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EDITORIAL COMMENTARY

Cardiovascular risk assessment: The key path toward precision prevention

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1 | INTRODUCTION

Cardiovascular disease (CVD) is the most common noncommunicable disease and the leading cause of death globally.[1] It has resulted in enormous economic and social burdens, while posing a great challenge for the prevention and control of CVD worldwide, especially in China. Assessment and management of cardiovascular risk is the foundation of CVD prevention, and is strongly recommended by guidelines.[2–4] Additionally, it can help screen the target population who would benefit most from the lower-cost intervention, while informing them the cardiovascular risk, which will help in promoting self-management. It can also guide doctors in making logical management decisions, and implement precision prevention and treatment strategies to reduce the CVD burden.[2,4] Therefore, it is a key approach in achieving the goals of "Good Health and Well-being" in the United Nations and "Healthy China 2030" in China. Here, we briefly highlight several advances in cardiovascular risk assessments.

2 | CONVENTIONAL CARDIOVASCULAR RISK ASSESSMENT

The Framingham Heart Study introduced the term "risk factor" in 1961, and identified a series of risk factors of CVD subsequently, such as cholesterol, blood pressure, glucose, and obesity.[5] By integrating multiple conventional risk factors, a general cardiovascular risk instrument was further developed to assist in identifying and treating individuals at high risk.[6] Since the concept of cardiovascular risk assessment and stratification was adopted by the third Adult Treatment Panel of the National Cholesterol Education Program in 2001, it has led to the development of effective treatment and preventive strategies in clinical practice.

A systematic approach to cardiovascular risk assessment includes the collection of information to calculate the cardiovascular risk, identification of the target high-risk population, and implementation of individual management according to the risk level. Therefore, risk-prediction models are major

components of risk-based CVD prevention and control efforts. Several cardiovascular risk models have been developed using conventional risk factors to assist in clinical practice, such as the Reynolds Risk Score[7,8] and the Pooled Cohort Equations (PCE)[9] in the United States, the QRISK in the United Kingdom,[10] the ASSIGN Score in Scotland,[11] the Systematic Coronary Risk Evaluation (SCORE) model in Europe,[12] and the Prediction for Atherosclerotic CVD Risk in China (China-PAR) equations.[13] In addition, World Health Organization has derived the risk prediction charts for 21 Global Burden of Disease regions to facilitate the risk-based CVD prevention in low- and middle-income countries.[4] These models, taking account of balance between good performance and accessibility of predictors, were subsequently validated and optimized for practicability.[14]

Although these models have achieved promising results, several potential reasons limit their widespread implementation. First, risk prediction models developed from one population tend to overestimate or underestimate the CVD risk in other populations due to the heterogeneity in the patterns of CVD and risk factors.[13] Thus, these models need to be validated and recalibrated for better performance in the target population through future research. Second, the convenience of these models is crucial for risk assessment. Therefore, many teams have been working on improving the accessibility of these models using free web-based estimators such as the PCE models (tools.acc.org/ascvd-risk-estimator-plus), China-PAR equations (website [www.cvdrisk.com.cn], mobile apps, and WeChat applets). It is urgently required to incorporate these tools into electronic platforms in hospitals, community health centers, and the Centers for Disease Control and Prevention, and convey the automatically estimated cardiovascular risk to the potential benefit of interventions through lifestyle changes and/or therapeutic approaches by physicians and health providers. Moreover, user-friendly tools can facilitate self-assessment and self-management by the general public to raise awareness of the importance of maintaining a healthy lifestyle, planning individualized intervention strategies, and can further improve the accessibility and equality of health care. Third, the greatest challenge is not the models with better performance but government policies to encourage the implementation of the risk assessment and management. Currently, guidelines on the assessment and management of cardiovascular risk have been released in many countries to be easily and readily practiced in clinical or primary care settings.[2,3,15] Policies are urgently needed to implement guidelines on cardiovascular risk assessment and risk factor management, promote individualized prevention and treatment of CVD, and further reduce disease burden.

3 | RISK-ENHANCING FACTORS

All risk assessment models, when applied to specific subgroups, might carry a risk misjudgment and further affect intervention and treatment strategies. Therefore, the American College of Cardiology/American Heart Association Guidelines introduced the novel concept of risk-enhancing factors as a supplement to risk models, such as metabolic syndrome, chronic kidney disease, chronic inflammatory conditions, history of premature menopause, and lipids/biomarkers.[2] These risk-enhancing factors can effectively improve the estimation of CVD risk and guide the implementation of preventive measures, especially in populations at borderline or intermediate cardiovascular risk. This finding emphasizes that risk-enhancing factors may affect the threshold for statin initiation or intensification. For example, the presence of risk-enhancing factors in individuals with a borderline risk may justify the initiation of moderate-intensity statin therapy. Additionally, the coronary artery calcium score should also be considered to optimize treatment decisions for these patients if risk-based decisions remain uncertain. Compared to traditional risk factors, risk-enhancing factors, such as coronary artery calcium, may not be available in all settings because their assessment may be expensive or even cause unnecessary radiation exposure. Moreover, some of them are not modifiable treatment targets but are simply markers of biological processes. Therefore, further evidence for their reclassification and cost-effectiveness is required.

4 | POLYGENIC RISK SCORE

Genetic factors, beyond traditional risk factors, also contribute to the vulnerability to CVD. Genome-wide association studies (GWASs) have identified hundreds of loci associated with CVD or related traits. By incorporating common genetic variants from GWASs to quantify genetic risk, the polygenic risk score (PRS) offers the opportunity to refine risk earlier in life, when few individuals express risk factors that exceed treatment thresholds. Contemporary PRS has broadened to include millions of variants using advanced statistical methods, displaying power in risk prediction.[16] The majority of PRSs have been derived and optimized using European GWASs. However, genetic heterogeneity across ancestry groups may influence the effect sizes of variants, leading to poor generalizability of these PRSs to other ancestry groups. Subsequently, PRSs for non-Europeans were developed. For example, PRSs of coronary artery disease and stroke in East Asians have been constructed using more than 500 genetic variants for CVD or related traits, showing good performance in the Chinese population.[17–19]

The PRS plays an important role in the prevention of CVD and can stratify individuals into different trajectories of the CVD risk and indicate great potential for identifying high-risk individuals for targeted intervention. For example, polygenic risk determines the patterns of blood lipid changes, and individuals at high polygenic risk show the greatest annual changes toward unfavorable lipid profiles and require intensive lifestyle intervention.[20] Furthermore, adherence to cardiovascular health metrics could mitigate the genetic risk, and individuals with high genetic susceptibility would gain greater lifetime risk reductions.[21,22] Thus, the PRS can be used to identify target populations and guide early lifestyle management to alleviate or even reverse their risks from a high genetic background. Moreover, incorporating the polygenic risk into conventional cardiovascular risk could further refine the risk stratification for CVD within each clinical risk stratum and provide useful risk stratification recommendations for identifying patients who should be initiated or administered intensive lifestyle changes and/or drug treatments.[17] Therefore, the PRS is a pragmatic tool in clinical practice for identifying high-risk individuals, guiding lifestyle interventions, and implementing precision preventive measures. However, more clinical trials and health economic evaluations are required to support the incorporation of PRS into existing CVD guideline-based prevention models and to determine the extent to which lifestyle improvements could reduce the polygenic risk of CVD. In addition, we need to identify the optimal cut-off for high genetic risk instead of directly using the highest quintile, as reported in several studies.

5 | MULTI-OMICS BIOMARKERS FOR CARDIOVASCULAR RISK ASSESSMENT

Increasing evidence supports the measurement of various omics levels to improve the risk prediction and identify the development of CVD.[23] These potential biomarkers have pro-inflammatory or proatherogenic effects and represent mechanistic relationships between clinical risk factors and CVD. Based on new proteomic technologies, novel protein biomarkers of CVD have been discovered, such as albumin, immunoglobulins, hemostatic factors, natriuretic peptides, interleukins, troponin, and creatine kinase.[24] Subsequently, proteome-based scores have been constructed and show better accuracy than conventional risk scores.[25] Small molecule metabolites, such as amino acids, lipids, and by-products of metabolism, can reflect multiparametric host responses to external exposures. They may explain some of the interindividual variability in the associations of CVD with traditional risk factors and provide potential information for cardiovascular risk assessment.[23] In addition, other omics biomarkers, such as epigenetics, transcriptomics, and gut microbiome, can also help provide a longitudinal snapshot of individuals health status and enable more precise risk prediction and treatment approaches.[23] Although multi-omics biomarkers are promising, future investigation is warranted to better evaluate their role in CVD risk assessment and determine the cost-effectiveness and availability of the integration of these biomarkers into CVD primary prevention.

6 | MACHINE LEARNING (ML) IN CARDIOVASCULAR RISK ASSESSMENT

ML, a branch of artificial intelligence, can improve the accuracy of CVD risk prediction and help translate big data into clinical decision-making. ML has been used in assessing the cardiovascular risk and has outperformed conventional risk models.[26] Furthermore, the ML-driven incorporation of data from omics is promising for risk prediction.[27] Performing personalized risk prediction with ML could tailor better therapy for patients in urgent need of optimized care. However, ML is not the master key for every problem in the medical sciences. ML models are limited by the quality and magnitude of the data used to train them. Adding variables to models can cause noise owing to measurement methods and errors. Thus, more effort should be focused on validating the established ML models rather than developing new approaches.

7 | CONCLUSION

Cardiovascular risk assessment is the foundation of CVD prevention efforts, while being an important stepping stone toward precision prevention. It is crucial to improve the accessibility of risk assessments using the Internet or smartphones, facilitate precision prevention by incorporating them into electronic health record platforms, and develop effective policies for their widespread implementation. Incremental improvements in risk assessment can be achieved through risk-enhancing factors, genetics, proteomics, metabolomics, and ML-driven data mining. However, their cost-effectiveness and availability should be evaluated in future studies.

AUTHOR CONTRIBUTIONS

Jianxin Li and Xiangfeng Lu drafted and revised this manuscript. All authors read and edited the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest. Professor Xiangfeng Lu is a member of Chronic Diseases and Translational Medicine editorial board and is not involved in the peer review and decision process of this article.

DATA AVAILABILITY STATEMENT

None.

ETHICS STATEMENT

None.

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