Pitfalls in Risk Stratification: The Case of Acute Pulmonary Embolism

Cardiovascular disease is spreading at an alarming rate around the world, becoming the leading cause of death. Before the COVID-19 pandemic put an unprecedented pressure on the resilience of health systems, an estimated 18 million deaths from cardiovascular disease occurred in 2019, accounting for about 32% of all global deaths. There are numerous guidelines for the primary and secondary prevention of these pathologies and for the prognostic stratification of the subjects at risk or with evidence of the disease. For example, several studies have demonstrated that the management of modifiable cardiovascular risk factors, particularly hypertension and dyslipidemia, can reduce cardiovascular morbidity and mortality. Adequate risk quantification is a sine qua non for optimizing the prevention strategies and personalizing therapy.

Over the years, numerous algorithms for personalized cardiovascular risk assessment have been published.[1] In the era of precision medicine, more and more prognostic models have been developed, including flow charts, classification and regression trees, nomograms, and point-based risk-scoring algorithms. However, it is not yet clear what the optimal prediction risk equation is.[2] These models are not perfect and require continuous checks and adjustments because of the progress in basic research, clinical knowledge, development of ever more refined diagnostic systems, epidemiologic changes, and appropriate therapeutic innovations for specific disease endotypes.

The overall picture is destined to become even more complicated with the widespread availability of computational methods applied in the context of statistical inferences, namely machine learning, a subset of artificial intelligence, and the possibility of accessing big data that can be extracted from electronic health records and optimized natural language processing.[3]

Despite the immense promise, several considerations have hindered the implementation of machine learning in clinical practice, including cardiovascular medicine. In particular, the so-called black box nature of machine learning produces decisions that can be difficult to interpret, seemingly opaque and inscrutable. Indeed, a low explainability can generate doubts both in physicians and in patients about the reliability and efficacy of the model and how it should be concretely adopted in the clinical practice.[4] Therefore, there is a growing demand for explainable machine learning models, especially for high-risk diseases, before a large-scale application of such computational approaches. It is probably because of the difficulty in interpreting the more complex machine learning models that many scientific societies currently support the use of simpler prognostic models, which are perhaps slightly less accurate but certainly more suitable for a constructive doctor-patient relation.

Pulmonary thromboembolism is the most common cause of acute right ventricular (RV) pressure overload in adults. Despite the significant advances in cardiovascular medicine, pulmonary thromboembolism remains an important cause of mortality and morbidity.[5] It is not possible to calculate exactly how many people develop deep vein thrombosis or acute pulmonary embolism (PE) each year, but it is estimated that up to 900,000 people could be affected each year in the United States, with significant morbidity and mortality.[6] Both deep vein thrombosis and PE have been increasingly recognized among patients diagnosed with COVID-19. Several classifications of acute PE are available for prognostic stratification and clinical management.[7,8] The elements derived from clinical examination, assessment of RV size and function, and quantification of cardiac biomarkers are important for risk stratification of patients with PE. In particular, the prognosis of PE is closely related to the degree of RV failure and hemodynamic instability. Indeed, one of the most recommended parameters to estimate the prognostic risk of PE is the ratio of RV to left ventricular (LV) diameter measured by computed tomography pulmonary angiography or transthoracic echocardiogram. However, a history of pre-existing heart failure (HF) is another strong predictor of worse prognosis in the setting of acute PE.

In this issue of the journal, Katterle et al[9] retrospectively evaluated the prognostic role of RV/LV ratio and B-type natriuretic peptide (BNP) levels in 182 in-patients with acute PE from 2010 to 2015 at their institution, stratified as without HF, HF with reduced ejection fraction (HFrEF), or HF with preserved ejection fraction. Those with a history of HFrEF had a higher risk of 90-day mortality despite a lower RV/LV diameter ratio than the other 2 groups. Subjects with HFrEF also had significantly higher BNP levels, likely driven by HFrEF-related LV changes. These findings raise questions about the ability of BNP and RV/LV values to further stratify the risk in patients with PE with a history of HF, particularly those with HFrEF.

This is an important issue, considering that patients with a previous HF who underwent PE are burdened with a high mortality, and the normal values of the RV/LV ratio could instead suggest a less ominous clinical course. The study of Katterle et al[9] extends a previous observation that in patients with acute PE treated at home based on the absence of all Hestia criteria, there was no difference in the incidence of adverse events in those with an RV/LV diameter ratio >1.0 on computed tomographic pulmonary angiography compared with those without an abnormal RV/LV diameter ratio.[10] It must be noted that the study of Katterle et al[9] has some limitations, including its retrospective and single-center study design and a small sample size with a low number of HFrEF subjects. However, it has the merit of pointing out that more detailed risk stratification features not influenced by the structure of the LV function are

Funding: none.

See page 233 for Declaration of Conflict of Interest.

https://doi.org/10.1016/j.amjcard.2023.05.034

needed to accurately assess the risk of acute PE, particularly in patients with a history of HF.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

Mario Petretta, MD[a]*
Carmela Nappi, MD[b]
Alberto Cuocolo, MD[b]
[a] *Scientific Institute for Research, Hospitalization and Healthcare SYNLAB SDN, Naples, Italy*
[b] *Department of Advanced Biomedical Sciences, University of Naples Federico II, Naples, Italy*
* Corresponding author: Tel: 39 081 7462233; fax: 410-367-2151.
(mariopetretta2009@yahoo.it).

1. Petretta M, Cuocolo A. Prediction models for risk classification in cardiovascular disease. *Eur J Nucl Med Mol Imaging* 2012;39:1959–1969.
2. Mohd Faizal AS, Thevarajah TM, Khor SM, Chang SW. A review of risk prediction models in cardiovascular disease: conventional approach vs. artificial intelligent approach. *Comput Methods Programs Biomed* 2021;207:106190.
3. Cuocolo R, Perillo T, De Rosa E, Ugga L, Petretta M. Current applications of big data and machine learning in cardiology. *J Geriatr Cardiol* 2019;16:601–607.
4. Markus AF, Kors JA, Rijnbeek PR. The role of explainability in creating trustworthy artificial intelligence for health care: A comprehensive survey of the terminology, design choices, and evaluation strategies. *J Biomed Inform* 2021;113:103655. https://doi.org/10.1016/j.jbi.2020.103655.
5. Quezada CA, Bikdeli B, Barrios D, Barbero E, Chiluiza D, Muriel A, Casazza F, Monreal M, Yusen RD, Jiménez D. Meta-Analysis of prevalence and short-term prognosis of hemodynamically unstable patients with symptomatic acute pulmonary embolism. *Am J Cardiol* 2019;123:684–689.
6. CDC. Data and statistics on venous thromboembolism. Available at: https://www.cdc.gov/ncbddd/dvt/data.html. Accessed on May 14, 2023.
7. Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjola VP, Huisman MV, Humbert M, Jennings CS, Jiménez D, Kucher N, Lang IM, Lankeit M, Lorusso R, Mazzolai L, Meneveau N, Ní Áinle F, Prandoni P, Pruszczyk P, Righini M, Torbicki A, Van Belle E, Zamorano JL. European Society of Cardiology Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). *Eur Heart J* 2020;41:543–603.
8. Bavalia R, Stals MAM, Mulder FI, Bistervels IM, Coppens M, Faber LM, Hendriks SV, Hofstee HMA, Huisman MV, T van der Hulle, Mairuhu ATA, Kruip MJHA, Middeldorp S, Klok FA, Hutten BA, Holleman F. Use of the National Early Warning Score for predicting deterioration of patients with acute pulmonary embolism: a post-hoc analysis of the YEARS Study. *Emerg Med J* 2023;40:61–66. https://doi.org/10.1136/emermed-2021-211506.
9. Katterle KR, Niedoba MJ, Pasadyn VE, Mann A, Brewster PS, Dasa O, Ruzieh M, Ammari Z, Gupta R. Impact of Baseline Heart Failure on Acute Pulmonary Embolism Risk Stratification and Clinical Outcomes. *Am J Cardiol* 2023;200:26–31. https://doi.org/10.1016/j.amjcard.2023.05.008.
10. Hendriks SV, Klok FA, den Exter PL, Eijsvogel M, Faber LM, Hofstee HMA, Iglesias Del Sol A, Kroft LJM, Mairuhu ATA, Huisman MV. Right ventricle-to-left ventricle diameter ratio measurement seems to have no role in low-risk patients with pulmonary embolism treated at home triaged by Hestia criteria. *Am J Respir Crit Care Med* 2020;202:138–141.