A machine-learning-based bio-psycho-social model for the prediction of non-obstructive and obstructive coronary artery disease

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Background: Although cardiovascular disease is the leading cause of mortality in both females and males, women are more likely to have non-obstructive ischemic heart disease (IHD) than men. However, the underlying sex- and gender-specific mechanisms and differences in IHD manifestations are still not fully understood.

Aim: To develop an interpretable machine learning (ML) model to gain insight on the clinical, functional, biological and psychosocial features playing a major role in the supervised prediction of non-obstructive versus obstructive CAD.

Methods: From the EVA study, we analyzed a consecutive unselected cohort of adults hospitalized for IHD undergoing coronary angiography. Non-obstructive CAD was defined by a coronary stenosis at the angiogram $<$50%. Baseline clinical and psycho-socio-cultural characteristics were used for computing a frailty index based on Rockwood and Mitnitsky model, and gender score according to GENESIS-PRAXY methodology. The serum concentration of inflammatory cytokines was measured with a multiplex flow cytometric assay. An XGBoost classifier combined to an explainable artificial intelligence tool (SHAP) was employed to identify the most influential features in discriminating obstructive versus non-obstructive CAD.

Results: Among the overall EVA cohort (n=509), 311 individuals (mean age 67±11 years, 38% females; 67% obstructive CAD) with complete data were analyzed. The ML-based model (83% accuracy and 87% precision) revealed that while obstructive CAD associated with higher frailty index (i.e., lower physiological reserve), older age and a cytokine signature characterized by IL-1β, IL-12p70 and IL-33, non-obstructive CAD was more likely associated with higher gender score (i.e., social characteristics traditionally ascribed to women, regardless of biological sex) and with a cytokine signature characterized by IL-18, IL-8, IL-23.

Conclusions: Integrating clinical, biological and psycho-social features, we have optimized a sex- and gender-unbiased model that discriminates obstructive and non-obstructive CAD. Further mechanistic studies will shed light on the biological plausibility of the observed associations.