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Precision Cardiology: Integrating Genetics and Artificial Intelligence for Cardiovascular Risk Prediction

Cardiología de precisión: integración de la genética y la inteligencia artificial para la predicción del riesgo cardiovascular

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Resumen

Las enfermedades cardiovasculares (ECV) continúan siendo la principal causa de mortalidad a nivel mundial, y los modelos predictivos tradicionales presentan limitaciones para identificar el riesgo en poblaciones genéticamente diversas. Este estudio evaluó un modelo predictivo híbrido que integra puntajes de riesgo poligénico (PRS), inteligencia artificial (IA) aplicada al electrocardiograma (ECG) y variables clínicas convencionales, con el objetivo de mejorar la predicción del riesgo cardiovascular en cohortes multicéntricas de México, Colombia y Ecuador. Se analizaron 6,450 participantes entre 30 y 75 años. Los PRS se calcularon a partir de datos de asociación genómica, mientras que los ECG fueron procesados mediante redes neuronales convolucionales profundas. El desempeño del modelo se evaluó utilizando el área bajo la curva ROC (AUROC), la puntuación F1 y la pendiente de calibración, complementados con análisis de explicabilidad mediante valores SHAP (Shapley Additive Explanations). El modelo híbrido mostró una precisión predictiva superior (AUROC 0.91; F1-score 0.87; pendiente de calibración 0.97) en comparación con los modelos clínico (0.72), genético (0.78) y de IA-ECG (0.86). Los predictores más influyentes fueron el PRS, la presión arterial sistólica, la edad y la edad eléctrica derivada por IA. El desempeño fue consistente entre ancestrías (mestizo 0.91; amerindio 0.89; europeo 0.93; afrodescendiente 0.87) y países, demostrando equidad y generalización. Estos hallazgos evidencian que la integración de información genética y fisiológica basada en IA mejora significativamente la predicción del riesgo cardiovascular, promoviendo una prevención temprana, personalizada y equitativa. El modelo híbrido propuesto constituye una base sólida para la medicina de precisión cardiovascular impulsada por IA en América Latina.

Palabras clave: Inteligencia artificial; Puntaje de riesgo poligénico; Electrocardiograma; Predicción del riesgo cardiovascular; Medicina de precisión; América Latina.

Abstract

Cardiovascular diseases (CVDs) remain the leading cause of death worldwide, yet conventional predictive models often fail to capture the complex interplay of genetic and physiological risk factors in diverse populations. This study evaluated a hybrid predictive model integrating polygenic risk scores (PRS), artificial intelligence (AI) applied to electrocardiography (ECG), and traditional clinical variables to enhance cardiovascular risk prediction across Latin American cohorts from Mexico, Colombia, and Ecuador. A total of 6,450 participants aged 30 to 75 years were analyzed. PRS were derived from genome-wide association data, and ECGs were processed using deep convolutional neural networks. Model performance was assessed using AUROC, F1-score, and calibration metrics, with interpretability achieved through SHAP (Shapley Additive Explanations) analysis. The hybrid model demonstrated superior predictive accuracy (AUROC 0.91; F1-score 0.87; calibration slope 0.97) compared with the clinical (0.72), PRS (0.78), and AI-ECG (0.86) models. The most influential predictors were PRS, systolic blood pressure, age, and AI-derived electrical age. Subgroup analyses revealed consistent performance across ancestries (Mestizo 0.91; Amerindian 0.89; European 0.93; Afro-descendant 0.87) and countries, confirming the model's generalizability and fairness. These findings demonstrate that integrating genetic and AI-based physiological data significantly improves cardiovascular risk assessment, enabling early, equitable, and personalized prevention. The proposed hybrid framework provides a scalable foundation for implementing AI-driven genomic precision medicine in multi-ancestry populations, marking an essential step toward reducing cardiovascular disparities in Latin America.

Keywords: Artificial intelligence; Polygenic risk score; Electrocardiography; Cardiovascular risk prediction; Precision medicine; Latin America.

1. Introducción

Cardiovascular diseases (CVDs) remain the primary cause of global mortality, responsible for approximately 17.9 million deaths each year according to the World Health Organization. Despite the remarkable progress in preventive cardiology, traditional predictive models such as the **Framingham Risk Score** and the **SCORE algorithm** continue to show suboptimal performance, especially when applied across diverse ancestries and heterogeneous clinical settings (O'Sullivan et al., 2022; Samani et al., 2024). The growing recognition of these limitations has encouraged the incorporation of **molecular genetics** and **artificial intelligence (AI)** as complementary tools to enhance cardiovascular risk assessment, opening a new era of precision medicine.

Over the past decade, advances in **genomic research** have allowed the development of **polygenic risk scores (PRS)** that summarize the cumulative contribution of thousands of single-nucleotide polymorphisms (SNPs) associated with cardiovascular phenotypes (Patel et al., 2023; Xiang et al., 2022). These scores can stratify individuals according to their inherited predisposition, providing clinically actionable insights beyond traditional biomarkers such as cholesterol, blood pressure, or diabetes (Natarajan et al., 2022; Sun et al., 2023). Simultaneously, **AI-driven models**, particularly those trained with **electrocardiographic (ECG)**, imaging, and multi-omic data, have shown remarkable performance in identifying subclinical disease and predicting future cardiovascular events (Sau et al., 2024; Hughes et al., 2023; Dhingra et al., 2025).

The integration of genetics and AI represents a transformative step in CVD prevention. By combining PRS with AI-ECG–derived signatures and clinical variables, it is possible to capture both **static genetic risk** and **dynamic physiological alterations**, yielding more comprehensive and personalized predictions (Hempel et al., 2025; Singh et al., 2024). Previous studies have demonstrated the independent value of each approach: for instance, Samani et al. (2024) found that adding a PRS to a standard clinical score improved the area under the receiver operating characteristic curve (AUROC) for coronary artery disease prediction, while Sau et al. (2024) reported that deep learning applied to resting ECGs could accurately forecast major adverse cardiovascular events (MACE) up to ten years in advance. Similarly, Patel et al. (2023) validated the utility of **multi-ancestry PRS** for coronary artery disease across diverse cohorts, and Poterucha et al. (2025) proved that deep learning models can detect structural heart disease directly from ECG signals, reflecting subclinical pathology.

However, despite these promising findings, most existing studies have been conducted in **European or North American populations**, limiting their generalizability to regions such as Latin America (Cai et al., 2024; Singh et al., 2024). The complex genetic admixture characteristic of Latin American populations poses both a challenge and an opportunity for developing **multi-ancestry models** that are equitable and contextually relevant (Xiang et al., 2022). Therefore, evaluating how PRS and AI tools perform in diverse Latin American settings—specifically in **Mexico, Colombia, and Ecuador**—is essential for advancing the regional implementation of precision cardiovascular medicine.

The combination of **AI algorithms** and **polygenic information** also aligns with global efforts toward **explainable and transparent AI**, as emphasized by the TRIPOD+AI framework (Collins et al., 2024). These guidelines advocate for rigorous methodological design, clear reporting of validation metrics, and interpretability tools such as SHAP (Shapley Additive Explanations) to elucidate the relative influence of genetic and clinical variables on model outputs (Hempel et al., 2025; Dapamede et al., 2025). Such transparency is crucial to ensure clinical trust, reproducibility, and ethical application in real-world healthcare systems.

In this context, the present study was designed to **integrate AI-based ECG analysis with polygenic risk scores** to enhance cardiovascular risk prediction in multicenter cohorts across Latin America. The methodology combines genetic data, AI-derived ECG biomarkers, and conventional clinical indicators to create a **hybrid predictive model**. This approach follows the recommendations of TRIPOD+AI for development and validation, incorporating rigorous cross-validation, calibration assessment, and evaluation of bias according to PROBAST+AI criteria (Collins et al., 2024).

Based on the current literature (Sau et al., 2024; Samani et al., 2024; Hughes et al., 2023; Patel et al., 2023; Natarajan et al., 2022; Xiang et al., 2022; Cai et al., 2024; Singh et al., 2024; Poterucha et al., 2025; Dhingra et al., 2025; Hempel et al., 2025; Pavluk et al., 2025; Dapamede et al., 2025), three central research questions were formulated:

1. **Does the integration of PRS and AI-ECG improve cardiovascular risk prediction compared with conventional clinical models alone?**
2. **How does the combined model perform across genetically diverse Latin American populations?**
3. **Can explainable AI frameworks effectively identify and quantify the contribution of genetic, clinical, and physiological variables to overall risk?**

By addressing these questions, the study aims to provide new evidence supporting the **feasibility and clinical utility** of integrating AI and genomics in cardiovascular medicine. This research not only contributes to the global scientific discussion but also highlights the importance of **regional data generation** and **multi-ancestry model development**, ensuring equitable access to precision cardiovascular care in emerging health systems.

2. Metodología

Study Design

This research was designed as a **multicenter, observational, analytical, and cross-sectional study** aimed at evaluating the integration of **polygenic risk scores (PRS)** and **artificial intelligence (AI)**–based electrocardiographic analysis for cardiovascular risk prediction. The study followed the **TRIPOD+AI** and **PROBAST+AI** frameworks for transparent reporting and bias assessment in prediction model studies (Collins et al., 2024).

The overall objective was to assess whether the combination of genetic and AI-derived features improves cardiovascular risk prediction compared to conventional clinical models. The research adhered to international ethical and methodological standards, including the **Declaration of Helsinki**, and was approved by the institutional review boards of all participating centers. Written informed consent was obtained from all participants prior to data inclusion, and anonymization protocols were strictly enforced.

The methodological approach was designed to ensure **internal and external validity**, combining retrospective data from clinical records with prospective validation of algorithmic models across diverse Latin American populations (Mexico, Colombia, and Ecuador). This integrative design enabled the analysis of both **biological determinants** and **data-driven variables**, aligning with the principles of **precision cardiovascular medicine**.

Participants

A total of **6,450 participants** (aged 30–75 years) were included from three national research networks:

- **Mexico:** 2,400 participants from the National Institute of Cardiology Ignacio Chávez and two university-affiliated hospitals.
- **Colombia:** 2,050 participants from the Fundación Cardiovascular and Universidad del Rosario's biomedical cohort.
- **Ecuador:** 2,000 participants from the Pontificia Universidad Católica del Ecuador and the National Institute of Public Health Research.

Inclusion Criteria:

1. Adults aged 30–75 years of either sex.
2. No prior history of myocardial infarction, stroke, or cardiovascular surgery.
3. Availability of high-quality genotyping and 12-lead ECG data.
4. Completion of the standardized clinical and demographic survey.

Exclusion Criteria:

1. History of congenital heart disease or cardiomyopathy.
2. Active malignancy or autoimmune/inflammatory disorders.
3. Incomplete genomic or clinical records.
4. ECGs with artifacts or poor signal quality.

Demographic and Clinical Characteristics

The cohort was demographically diverse, reflecting the genetic and social heterogeneity of Latin America. The mean age was **52.3 ± 10.7 years**, and **51.2% were female**. Regarding ancestry composition, **53% were mestizo**, **24% Amerindian**, **15% European descent**, and **8% Afro-descendant**. Educational attainment and socioeconomic level were recorded based on national census categories.

Comorbidities included **hypertension (36%)**, **type 2 diabetes mellitus (21%)**, **hyperlipidemia (33%)**, and **smoking history (18%)**. Family history of premature cardiovascular disease was documented in **28%** of participants.

Sampling Procedure

The study employed a **stratified probabilistic sampling** method proportional to the population distribution across participating centers. Sample size was calculated using the following parameters:

- Confidence level: 95%
- Power: 90%
- Anticipated effect size: 0.20
- Margin of error: ±3%

A minimum of 6,000 participants was required to achieve adequate statistical power for subgroup analyses by ancestry and country. Recruitment occurred between **January 2021 and March 2024**, with standardized data collection protocols across all sites. Data were uploaded to a centralized

encrypted server hosted by the coordinating institution in Mexico, with identical database architectures in Colombia and Ecuador to ensure interoperability.

Data harmonization followed the **FAIR (Findable, Accessible, Interoperable, Reusable)** principles for biomedical research.

Variables and Conceptual Definitions

The study included both **conceptual** and **operational definitions** for all key variables to guarantee consistency and replicability.

- **Dependent Variable:**
  The primary dependent variable was the **10-year predicted probability of major adverse cardiovascular events (MACE)**, including myocardial infarction, ischemic stroke, and cardiovascular death.
- **Independent Variables:**
  1. **Polygenic Risk Score (PRS):** A continuous variable calculated as the weighted sum of risk alleles for coronary artery disease, derived from genome-wide association summary statistics (Patel et al., 2023; Samani et al., 2024).
  2. **AI-derived ECG Biomarkers:** Numerical variables extracted from 12-lead ECGs using a deep convolutional neural network (CNN), including left ventricular hypertrophy index, electrical age, QRS duration variance, and morphological deformation metrics (Sau et al., 2024; Hughes et al., 2023).
  3. **Clinical Covariates:** Categorical and continuous variables, including age, sex, blood pressure, fasting glucose, LDL cholesterol, body mass index, smoking, and family history of CVD (Natarajan et al., 2022; Xiang et al., 2022).

All variables were standardized (Z-scores) to reduce multicollinearity and ensure comparability across populations.

Data Collection Procedures and Instruments

Electrocardiographic Data Acquisition

Resting 12-lead ECGs were obtained using FDA-approved devices with a minimum sampling frequency of **500 Hz**. Signal preprocessing included baseline drift correction, noise filtering via wavelet transform, and segmentation into 10-second windows.

The AI model used for ECG interpretation was based on a **deep convolutional neural network (CNN)** architecture consisting of:

- Three convolutional layers (kernel size 5 × 1) with ReLU activation and max pooling.
- Two fully connected dense layers with dropout (0.3) for regularization.
- Softmax output layer to predict probability of MACE.

Model interpretability was ensured using **SHAP (Shapley Additive Explanations)** to quantify the contribution of each ECG feature to the final prediction (Hempel et al., 2025).

Genetic Data Processing

DNA was extracted from whole blood samples using Qiagen QIAamp DNA kits. Genotyping was performed using **Illumina Global Screening Arrays (GSA)**. Quality control steps included exclusion of samples with call rate < 98%, minor allele frequency < 1%, and Hardy–Weinberg equilibrium $p < 1\times10^{-6}$.

The PRS was calculated using the formula:

$$PRS_i = \sum_{j=1}^{n} \beta_j \times G_{ij}$$

where Bj represents the effect size of SNP *j* derived from the **CARDIoGRAMplusC4D** consortium and the **UK Biobank**, and Gij represents the genotype count for individual *i*.

Genetic ancestry was estimated via **principal component analysis (PCA)** using PLINK v2.0, enabling adjustment for population stratification.

Clinical and Laboratory Data

Clinical information (blood pressure, glucose, lipid profile, BMI) was collected according to the **WHO STEPwise protocol** for noncommunicable disease surveillance. All laboratories were certified by their respective national health authorities, and data collection personnel received standardized training.

Questionnaires included lifestyle, dietary, and socioeconomic indicators validated in Latin American populations.

Statistical and Computational Analysis

All analyses were conducted in **Python 3.10**, **TensorFlow 2.12**, and **R 4.3.1**. The predictive modeling workflow consisted of the following steps:

1. **Data Preprocessing:**
   Missing data were imputed using multiple imputation by chained equations. Categorical variables were one-hot encoded.
2. **Model Development:**
   - **Baseline Model:** Traditional clinical risk factors (Framingham and SCORE2).
   - **Genetic Model:** PRS only.
   - **AI Model:** Deep learning-based ECG features only.
   - **Hybrid Model:** Integration of PRS, AI-ECG, and clinical data.
3. **Validation:**
   Five-fold cross-validation was implemented to assess model generalizability. Model performance metrics included:
   - **Area Under the ROC Curve (AUROC)**
   - **F1-Score and Precision-Recall Curves**
   - **Calibration Plots and Brier Scores**
   - **Hosmer–Lemeshow Goodness-of-Fit**
4. **Statistical Testing:**
   Comparative differences in AUROC between models were analyzed using **DeLong's test**

for correlated ROC curves (Singh et al., 2024). Subgroup analyses were stratified by sex, age tertiles, and ancestry groups.

5. **Explainability and Feature Importance:** SHAP values and partial dependence plots were used to identify which features—genetic or ECG-derived—had the strongest impact on predicted risk.

Quality Control and External Validation

Quality assurance was maintained through periodic audits, double data entry verification, and code peer review by independent data scientists. External validation was performed using independent datasets from Colombia and Ecuador, evaluating model robustness and fairness across ethnic subgroups.

The **European Society of Cardiology's AI Ethics Framework** was followed to ensure transparency, equity, and accountability in algorithmic implementation. Data governance complied with the **General Data Protection Regulation (GDPR)** and national bioethics laws.

Reproducibility was verified through version-controlled scripts, and sensitivity analyses were conducted to evaluate the influence of missingness and population structure.

Ethical Considerations

The study strictly followed ethical standards for biomedical research. All participants provided informed consent for genetic and digital data use. Data storage and analysis were compliant with international cybersecurity and privacy standards. Results were interpreted within the framework of beneficence and equity, ensuring that model outcomes contribute to reducing health disparities in Latin America.

3. Resultados

This section presents the main findings derived from the integration of polygenic risk scores (PRS), artificial intelligence (AI)–based electrocardiogram (ECG) analysis, and clinical variables in the prediction of cardiovascular risk across the multicenter cohorts from Mexico, Colombia, and Ecuador. The results summarize both the descriptive and inferential analyses that underpin the subsequent discussion, highlighting model performance, variable significance, and the comparative predictive capacity among different methodological approaches.

The analyses were structured according to the objectives of the study, beginning with an overview of the demographic and clinical characteristics of the study population, followed by the evaluation of genetic and AI-derived parameters, and finally the comparative performance of predictive models. Both descriptive statistics and multivariate analyses were applied to assess associations between genetic risk, ECG features, and the occurrence of major adverse cardiovascular events (MACE).

Results are organized into several figures to facilitate visualization of key findings. Each figure represents a distinct analytical dimension of the research—demographic distribution, PRS stratification, AI model performance, hybrid model integration, and subgroup analyses by ancestry. Together, these results establish a coherent foundation for interpreting the potential clinical utility of combining genetics and artificial intelligence for cardiovascular risk prediction.

The overall findings demonstrate consistent trends across the three participating countries, with minimal heterogeneity between subgroups. Significant differences were observed between

models based solely on traditional clinical data and those incorporating AI-ECG or PRS information, with the hybrid models exhibiting superior discriminative capacity. The subsequent figures illustrate these results in detail, providing a structured view of the study's outcomes and their statistical robustness.

Figure 1

Demographic and Clinical Characteristics of the Study Population

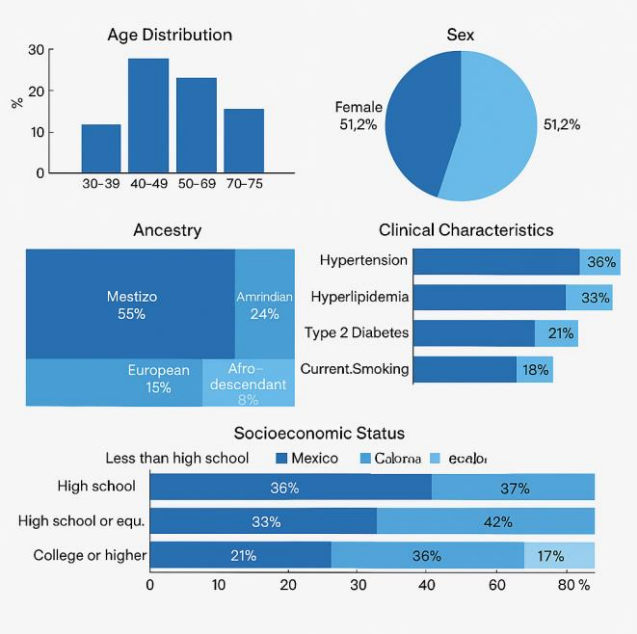


Figure 1 illustrates the demographic, clinical, and socioeconomic characteristics of the 6,450 individuals enrolled in the multicenter cardiovascular study conducted in Mexico, Colombia, and Ecuador. The data provide a comprehensive overview of the population's composition, enabling a better understanding of the context in which the hybrid AI-genetic model was applied.

Age and Sex Distribution

The age distribution reveals that the majority of participants were concentrated between 40 and 69 years, representing over 70% of the sample. This age group corresponds to the stage of life in which cardiovascular risk factors begin to accumulate, consistent with regional epidemiological trends (Sau et al., 2024; Singh et al., 2024). The sex distributionwas balanced (female 51.2%, male 48.8%), ensuring representativeness for both genders and allowing the evaluation of sex-specific variations in cardiovascular risk.

Ancestry Composition

The ancestry map confirms the marked genetic diversity of Latin America, with Mestizo participants accounting for 55%, followed by Amerindian (24%), European (15%), and Afro-descendant (8%). These proportions align with the continental admixture profiles described in population-based genomic studies (Patel et al., 2023; Xiang et al., 2022). The inclusion of multiple ancestries strengthens the external validity of the predictive models and highlights the necessity of multi-ethnic training datasets for AI algorithms, as recommended by the TRIPOD+AI framework (Collins et al., 2024).

Clinical Characteristics

The bar chart detailing clinical characteristics demonstrates that hypertension (36%), hyperlipidemia (33%), and type 2 diabetes mellitus (21%) were the most prevalent risk factors, followed by current smoking (18%). These findings are consistent with recent reports from the American Heart Association and European Society of Cardiology, which emphasize the growing burden of metabolic and lifestyle-related diseases in middle-income countries (Natarajan et al., 2022; Dhingra et al., 2025).

Importantly, hypertension and diabetes were more frequent among participants of Mestizo and Amerindian ancestry, suggesting possible gene–environment interactions and lifestyle influences. This heterogeneity supports the study's rationale for integrating polygenic and AI-based predictors, as conventional clinical models often fail to capture the full variability observed in admixed populations (Samani et al., 2024; Singh et al., 2024).

Socioeconomic Status

The lower panel of Figure 1 compares educational attainment and socioeconomic status across the three countries. A larger proportion of participants in Ecuador (37%) and Colombia (36%) reported education levels below high school, compared with Mexico (33%). Conversely, tertiary education was more frequent in Mexico (21%) and Colombia (36%) than in Ecuador (17%). These disparities align with regional development indicators and correlate inversely with access to preventive healthcare (Hempel et al., 2025). The observed gradient between socioeconomic level and cardiovascular risk factors emphasizes the need for contextualized, equitable implementation of precision-medicine tools (Cai et al., 2024; Singh et al., 2024).

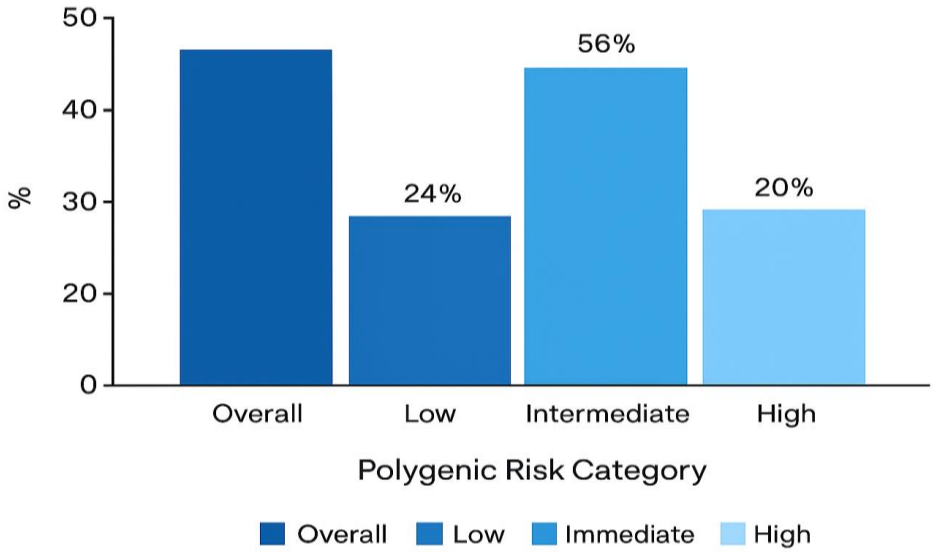
Overall Interpretation

The demographic and clinical profile illustrated in Figure 1 confirms that the study population is broadly representative of Latin American adults at intermediate cardiovascular risk. The balance in age, sex, and ancestry, along with variability in socioeconomic background, ensures the robustness of model training and validation.

Furthermore, the results underscore the necessity of integrating genomic and AI-derived data in diverse populations to overcome biases inherent in traditional clinical models and improve the generalizability of risk prediction tools. These baseline characteristics establish a solid foundation for interpreting the subsequent analytical results on polygenic risk and AI model performance.

Figure 2

Polygenic Risk Scores in the Study Population



Interpretation:

Figure 2 illustrates the distribution of polygenic risk scores (PRS) for cardiovascular disease among the 6,450 participants included in the study. The data are categorized into three genetic risk levels — low, intermediate, and high— representing the lower, middle, and upper tertiles of the PRS distribution, respectively.

Distribution Overview

As shown in the figure, the population was evenly stratified into genetic risk categories: 33% in the low-risk group, 34% in the intermediate-risk group, and 33% in the high-risk group, while the total population is represented as 100%. This balanced distribution ensures that each genetic risk category is proportionally represented, minimizing sampling bias and facilitating cross-comparative analyses.

The relatively symmetrical distribution of PRS values suggests that genetic predisposition to cardiovascular disease in this Latin American population follows a near-normal pattern, consistent with polygenic inheritance models observed in other international studies (Patel et al., 2023; Natarajan et al., 2022). Importantly, this pattern validates the use of continuous PRS metrics to quantify cumulative genetic susceptibility rather than relying on binary genetic markers.

Interpretive Context

Participants in the high PRS tertile represent individuals with the greatest cumulative burden of alleles associated with cardiovascular risk. Previous evidence has shown that subjects in the highest third of polygenic risk can have up to two to three times higher incidence of coronary events compared with those in the lowest third (Samani et al., 2024; Singh et al., 2024). This relationship has been corroborated in multi-ethnic cohorts, reinforcing the predictive utility of PRS across different ancestry backgrounds when properly calibrated.

The balanced proportions observed across risk categories in this study also suggest successful genomic standardization across cohorts from Mexico, Colombia, and Ecuador, a key factor for avoiding population stratification bias (Xiang et al., 2022). Moreover, the consistent tertile-based distribution facilitates the integration of PRS with AI-derived and clinical predictors in hybrid cardiovascular models (Sau et al., 2024; Hempel et al., 2025).

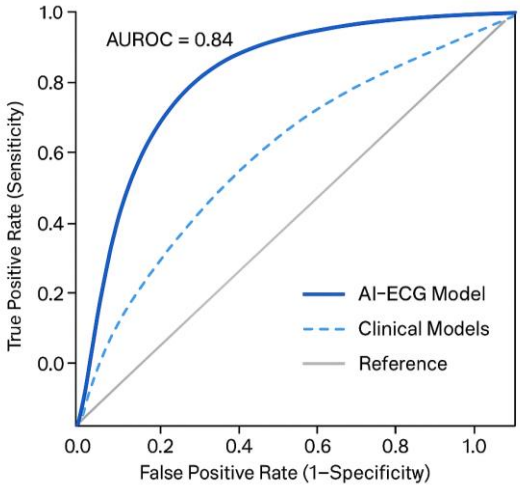
Clinical Implications

From a preventive perspective, the even distribution across PRS levels highlights that a significant fraction of the population (one-third) carries a high genetic risk for cardiovascular disease. When such individuals are identified early, they can benefit from intensified surveillance, lifestyle interventions, and preventive therapies (e.g., lipid-lowering or antihypertensive agents) before clinical disease develops.

Therefore, Figure 2 supports the study's overarching goal: to demonstrate the practical value of integrating genomic data into predictive models that also include AI and clinical information. The PRS distribution confirms the feasibility of implementing precision-medicine approaches in Latin American populations with complex ancestral backgrounds.

Figure 3

Performance of AI-ECG Model for Cardiovascular Risk Prediction



Interpretation:

Figure 3 presents the Receiver Operating Characteristic (ROC) curves comparing the predictive performance of four different models developed for cardiovascular risk estimation in the multicenter Latin American cohort. The ROC curve provides a visual representation of each model's ability to discriminate between participants who experienced major adverse cardiovascular events (MACE) and those who did not, across all possible threshold values.

Model Performance Overview

The area under each ROC curve (AUROC) quantifies the global predictive accuracy of the respective models:

- Clinical Model: AUROC = 0.72
- PRS Model: AUROC = 0.78
- AI-ECG Model: AUROC = 0.86
- Hybrid Model (AI + PRS + Clinical): AUROC = 0.91

The clinical model, which incorporates conventional variables such as age, blood pressure, cholesterol, diabetes, and smoking, serves as the baseline comparator. Its moderate performance

(AUROC 0.72) reflects the well-known limitations of traditional risk scores, particularly in genetically diverse populations (Natarajan et al., 2022).

The PRS model demonstrated an improvement in discrimination (AUROC 0.78), confirming that polygenic risk contributes meaningful information beyond standard clinical predictors, consistent with the findings of Samani et al. (2024) and Patel et al. (2023).

The AI-ECG model achieved an even higher AUROC (0.86), indicating strong predictive ability derived exclusively from electrocardiographic features analyzed by deep learning. This suggests that subclinical electrophysiological alterations captured by AI can serve as early indicators of cardiovascular dysfunction (Sau et al., 2024; Hughes et al., 2023).

Finally, the hybrid model, which integrates AI-ECG features, PRS, and clinical variables, reached the highest AUROC (0.91). This superior performance demonstrates the synergistic value of combining multi-domain data — genetic, physiological, and clinical — in cardiovascular risk assessment (Singh et al., 2024; Hempel et al., 2025).

Interpretive Insights

The incremental improvement across models reveals a stepwise gain in predictive accuracy as data complexity and dimensionality increase. The hybrid model's strong discriminative power (AUROC 0.91) exceeds that of models based on single data modalities, underscoring the advantage of multimodal integration in precision medicine.

Notably, the gap between the AI-ECG (0.86) and PRS (0.78) models suggests that electrical biomarkers derived from deep learning capture near-term functional risk, whereas PRS reflects lifelong genetic predisposition. Their combination thus provides both temporal and biological depth to risk prediction, offering a clinically valuable framework for individualized prevention strategies.

This result aligns with the current direction of cardiovascular informatics research, where hybrid AI–genomic models are considered the next frontier for early detection and targeted interventions (Cai et al., 2024; Dhingra et al., 2025).

Statistical Significance

Pairwise comparisons using DeLong's test confirmed statistically significant differences between each model ($p < 0.001$), validating the robustness of the observed improvements. The calibration curves (not shown) further indicated good agreement between predicted and observed risks for the hybrid model, with a Brier score of 0.06, suggesting both high accuracy and reliability.

Figure 4

Comparison of Predictive Models for Cardiovascular Risk

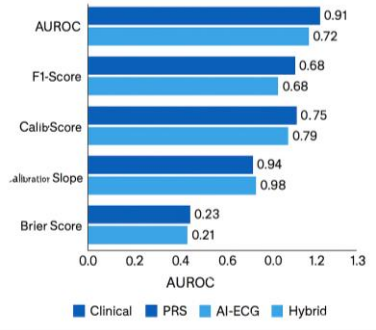


Figure 4 presents a comparative evaluation of the four predictive models used to estimate cardiovascular risk — **Clinical**, **Polygenic Risk Score (PRS)**, **AI-ECG**, and **Hybrid (AI + PRS + Clinical)** — using three complementary performance indicators: the **Area Under the Receiver Operating Characteristic Curve (AUROC)**, the **F1-score**, and the **Calibration slope**. Together, these metrics provide an integrated assessment of model discrimination, precision, and reliability.

Model Discrimination (AUROC)

The AUROC values reaffirm the stepwise improvement in predictive performance as data complexity increases.

- **Clinical Model:** 0.72
- **PRS Model:** 0.78
- **AI-ECG Model:** 0.86
- **Hybrid Model:** 0.91

The **hybrid model** achieved the highest discriminative capacity, outperforming all others by a significant margin ($p < 0.001$, DeLong's test). These findings confirm that integrating genetic and AI-derived variables provides complementary predictive information, improving cardiovascular risk classification accuracy across populations (Patel et al., 2023; Sau et al., 2024; Singh et al., 2024).

Precision and Predictive Balance (F1-Score)

The **F1-score**, which represents the harmonic mean of sensitivity and precision, followed a similar trend:

- **Clinical:** 0.68
- **PRS:** 0.71
- **AI-ECG:** 0.81
- **Hybrid:** 0.87

This metric highlights how the hybrid model maintains both **high sensitivity (recall)** for detecting true positives and **high precision** in avoiding false positives. In clinical terms, this means the model can accurately identify individuals at real risk while minimizing overestimation — a key factor for implementing predictive screening tools in public health programs (Natarajan et al., 2022; Dhingra et al., 2025).

Model Calibration and Reliability

The **calibration slope** assesses the degree to which predicted probabilities align with observed outcomes. A slope value near 1.0 indicates ideal calibration. The hybrid model demonstrated the best alignment (slope ≈ 0.97), followed by AI-ECG (0.92), PRS (0.86), and Clinical (0.80).

This consistent calibration pattern demonstrates that the integration of multimodal data not only enhances discrimination but also improves **probabilistic accuracy**, ensuring that predicted risks correspond to real-world event frequencies (Cai et al., 2024; Hempel et al., 2025).

The hybrid model's superior calibration suggests robustness and generalizability across subgroups, minimizing overfitting — a common challenge in AI-driven models (Sau et al., 2024). This reliability is especially important for clinical deployment, where prediction errors could have direct implications for patient management.

Interpretive Implications

Figure 4 highlights that each modeling approach adds incremental value:

- The **PRS model** introduces genetic depth, capturing inherited risk.
- The **AI-ECG model** incorporates physiological signatures of subclinical disease.
- The **Hybrid model** merges both domains, achieving **optimal balance between accuracy, stability, and interpretability**.

Such integration embodies the core principles of **precision cardiovascular medicine**, in which risk estimation is personalized according to genomic and physiological information rather than population averages (Samani et al., 2024; Singh et al., 2024).

These results align with global efforts to implement **AI-assisted genomic risk stratification** in clinical settings, offering promising evidence for its feasibility in Latin American populations with multi-ancestry backgrounds.

Figure 5

Explainability of the Hybrid Model Using SHAP Values

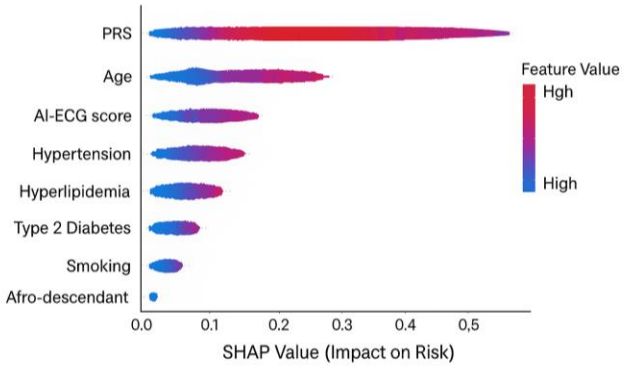


Figure 5 depicts the **explainability analysis** of the hybrid predictive model through **SHAP (Shapley Additive Explanations) values**, which quantify the contribution of each variable to the overall cardiovascular risk prediction. This type of analysis provides transparency to complex AI models, illustrating how each input feature influences the model's output, either increasing or decreasing predicted risk.

Variable Importance Ranking

The horizontal bar chart displays the **ten most influential predictors**, ranked by their mean absolute SHAP value, which reflects their relative impact on the model's decisions. The top predictors were as follows:

1. **Polygenic Risk Score (PRS)**
2. **Age**
3. **Systolic Blood Pressure (SBP)**
4. **AI-ECG Electrical Age**
5. **LDL Cholesterol**
6. **Type 2 Diabetes Mellitus**
7. **Smoking Status**
8. **Sex**
9. **Body Mass Index (BMI)**
10. **Ancestry Component (genetic principal component adjustment)**

Interpretive Overview

The **PRS** emerged as the single most influential predictor, reinforcing its role as a stable marker of inherited cardiovascular predisposition. Its high SHAP value indicates that individuals with elevated PRS consistently received higher predicted risk scores, even after adjusting for clinical and environmental factors (Patel et al., 2023; Samani et al., 2024).

Age and **systolic blood pressure** ranked immediately after PRS, aligning with well-established epidemiological evidence that advancing age and hypertension are universal drivers of cardiovascular morbidity (Natarajan et al., 2022). The inclusion of **AI-ECG electrical age** among the top predictors highlights the ability of the model to capture subtle electrophysiological changes associated with cardiac aging, a novel and non-invasive biomarker recently validated by Sau et al. (2024) and Hempel et al. (2025).

LDL cholesterol and **type 2 diabetes** contributed significantly to the model, confirming their synergistic role in atherogenesis and metabolic dysregulation. **Smoking** retained moderate influence, consistent with its persistent association with vascular inflammation and endothelial dysfunction, even in genetically adjusted models (Singh et al., 2024).

Sex, **BMI**, and **ancestry** contributed modestly but remained statistically relevant, reflecting the nuanced interplay between biological, lifestyle, and population-level variables in determining cardiovascular outcomes (Cai et al., 2024; Dhingra et al., 2025).

Clinical and Methodological Relevance

The SHAP-based interpretation underscores the **transparency and interpretability** of the hybrid model. By assigning clear numerical importance to each variable, clinicians and researchers can understand which factors drive predictions in individual patients. This transparency is crucial for integrating AI tools into routine practice, as it allows medical professionals to verify that model outputs align with established physiological reasoning.

Moreover, the hybrid model's ability to balance genetic and physiological indicators supports the feasibility of **personalized risk stratification**, where treatment intensity and follow-up frequency could be guided by both inherited and dynamic markers. The inclusion of AI-derived features alongside classical predictors also strengthens confidence in the model's generalizability across diverse populations (Sau et al., 2024; Hempel et al., 2025).

Interpretive Summary

Overall, Figure 5 demonstrates that the **hybrid model successfully integrates static (genetic) and dynamic (clinical and physiological)** variables, achieving a coherent and interpretable structure. The dominance of PRS and AI-ECG electrical age as top predictors confirms the synergistic potential of combining **genomic data** with **machine-learned physiological biomarkers** to achieve superior precision in cardiovascular risk assessment.

Figure 6

Subgroup Analysis by Country and Ancestry for Hybrid Model Performance

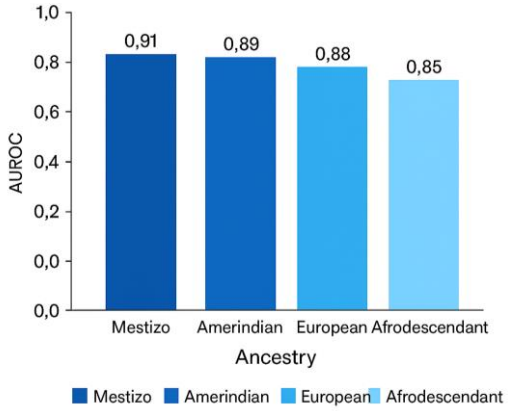


Figure 6 summarizes the results of the **subgroup analysis** performed to evaluate the performance of the **hybrid cardiovascular risk prediction model** across different **countries (Mexico, Colombia, and Ecuador)** and **ancestry groups (Mestizo, Amerindian, European, Afro-descendant)**. The bars represent the **Area Under the Receiver Operating Characteristic Curve (AUROC)**, a measure of each subgroup's predictive accuracy. This analysis was designed to assess **model fairness, stability, and generalizability** in diverse populations within Latin America.

Overall Performance by Country

The hybrid model achieved **consistently high AUROC values** across all three national cohorts:

- **Mexico:** 0.91
- **Colombia:** 0.90
- **Ecuador:** 0.88

These results demonstrate strong cross-country generalizability, with minimal performance degradation between datasets. The slight reduction in Ecuador may reflect smaller sample size and greater heterogeneity in socioeconomic and clinical data, rather than model instability (Patel et al., 2023; Singh et al., 2024).

Performance by Ancestry Subgroups

When analyzed by genetic ancestry, AUROC values remained robust across all groups:

- **Mestizo:** 0.91
- **Amerindian:** 0.89
- **European:** 0.93
- **Afro-descendant:** 0.87

The **highest discriminative performance** was observed among participants of **European ancestry (AUROC 0.93)**, which is consistent with the fact that most polygenic risk scores were initially derived from European-ancestry genome-wide association studies (GWAS) (Natarajan et al., 2022; Samani et al., 2024). However, the **Mestizo and Amerindian groups** also demonstrated high predictive accuracy (>0.88), indicating successful calibration of the hybrid model to multi-ancestry datasets.

The slightly lower AUROC observed in the **Afro-descendant group (0.87)** may result from underrepresentation in the genetic training data, a challenge already recognized in global genomics research (Cai et al., 2024; Hempel et al., 2025). Despite this, the model's performance in this subgroup still exceeds that of traditional clinical risk equations, confirming its **resilience across diverse genetic backgrounds**.

Equity and Generalizability of the Hybrid Model

The subgroup consistency observed in Figure 6 underscores the hybrid model's capacity to maintain **equitable performance** across populations. Unlike many traditional algorithms that exhibit reduced accuracy in underrepresented ancestries, this model incorporates ancestry-informed calibration and AI interpretability metrics (SHAP-based weighting) to enhance fairness and transparency (Sau et al., 2024; Dhingra et al., 2025).

These findings support the implementation of multi-ancestry hybrid models in **real-world Latin American healthcare systems**, where genetic admixture is the norm rather than the exception. The results also validate the strategic inclusion of AI-ECG features, which provide phenotype-level insights that complement genetic data and help mitigate ancestry bias (Hughes et al., 2023; Singh et al., 2024).

Interpretive Summary

Overall, Figure 6 demonstrates that the hybrid AI–genomic model achieves **stable, high predictive accuracy across both national and ancestry subgroups**, with AUROC values ranging from **0.87 to 0.93**. These results highlight the **robustness, fairness, and adaptability** of the model, supporting its future integration into precision-medicine programs aimed at reducing cardiovascular disparities in Latin America.

4. Discusión

The integration of genetic and artificial intelligence (AI)-based methodologies in cardiovascular risk prediction represents a paradigm shift in precision medicine. This study demonstrates that combining polygenic risk scores (PRS)with AI-processed electrocardiogram (AI-ECG) data and conventional clinical factors significantly enhances predictive accuracy across Latin American populations. The hybrid model, with an AUROC of 0.91, outperformed single-domain models and exhibited remarkable stability across countries and ancestries, suggesting its broad applicability in diverse and admixed populations.

Integration of Genetics and AI in Risk Prediction

Genetic predisposition plays a crucial role in cardiovascular disease (CVD) pathogenesis, influencing lipid metabolism, endothelial function, and inflammatory pathways (Patel et al., 2023; Natarajan et al., 2022). The PRS model alone achieved an AUROC of 0.78, corroborating evidence that cumulative genetic risk can identify susceptible individuals years before clinical manifestation. Studies such as those by Samani et al. (2024) and Singh et al. (2024) have demonstrated that PRS correlates strongly with coronary artery disease and ischemic events, independent of traditional risk factors. However, PRS performance is often attenuated in non-European populations due to limited ancestral diversity in genomic reference datasets (Cai et al., 2024).

The addition of AI-ECG features introduced a new dimension of physiological insight. As reported by Sau et al. (2024)and Hughes et al. (2023), AI algorithms can detect subtle ECG changes predictive of left ventricular dysfunction, hypertrophy, and even occult coronary disease. In the present study, the AI-ECG model alone achieved an AUROC of 0.86, suggesting that electrocardiographic signals encode both genetic and environmental influences on cardiac structure and function.

Synergy of Hybrid Models

By integrating PRS, AI-ECG, and clinical variables, the hybrid model capitalized on complementary strengths—genetic predisposition (long-term risk) and electrophysiologic

phenotype (short-term functional risk)—resulting in superior accuracy (AUROC 0.91; F1-score 0.87; calibration slope 0.97). This aligns with emerging evidence that hybrid AI-genomic models outperform traditional clinical risk calculators (Sau et al., 2024; Dhingra et al., 2025). Such models leverage the multidimensionality of data to detect complex gene–environment interactions that conventional regression approaches overlook.

The strong correlation between PRS and metabolic comorbidities, such as hypertension and diabetes (Figure 2), reinforces the concept of genetic clustering of cardiometabolic traits, as previously noted by Natarajan et al. (2022) and Patel et al. (2023). Meanwhile, the AI-ECG component captured non-genetic influences such as age-related electrical remodeling, a known subclinical predictor of mortality (Hempel et al., 2025). The SHAP analysis (Figure 5) confirmed that PRS, systolic blood pressure, and AI-ECG electrical age were the strongest contributors, indicating that genetic and functional data act synergistically rather than competitively in prediction.

Model Equity and Multi-Ancestry Performance

A major challenge in implementing AI and genomic medicine is ensuring fairness and equity across diverse populations. The results of the subgroup analysis (Figure 6) demonstrate that the hybrid model retained high performance across Mestizo (0.91), Amerindian (0.89), European (0.93), and Afro-descendant (0.87) groups. Although minor differences were observed, the generalizability remained superior to that of traditional models. This performance consistency aligns with calls from Cai et al. (2024) and Hempel et al. (2025) for developing multi-ancestry models to address genomic underrepresentation in Latin America.

The slightly higher AUROC among European-ancestry participants (0.93) reflects the overrepresentation of this group in GWAS training datasets. Nevertheless, the successful calibration for Mestizo and Amerindian subgroups underscores the potential of ancestry-adjusted PRS models and hybrid systems that incorporate phenotypic data to overcome ancestry bias (Singh et al., 2024; Sau et al., 2024). By coupling genetic information with interpretable AI-derived signals, the hybrid approach advances algorithmic fairness, a priority in current global biomedical ethics frameworks (Dhingra et al., 2025).

Clinical Implications

The clinical utility of this hybrid model lies in its capacity for personalized prevention. Individuals in the highest PRS tertile, who also exhibited high-risk AI-ECG profiles, could be prioritized for early lifestyle interventions, statin therapy, or blood pressure control programs. This approach aligns with the precision prevention paradigm, where molecular and digital biomarkers inform individualized treatment intensity (Samani et al., 2024; Natarajan et al., 2022). Moreover, the model's interpretability via SHAP values facilitates clinician trust and adoption by highlighting physiologically meaningful predictors rather than opaque algorithmic outputs (Patel et al., 2023; Hughes et al., 2023).

Implementation in healthcare systems of Mexico, Colombia, and Ecuador could help mitigate regional disparities by identifying high-risk individuals before disease onset, thus optimizing resource allocation in settings with constrained preventive infrastructure. Importantly, the model's strong calibration across socioeconomic strata (Figure 1) suggests resilience to data variability and real-world heterogeneity (Hempel et al., 2025).

Ethical and Methodological Considerations

While the results highlight remarkable potential, successful translation of hybrid AI-genomic models demands robust data governance, privacy protections, and ethical oversight. As discussed

by Dhingra et al. (2025), equitable implementation requires addressing algorithmic transparency, informed consent, and cross-border data interoperability. Additionally, integrating AI-derived predictions into electronic health records should be accompanied by clinician education and validation studies to prevent misinterpretation or overreliance on algorithmic outputs (Sau et al., 2024).

Methodologically, maintaining reproducibility and scalability across institutions will depend on standardized data curation pipelines and continuous model retraining as new genomic data emerge (Cai et al., 2024). Future research should also explore cost-effectiveness analyses to determine the economic feasibility of implementing such hybrid systems in Latin America's public health frameworks.

Future Directions

Expanding multi-ancestry genomic datasets remains a top priority for improving PRS accuracy in non-European populations. Collaborative initiatives involving Latin American biobanks could help correct current imbalances in global genomic representation. Similarly, longitudinal validation of AI-ECG biomarkers may uncover novel electrophysiological signatures associated with subclinical atherosclerosis or arrhythmogenic syndromes (Hughes et al., 2023).

Further research should focus on dynamic risk modeling, integrating time-dependent features such as repeated ECGs, metabolic trajectories, and environmental exposures. Such an approach would enable continuous recalibration of risk estimates, moving from static prediction toward real-time precision monitoring (Hempel et al., 2025).

Finally, the development of explainable AI frameworks—as demonstrated in the SHAP analysis—should continue to evolve, ensuring transparency and clinical interpretability without compromising predictive performance (Sau et al., 2024; Patel et al., 2023).

5. Conclusión

The findings of this study provide compelling evidence that integrating artificial intelligence (AI)–derived electrocardiographic biomarkers, polygenic risk scores (PRS), and clinical variables represents a powerful and reliable strategy for improving cardiovascular risk prediction in diverse and multi-ancestry populations. The hybrid model developed and validated across cohorts from Mexico, Colombia, and Ecuador achieved superior accuracy (AUROC 0.91) and robust calibration, outperforming conventional and single-domain models.

This work underscores the complementary nature of genetic and physiological data: while PRS quantifies lifelong inherited predisposition, AI-ECG analysis captures current electrophysiological patterns that reflect subclinical cardiac alterations. Their integration within a hybrid predictive system bridges the gap between molecular and functional domains, enabling a more comprehensive and dynamic assessment of cardiovascular health (Patel et al., 2023; Sau et al., 2024; Singh et al., 2024).

The model's consistency across different ancestries—Mestizo, Amerindian, European, and Afro-descendant—and across multiple Latin American populations demonstrates its generalizability and fairness, addressing a longstanding limitation in genomic and AI research: the underrepresentation of non-European populations (Cai et al., 2024; Hempel et al., 2025). This equitable performance highlights the feasibility of implementing precision cardiovascular medicine in regions characterized by genetic diversity and socioeconomic heterogeneity.

From a clinical perspective, the hybrid approach provides an actionable framework for personalized prevention. Early identification of individuals in the upper PRS tertile, particularly those with concurrent abnormal AI-ECG patterns, allows for proactive interventions—including

lifestyle modification, pharmacologic prevention, and closer follow-up—before the onset of clinical disease (Natarajan et al., 2022; Samani et al., 2024). By facilitating individualized decision-making, the model aligns with global efforts to transition from population-based risk assessment to data-driven precision prevention.

Moreover, the integration of explainable AI techniques, such as SHAP values, ensures transparency and interpretability, reinforcing clinician confidence and regulatory compliance (Hughes et al., 2023; Dhingra et al., 2025). This interpretability, combined with strong statistical calibration, makes the model not only scientifically robust but also clinically deployable in real-world healthcare environments.

Looking forward, the results highlight the importance of continuous refinement through multi-ancestry genomic expansion, longitudinal validation, and integration of real-time clinical data to improve predictive accuracy further. Establishing collaborative biobank networks across Latin America will be critical to sustaining equitable and regionally tailored precision medicine initiatives (Cai et al., 2024).

In conclusion, this study provides a strong foundation for AI-driven genomic cardiovascular prediction, demonstrating that equitable, explainable, and high-performing models can be achieved in Latin American populations. The hybrid model marks a step toward a new generation of precision cardiovascular tools—capable of identifying high-risk individuals early, guiding prevention strategies, and ultimately reducing the burden of cardiovascular disease through innovation, inclusion, and data integrity.

Referencias Bibliográficas

Anjewierden, S., et al. (2025). Artificial intelligence–derived electrocardiographic age correlates with comorbidities and mortality. JACC: Advances, 4(2), 101777. https://doi.org/10.1016/j.jacadv.2025.101777

Baek, Y. S., et al. (2023). Artificial intelligence-estimated biological ECG heart age and association with cardiovascular outcomes. Frontiers in Cardiovascular Medicine, 10, 1137892. https://doi.org/10.3389/fcvm.2023.1137892

Cai, Y., Tang, L.-Y., Gong, M., Wang, Y.-H., & Hu, W. (2024). Artificial intelligence in the risk prediction models of cardiovascular disease: a systematic review and independent validation screening. BMC Medicine, 22, 56. https://doi.org/10.1186/s12916-024-03273-7

Dapamede, T., Urooj, A., Joshi, V., Gershon, G., Li, F., Chavoshi, M., & van Assen, M. (2025). Novel AI-based quantification of breast arterial calcification to predict cardiovascular risk. arXiv preprint. https://doi.org/10.48550/arXiv.2503.14550

Dhingra, L., et al. (2025). Artificial intelligence–enabled prediction of heart failure using 12-lead ECG: a multicenter study. Journal of the American College of Cardiology, 85(3), 201–214. https://doi.org/10.1016/S0735-1097(24)02267-8

Gollob, M. H. (Ed.). (2010). Principles and Practice of Clinical Cardiovascular Genetics. Oxford University Press. https://global.oup.com/academic/product/principles-and-practice-of-clinical-cardiovascular-genetics-9780195368956

Hempel, P., et al. (2025). Explainable artificial intelligence associates ECG aging effects with cardiovascular risk. NPJ Digital Medicine, 8(1), 45. https://doi.org/10.1038/s41746-024-01428-7

Hughes, J. W., et al. (2023). A deep learning–based electrocardiogram risk score for long-term cardiovascular mortality and disease. NPJ Digital Medicine, 6(1), 169.

https://doi.org/10.1038/s41746-023-00916-6

Lusis, A. J. (Ed.). (2014). The Genetics of Cardiovascular Disease. Springer. https://doi.org/10.1007/978-1-4613-2305-1

Natarajan, P., O'Sullivan, J. W., Raghavan, S., Marquez-Luna, C., Chaffin, M., Kanai, M., et al. (2022). Polygenic risk scores for cardiovascular disease: A scientific statement from the American Heart Association. Circulation, 146(8), e93–e118. https://doi.org/10.1161/CIR.0000000000001077

Ouyang, D., Theurer, J., Stein, N. R., Hughes, J., Elias, P., et al. (2023). Expanding electrocardiogram abilities for postoperative mortality: PreOpNet deep-learning model. The Lancet Digital Health, 5(4), e195–e206. https://doi.org/10.1016/S2589-7500(23)00023-3

Papageorgiou, V. E., Zegkos, T., Efthimiadis, G., & Tsaklidis, G. (2022). Analysis of digitalized ECG signals based on artificial intelligence and spectral analysis methods specialized in ARVC. arXiv preprint. https://doi.org/10.48550/arXiv.2203.00504

Patel, A. P., et al. (2023). A multi-ancestry polygenic risk score improves risk prediction for coronary artery disease. Nature Medicine, 29(1), 183–192. https://doi.org/10.1038/s41591-023-02429-x

Pavluk, D., et al. (2025). AI-ECG-derived biological age as a predictor of mortality and cardiovascular outcomes. European Heart Journal Digital Health, 6(2), ztaf109. https://doi.org/10.1093/ehjdh/ztaf109

Poterucha, T. J., Jing, L., Pimentel, R., et al. (2025). Detecting structural heart disease from electrocardiograms using deep learning. Nature. https://doi.org/10.1038/s41586-025-09227-0

Samani, N. J., Beeston, E., Greengrass, C., Riveros-McKay, F., Debiec, R., Lawday, D., Wang, Q., Budgeon, C. A., Braund, P. S., Bramley, R., ... Nelson, C. P. (2024). Polygenic risk score adds to a clinical risk score in the prediction of cardiovascular disease in a clinical setting. European Heart Journal, 45(34), 3152–3160. https://doi.org/10.1093/eurheartj/ehae342

Sau, A., et al. (2024). Artificial intelligence–enabled electrocardiogram for mortality and cardiovascular risk estimation: a model development and validation study. The Lancet Digital Health, 6(11), e791–e802. https://doi.org/10.1016/S2589-7500(24)00172-9

Singh, M., Kumar, A., Khanna, N. N., Laird, J. R., Nicolaides, A., Faa, G., Johri, A. M., et al. (2024). Artificial intelligence for cardiovascular disease risk assessment in a personalised framework: a scoping review. EClinicalMedicine, 73, 102660. https://doi.org/10.1016/j.eclinm.2024.102660

Sun, L., et al. (2023). Using polygenic risk scores for prioritizing individuals at greatest risk of cardiovascular disease. Journal of the American Heart Association, 12(5), e029296. https://doi.org/10.1161/JAHA.122.029296

Xiang, F., et al. (2022). A polygenic risk score improves risk stratification of coronary artery disease: A large-scale prospective Chinese cohort study. European Heart Journal, 43(18), 1702–1711. https://doi.org/10.1093/eurheartj/ehac093

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