients with coronary or cerebrovascular disease. Early interventions in asymptomatic patients including smoking cessation, blood pressure control, and management of diabetes could be initiated to prevent major adverse limb events and/or major adverse cardiovascular/cerebrovascular events. Notwithstanding ample evidence strongly supporting the *early* identification of patients with PAD, there are no consensus guidelines for PAD screening. Although the American Heart Association recommends ankle-brachial index (ABI) screening in high-risk patients, the United States Prevention Services Task Force does not recommend screening asymptomatic adults with ABIs, even in those with concomitant cardiovascular disease or known clinical risk factors.[2,3]

Consequently, alternative PAD screening methodologies have garnered much attention over the past several years.[4] Initially, these approaches primarily used variables obtained from a variety of sources including patient-reported lifestyle and social determinants of health, biomarkers, and comorbidities from the electronic health record (EHR).[5-9] Application of supervised machine learning (ML) techniques further improved the ability of clinical variables within the EHR to classify patients as having PAD. Particularly when coupled with genetic and imaging data, ML techniques demonstrate superior predictive performance in identifying PAD patients compared to methods relying on EHR data alone (area under the curve = 0.89).[10,11] The application of genetic, clinical, and imaging data to more advanced ML methods including natural language processing, computer vision, and convolutional neural networks holds promise to yield even more sensitive and specific models for PAD prediction.[12,13] However, the clinical application and implementation of these algorithms are limited by several factors. First, the required structured data for the model are not always available in every EHR. Second, ML models can suffer from overfitting and lack generalizability, resulting in poor performance on ethnically diverse populations. Most importantly, clinician acceptance of the model is hindered by the 'black box problem.' Difficulty understanding the mechanism by which the model predicts outcomes or classifies patients impairs the ability of the clinician to identify and act on modifiable risk factors.[14]

In this issue of *JACC: Advances*, Sonderman et al[15] describe the use of a supervised ML model on unstructured EHR data to prioritize variables associated with an abnormal ABI. After identification and weighting of the most important features, the authors tested and validated logistic regression models that had moderate predictive power (area under the curve = 0.70) across ethnically diverse

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populations. Another strength of this work is its generalizability. The necessary clinical features included blood pressures, medications, and cholesterol laboratory values—all of which are readily extractable from unstructured clinical notes and were confirmed to perform well across 2 validations cohort. As genetic and imaging data are not always readily available, the simplicity and transparency of a defined model composed of only clinical risk factors maximizes discovery of PAD patients from diverse data sets.

This work allows the reader a glimpse into the output of an ML algorithm and creates an interpretable model using globally available features for PAD prediction. Simple logistic regression models with good performance hold enormous power due to generalizability and identification of responsible risk factors. In addition, once tested in EHR data, the model is tunable. The test statistic threshold used to classify PAD patients can be modulated and optimized for each individual data set and population. However, at present the authors acknowledge this model cannot be directly applied to an asymptomatic population as it was not tested and evaluated in such a population. Future studies prospectively evaluating not only performance but also usability will be key for integration into clinical practice.

After the model is optimized and validated in a given cohort, one can easily imagine the development of a clinical support tool within the EHR that can alert providers when they encounter patients at high risk of PAD. Actionable items include measurement of ABIs, which would now be used to validate rather than screen and optimization of medical therapy (ie, initiation of antiplatelet agents and high intensity statin therapy). Clinical reminders of this nature have been shown to improve prescription of evidence-based medication in the context of heart failure and would be readily applicable to PAD.[16] Of course, this must be balanced by the burden of 'alarm fatigue' that already affects clinicians. Ultimately, improved screening of PAD patients in large and diverse health care systems will almost certainly be predicated on the integration of this type of interpretable tool in the clinical workspace.

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REFERENCES

1. Song P, Rudan D, Zhu Y, et al. Global, regional, and national prevalence and risk factors for peripheral artery disease in 2015: an updated systematic review and analysis. *Lancet Glob Health*. 2019;7(8):e1020-e1030. https://doi.org/10.1016/s2214-109x(19)30255-4

2. US Preventive Services Task Force, Curry SJ, Krist AH, et al. Screening for peripheral artery disease and cardiovascular disease risk assessment with the ankle-brachial index: US Preventive Services Task Force recommendation statement. *JAMA*. 2018;320(2):177-183. https://doi.org/10.1001/jama.2018.8357

3. Gerhard-Herman MD, Gornik HL, Barrett C, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2017;69(11):1465-1508. https://doi.org/10.1016/j.jacc.2016.11.008

4. Flores AM, Demsas F, Leeper NJ, Ross EG. Leveraging machine learning and artificial intelligence to improve peripheral artery disease detection, treatment, and outcomes. *Circ Res*. 2021;128(12):1833-1850. https://doi.org/10.1161/circresaha.121.318224

5. Zhang Y, Huang J, Wang P. A prediction model for the peripheral arterial disease using NHANES data. *Medicine*. 2016;95(16):e3454. https://doi.org/10.1097/md.0000000000003454

6. Mansoor H, Elgendy IY, Williams RS, Joseph VW, Hong Y, Mainous AG. A risk score assessment tool for peripheral arterial disease in women: from the National Health and Nutrition Examination Survey. *Clin Cardiol*. 2018;41(8):1084-1090. https://doi.org/10.1002/clc.23032

7. Duval S, Massaro JM, Jaff MR, et al. An evidence-based score to detect prevalent peripheral artery disease (PAD). *Vasc Med*. 2012;17(5):342-351. https://doi.org/10.1177/1358863x12445102

8. Wilson AM, Kimura E, Harada RK, et al. β2-Microglobulin as a biomarker in peripheral arterial disease. *Circulation*. 2007;116(12):1396-1403. https://doi.org/10.1161/circulationaha.106.683722

9. Cooke JP, Wilson AM. Biomarkers of peripheral arterial disease. *J Am Coll Cardiol*. 2010;55(19):2017-2023. https://doi.org/10.1016/j.jacc.2009.08.090

10. Ross EG, Jung K, Dudley JT, Li L, Leeper NJ, Shah NH. Predicting future cardiovascular events in patients with peripheral artery disease using electronic health record data. *Circ Cardiovasc Qual Outcomes*. 2019;12(3):e004741. https://doi.org/10.1161/circoutcomes.118.004741

11. Ross EG, Shah NH, Dalman RL, Nead KT, Cooke JP, Leeper NJ. The use of machine learning for the identification of peripheral artery disease and future mortality risk. *J Vasc Surg*. 2016;64(5):1515-1522.e3. https://doi.org/10.1016/j.jvs.2016.04.026

12. Weissler EH, Zhang J, Lippmann S, Rusincovitch S, Henao R, Jones WS. Use of natural language processing to improve identification of patients with peripheral artery disease. *Circ Cardiovasc Interv*. 2020;13(10):e009447. https://doi.org/10.1161/circinterventions.120.009447

13. Lareyre F, Behrendt C-A, Chaudhuri A, et al. Applications of artificial intelligence for patients with peripheral artery disease. *J Vasc Surg*.

2023;77(2):650–658.e1. https://doi.org/10.1016/j.jvs.2022.07.160

14. Petch J, Di S, Nelson W. Opening the black box: the promise and limitations of explainable machine learning in cardiology. *Can J Cardiol*. 2022;38(2):204–213. https://doi.org/10.1016/j.cjca.2021.09.004

15. Sonderman M, Aday AW, Farber-Eger E, et al. Identifying patients with peripheral artery disease using the electronic health record: a pragmatic approach. *JACC: Adv*. 2023;2:100566.

16. Heidenreich PA, Gholami P, Sahay A, Massie B, Goldstein MK. Clinical reminders attached to echocardiography reports of patients with reduced left ventricular ejection fraction increase use of β-blockers. *Circulation*. 2007;115(22):2829–2834. https://doi.org/10.1161/circulationaha.106.684753

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