

Review

A Pharmaceutical Paradigm for Cardiovascular Composite Risk Assessment Using Novel Radiogenomics Risk Predictors in Precision Explainable Artificial Intelligence Framework: Clinical Trial Tool

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Abstract

Background: Cardiovascular disease (CVD) is challenging to diagnose and treat since symptoms appear late during the progression of atherosclerosis. *Conventional risk factors* alone are not always sufficient to properly categorize at-risk patients, and *clinical risk scores* are inadequate in predicting cardiac events. Integrating *genomic-based biomarkers* (GBBM) found in plasma/serum samples with novel non-invasive *radiomics-based biomarkers* (RBBM) such as plaque area, plaque burden, and maximum plaque height can improve composite CVD risk prediction in the pharmaceutical paradigm. These biomarkers consider several pathways involved in the pathophysiology of atherosclerosis disease leading to CVD. **Objective:** This review proposes two hypotheses: (i) The composite biomarkers are strongly correlated and can be used to detect the severity of CVD/Stroke precisely, and (ii) an *explainable artificial intelligence* (XAI)-based composite risk CVD/Stroke model with survival analysis using deep learning (DL) can predict in preventive, precision, and personalized (aiP³) framework benefiting the pharmaceutical paradigm. **Method:** The PRISMA search technique resulted in 214 studies assessing composite biomarkers using radiogenomics for CVD/Stroke. The study presents a XAI model using AtheroEdge™ 4.0 to determine the risk of CVD/Stroke in the pharmaceutical framework using the radiogenomics biomarkers. **Conclusions:** Our observations suggest that the composite CVD risk biomarkers using radiogenomics provide a new dimension to CVD/Stroke risk assessment. The proposed review suggests a unique, unbiased, and XAI model based on AtheroEdge™ 4.0 that can predict the composite risk of CVD/Stroke using radiogenomics in the pharmaceutical paradigm.

Keywords: cardiovascular disease; stroke; biomarkers; radiomics; genomics; deep learning; bias; pruning; cloud; multicenter; pharmaceutical; explainable artificial intelligence



1. Introduction

Cardiovascular diseases (CVD) kill 17.3 million people each year. This figure is predicted to increase to 23.6 million by 2030 [1,2]. By 2030, this will cost \$920 billion in direct healthcare costs, a challenge for the public health system [3]. Among the various types of CVD, coronary heart disease (CHD) is the leading cause. This disease is due to atherosclerosis, the chronic inflammatory condition of the artery wall and one of the most common causes of death [4,5]. CVD is caused by many things, including genetic, metabolomic, environmental, behavioural, and lifestyle factors [6,7]. Although traditional risk factors such as age, gender, high cholesterol, high blood pressure [8], smoking, and comorbidities like diabetes mellitus [9], obesity [10], and hypertension [11,12] are commonly used risk factors for predicting CVD risk, laboratory-based biomarkers are not always feasible, particularly in developing countries with resource constraints [13,14]. Also, most scoring systems for CVD risk were made for Caucasians, and their validity and usefulness in other ethnic groups are still unknown [15]. As a result, CVD risk is frequently misdiagnosed. Although patients gain in some ways, it lacks the ethnic effect of medication design as well as the benefits of tailored therapy due to genomes and proteomics [16,17].

Furthermore, the current design of the risk assessment tool lacks CVD risk stratification due to the non-linear behavior caused by the amalgamation of all the risk predictors [18]. However, the benefit to the drug industry in medication design has not been realized due to the absence of artificial intelligence (AI) methodologies, which leads to CVD risk stratification with different grades [19]. So, to achieve the above objectives, one certainly needs AI strategies for CVD risk assessment, particularly in big data or large cohorts [20,21]. This requires composite CVD risk designs that can operate in batch (large cohort side) mode, sometimes called Pharma (Pharmaceutical) Mode, for automatically processing a large set of patients [22]. Previous studies conducted clinical trials but lacked AI-based solutions [22].

Further, it did not consider the composite risk of CVD stratification [23,24]. Studies that did CVD also lack AI-based solutions [25]. Thus, there is a need for AI-based CVD composite risk in large cohorts for pharmaceutical companies to benefit from their drug design [26].

The Precision Medicine Initiative (PMI), introduced by former US President Obama in 2015, can potentially reduce the worldwide burden of CVD by mobilizing collective resources and expertise to develop and spread knowledge [27]. The precision medicine approach makes it possible to start treatments earlier, use more advanced diagnostics, and make treatments more personalized and affordable [28]. The precision medicine approach, with the help of AI, can improve symptom-driven care by proactively combining multi-omics assessments with clinical [28], imaging [29,30], epidemiological [31], and demographic variables [32].

Precision medicine allows for earlier treatments for advanced diagnostics and tailoring better and more affordable personal treatment [29,33,34]. Advanced data analysis techniques are being employed more and more to aid in the development of successful CVD treatments [35]. Batch mode processing allows large data sets to be analyzed at once, facilitating a more thorough examination of patient risk factors and comorbidities to determine the best course of treatment [36]. Additionally, composite CVD risk stratification considers the combined effect of multiple risk factors to create a more comprehensive assessment of a patient's risk [37]. Finally, the ability to categorize patients into different risk classes ranging from low to high allows for more personalized and effective treatment approaches to be developed based on a patient's risk profile [38]. These tools provide valuable support to healthcare providers in managing CVD and improving patient outcomes. In this paragraph, we have to first give the spirit of using DL due to the success of DL in healthcare [39]. As a result, we propose that DL can be adapted for routine mode and pharmacological models for assessing CVD/Stroke risk.

This study proposes deep learning (DL) to stratify the risk of CVD/Stroke using *radiomics-based biomarker* (RBBM) and *genomics-based biomarker* (GBBM) as covariates in pharmaceutical mode. The study also investigates pruned or compacted AI systems for CVD risk using multi-omics data and uses an explainability model to illuminate AI's "Black Box Nature" [40]. Fig. 1 depicts the explainable AI (XAI) model integration of various CVD biomarkers, including (i) office-based biomarkers (OBBM), such as age, gender, ethnicity, BMI, hypertension, and smoking, (ii) laboratory-based biomarkers (LBBM), such as LDL, HDL, triglycerides, eGFR, and ESR, (iii) RBBM, such as plaque burden, cIMT, PA, and maximum each patient tries to help clinicians figure out how personalized medical information differences might affect health, so they can diagnose and plan the best way to treat the patient [41].

Finally, a cloud-based framework is implemented to make the results clinically explainable [42] and accessible through telemedicine [43,44]. The presented study aims to reduce bias, increase compression, and achieve aiP³ goals using the composite risk radio genomics model. The presented model discusses reliability, stability, and survival analysis by AtheroPoint 4.0™, Roseville, CA, USA, for CVD risk stratification.

2. Search Strategy

The search methodology employed the PRISMA framework, illustrated in Fig. 2; we employed various keywords to search for articles such as "cardiovascular disease", "stroke", "CVD", "genomics and CVD", "radiomics and CVD and pharmamode", "radiomics and stroke", "genomics and stroke batch mode", "prevention medicine and clinical trial", "preventive medicine and CVD", "personalized medicine and artificial intelligence", "atheroscle-

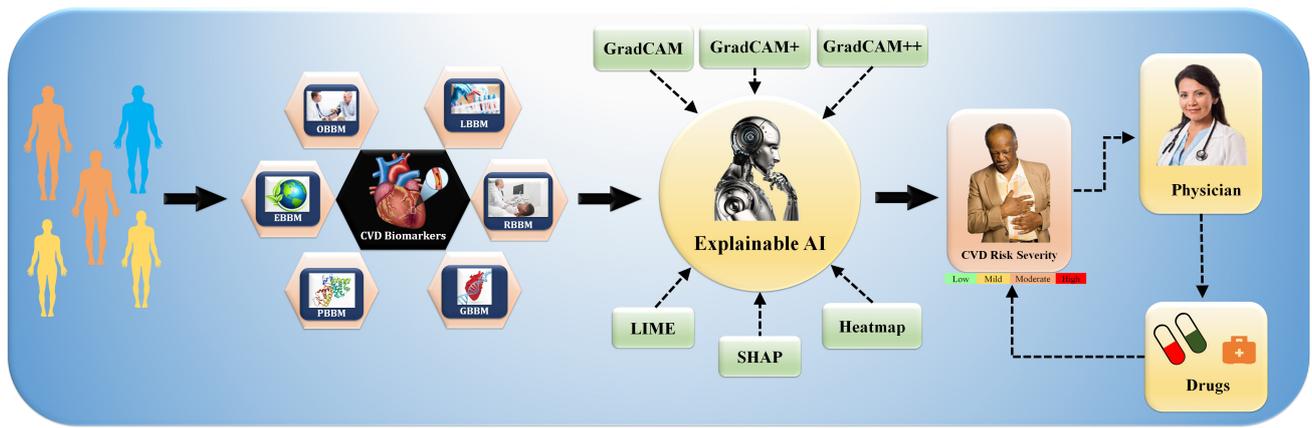


Fig. 1. An overview of composite biomarkers using the XAI model for CVD risk stratification in the pharmaceutical domain (Original image, AtheroPoint™ LLC, Roseville, CA, USA).

rotic in genomics”, “radiomics and AI”, “genomics and radiomics”. Out of these 698 articles, 326 publications were considered, while 289 studies were excluded based on three criteria: unrelated research, irrelevant papers, and inadequate data. These criteria led to eliminating 289, 174, and 21 studies, as indicated by E1, E2, and E3 (Fig. 2), respectively, resulting in a final assessment of 214 studies. Our focus was solely on articles that linked CVD/Stroke with radiomics and GBBM. Studies investigating diseases, such as Parkinson’s, cancer, and diabetes, were not considered.

The omitted E1 category included 289 studies unrelated to CVD/Stroke or RBBM/GBBM. The E2 category contained 174 papers that either needed more information to be included in our analysis or needed to show a link between RBBM/GBBM and CVD/Stroke. Additionally, these studies lacked selectable AI and CVD/Stroke characteristics for analysis that could be utilized for CVD/stroke risk stratification. Finally, we found 27 research studies with inadequate data sets designated as E3 in the PRISMA model.

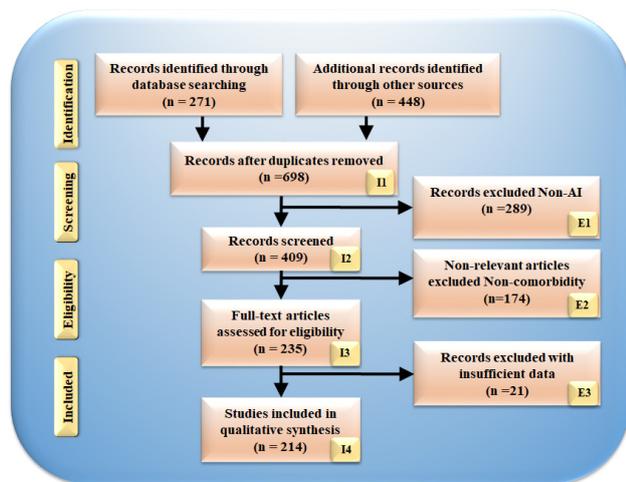


Fig. 2. PRISMA model for study selection.

3. Radiomics-Based CVD Risk Stratification in Pharmaceutical Mode

Various radiological methods have been invented and widely used in recent years to rule out and/or identify pre-clinical atherosclerotic-based CVD to advise optimal prophylactic therapy. Since the carotid artery can be used for the prediction of coronary artery disease [45–48], thus the most commonly used imaging modalities for its screening are Magnetic Resonance Imaging (MRI) [49–51], Computed Tomography Angiography (CTA) [52–56], Optical Coherence Tomography (OCT) [57], and Ultrasound (US) [58,59]. The US is the most common, user-friendly, cost-effective, high-resolution, non-invasive image acquisition modality capable of imaging and recognizing atherosclerotic plaque [58,60,61].

3.1 Non-AI-Based Radiomics and CVD Risk Stratification

Plaque segmentation attempts to identify plaques precisely and consistently to measure plaque burden and track progression over time. This can be used to diagnose and plan treatment for CVD patients. The segmentation results can be utilized to quantitatively analyze plaque features such as volume, shape, and composition. Regression and progression of the plaque in over 10,000 patients in a few hours retrospectively. Fig. 3 shows the carotid ultrasound image phenotype (CUSIP) parameters derived from carotid artery scans representing the surrogate makers for coronary atherosclerotic disease.

The segmentation process can be challenging due to the variability in plaque appearance and the presence of other structures in the images. A combination of multiple methods can be used to improve the accuracy and reliability of plaque segmentation as part of the radiomics features. Carotid ultrasound image phenotypes (CUSIP) have been tried before [62–64]. Therefore, it offers a wide range of applications for regular proactive monitoring of atherosclerotic plaque for CVD risk assessment [65–70]. The statistical reports in the Pharma Mode shown in Fig. 4 will give the regression or progression of the plaque based on

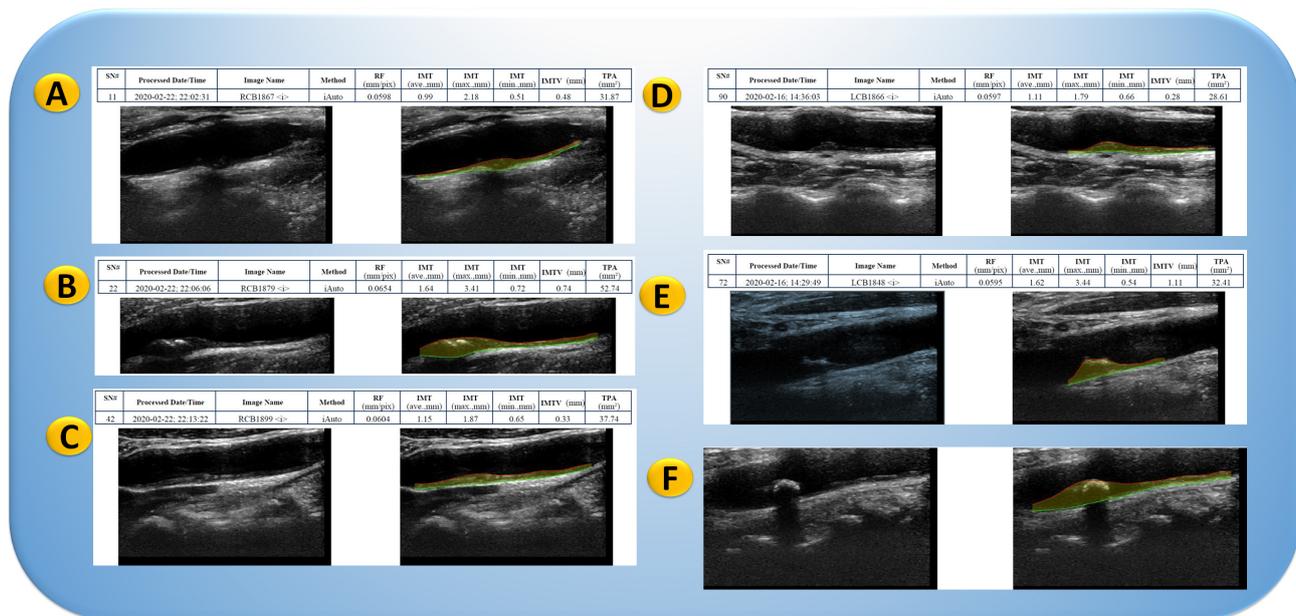


Fig. 3. Carotid artery scans show plaque in the far wall of the carotid artery. Carotid ultrasound image phenotype (CUSIP) consists of carotid intima-media thickness (IMT, ave., max., min.) and total plaque area (TPA). The shaded yellow region corresponds to the region of plaque burden. (A) Moderate plaque burden in carotid bulb; (B) Moderate plaque burden in common carotid artery; (C) Moderate-High plaque burden in carotid bulb artery; (D) High plaque burden in carotid bulb artery; and (E) High plaque burden in carotid bulb artery. LCB, left carotid bulb; RCB, right carotid bulb (Original image, AtheroPoint™ LLC, Roseville, CA, USA).

the statins during the 5–10-year follow-up of thousands of patients. The surrogate carotid artery disease and genetic-based biomarkers gathered from blood plasma will be used to track the atherosclerotic disease of the coronary artery disease. In addition, statistical regression plots will be constructed to link CVD risk to other clinical biomarkers.

3.2 AI-Based Radiomics and CVD Risk Stratification

AI-based radiomics techniques have been recently used to extract and analyze segmented features from the carotid artery based on carotid ultrasound imaging modalities [30,71]. The studies have used different DL algorithms, including convolutional neural networks (CNN), UNet, UNet+, and DenseNet, along with other machine learning (ML) algorithms such as support vector machine (SVM), random forest (RF) and logistic regression (LR) for classification. An example of AtheroEdge™ 3.0 in Pharma mode is seen in Fig. 5A. On clicking the “Pharma Mode” feature of the system, the epidemiologist or physician conducting the Pharma trial will select the spreadsheet with 100,000 patients.

The patient data file will be loaded into the system and ready to select the trained AI model for CVD risk prediction. On clicking the “Trained Model” button, the user can fetch the trained AI model and the number of risk classes. Finally, on clicking the “Predict” button, the user AtheroEdge™ 3.0 system will compute the risk of all the 100,000 patients in, say, five seconds per patient. Fig. 5B depicts an example report. Table 1 (Ref. [30,72–80]) also includes a list of the segment characteristics used in each in-

vestigation, such as carotid intima-media thickness (cMIT), carotid wall thickness (cWT), lumen diameter (LD), plaque load (PB), and plaque area (PA). Table 1 also displays the accuracy (ACC), area under the curve (AUC), and study conclusion for each algorithm. Saba *et al.* [72] used ML-based radiomics to assess intra/inter-observer variability in detecting the common carotid artery (CCA) using SVM and RF classifiers, achieving an ACC of 98.32%. Biswas *et al.* [30] used DL-based radiomics to detect joint cWT, and PB features with an accuracy of 93% and AUC of 0.89. Vila *et al.* [73] also used a DenseNet CNN model to detect and estimate the cMIT with an ACC of 96.45% and an AUC of 0.89. Jain *et al.* [74] used a UNet-based model to detect and segment the CCA plaque area (PA) with an ACC of 88% and an AUC of 0.91. In another study, Jain *et al.* [75] used UNet+ to detect and segment the PA in the internal carotid artery (ICA) with an ACC of 97% and AUC of 0.99%. Yuan *et al.* [76] used UNet-based radiomics to segment and analyze cMIT and plaque with an ACC of 97% and a Dice score of 83.3–85.7.

Molinari *et al.* [77] used a CNN-based radiomics model to analyze cMIT and cWT features, achieving an ACC of 95.6% and an AUC of 0.83. UNet-based tissue characterization of CCA plaque by Gago *et al.* [78] yielded an ACC of 79.00%. Shin *et al.* [79] used a CNN-based model to analyze the viscous plaque index with an ACC of 83% and an AUC of 0.87, while Lainé *et al.* [80] segmented the cWT with an ACC of 86% using a dilated U-Net architecture.

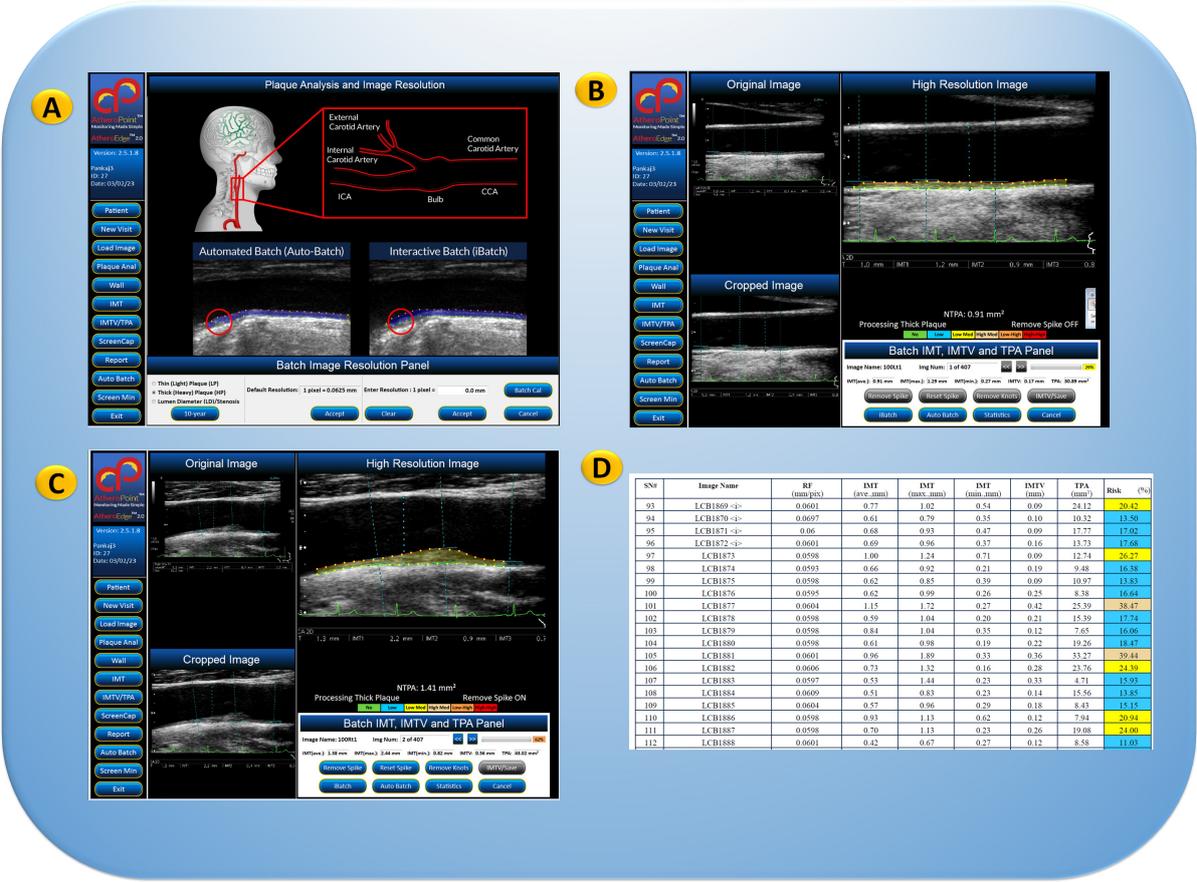


Fig. 4. GUI view of AtheroEdge™ 2.0, showing carotid artery plaque measurement. (A) Pharma Mode selection for selection of the image resolution. (B) CUSIP parameters showing cIMT and TPA measurements for low plaque patient. (C) CUSIP parameters (cIMT/TPA) measurements for the high-plaque patient. (D) Pharma Mode report showing the CUSIP parameters and composite CVD risk (marked in color code). This includes (i) renal effect on CVD risk via estimated glomerular filtration rate (eGFR) biomarkers, (ii) arthritis effect on CVD using erythrocyte sedimentation rate (ESR) biomarkers, (iii) diabetic effect on CVD using HbA1c, (iv) changes in CVD due to low-density lipoprotein (LDL) (Original image, AtheroPoint™ LLC, Roseville, CA, USA).

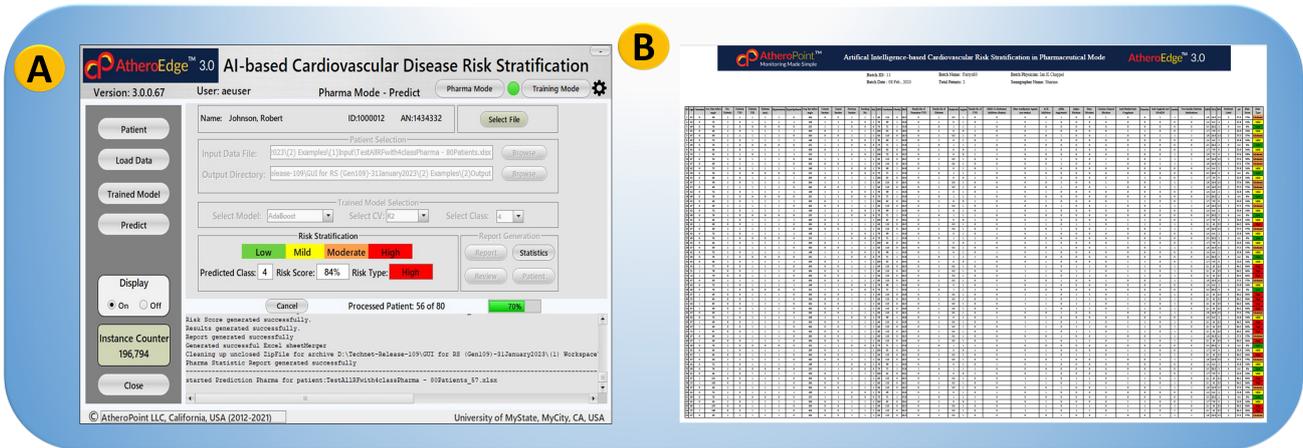


Fig. 5. GUI view of AtheroEdge™ 3.0, AI-based Cardiovascular Disease Risk Stratification system in Pharma mode. (A) AI-based system in Pharma Mode with 70% (green) patient cohort processed. (B) AtheroEdge™ 3.0: An example of the results of the Pharma Mode trial. The color code shows the CVD risk class. The percentage risk is shown in the second column from the right. The rest of the columns are the CVD risk predictors (zoomed version of Fig. 5B is shown in the **Supplementary Material**) (Original image, AtheroPoint™ LLC, Roseville, CA, USA).

Table 1. Studies using DL-based radiomics (covariates) for segmented features using CCA.

SN	Studies	Year	DS	AS	IM	AI (ML/DL)	AA	Segment Features	Performance	Conclusion
Segmentation										
1	Jain <i>et al.</i> [74]	2021	970	CCA	US	DL	UNet, UNet+	PA	ACC: 88%, AUC: 0.91 ($p < 0.0001$)	Detection of PA and segmentation
2	Jain <i>et al.</i> [75]	2022	379	ICA	US	DL	UNet, UNet+	PA	AUC: 97%, AUC: 0.99 ($p < 0.0001$)	Detection of PA and segmentation
3	Yuan <i>et al.</i> [76]	2022	115	CCA	US	DL	UNet	cMIT	ACC: 97%, Dice 83.3–85.7	cMIT and Plaque segmentation
4	Gago <i>et al.</i> [78]	2022	8000	CCA	US	DL	UNet	PA, cMIT, and cWT estimation	ACC: 79.00%	Tissue characterization of plaque
5	Lainé <i>et al.</i> [80]	2022	2676	CCA	US	DL	UNet	cWT	ACC: 86.00%	Dilated U-net architecture is used for cWT
Classification										
6	Saba <i>et al.</i> [72]	2018	100	CCA	US	ML	SVM, RF	LD	ACC: 98.32%	intra/inter-observer variability
7	Biswas <i>et al.</i> [30]	2020	250	CCA	US	DL	CNN, LR	cWT, PB	cMIT error $< 0.093 \pm 0.0677$ mm, AUC: 0.89 ($p < 0.0001$)	Joint detection cWT and PB
8	Vila <i>et al.</i> [73]	2020	8000	CCA	US	DL	CNN (Dense Net)	cIMT	ACC: 96.45%, AUC: 0.89 ($p < 0.0001$)	Plaque detection and cIMT estimation
9	Molinari <i>et al.</i> [77]	2022	500	CCA	US	DL	CNN	cMIT and cWT	ACC: 95.6%, AUC: 0.83 ($p < 0.0001$)	cMIT and cWT measurement
10	Shin <i>et al.</i> [79]	2022	1440	CCA	US	DL	CNN	Plaque viscous index	ACC: 83.00%, AUC: 0.87 ($p < 0.0001$)	Viscoelasticity index

SN, Serial number; DS, Data size; AS, Artery Segment; IM, Imaging modality; CCA, Carotid artery; COA, Coronary artery; CLA, Classifier; FE, Feature extraction; IVUS, Intra-vascular ultrasound; US, Ultrasound; cWT, Carotid wall thickness; cMIT, Carotid intima-media thickness; LD, Lumen diameter; PB, Plaque burden; PA, Plaque area; CCA, Common carotid artery; ICA, Internal carotid artery; ACC, Accuracy; AUC, Area under the curve; AI, Artificial Intelligence; AA, AI Algorithms; ML, Machine Learning; DL, Deep Learning; HDL, Hybrid Deep Learning; SVM, Support vector machine; RF, Random Forest; DT, Decision Tree; CNN, Convolution neural network; LR, Logistic regression; NR, Not Reported.

4. Genomics-Based CVD Risk Stratification in Pharmaceutical Model

Genetic factors play a significant role in the development and progression of plaque buildup in the arteries, and understanding an individual's genetic makeup can provide valuable insights into their risk for CVD. Genetic data is used to identify potential treatment and prevention strategies targets and can help personalize care for individual patients. To accurately assess and understand the plaque burden in an individual, it is essential to have access to genetic data. This section highlights conventional risk scores and AI-based composite risk score methods for the personalized predication of CVD.

4.1 Conventional Polygenic Risk Score and CVD Risk Stratification

A polygenic risk score, often known as a “polygenic risk score” or “PRS”, is a prediction tool that assesses an individual's genetic predisposition to various diseases, such as CVD [81]. The PRS is estimated by taking into account the presence and frequency of genetic variants associated with the disease [82,83].

SNPs associated with CVD can be used as markers to establish an individual's genetic profile [84]. Individual genotyping data is collected after SNP identification. Large-scale genotyping initiatives or DNA tests can provide genotype data [85]. After that, each person's PRS is calculated based on their genome's risk allele count [86]. The CVD association of risk alleles influences their weight [81]. The “effect size” measures how much an SNP affects CVD risk [87]. This statistic typically measures the strength of the relationship between two variables. The odds ratio compares the risk of CVD for those with a particular SNP to those without [88]. The odds ratio usually quantifies the effect [82]. An individual's PRS is calculated by summing the weights of all risk alleles found in their genotyping data [89]. Higher PRS scores indicate a higher CVD predisposition. Fig. 6 shows using the molecular data to calculate the PRS.

The PRS is not a diagnostic tool and should not be used alone to make clinical decisions [90]. The PRS should be used with family history, lifestyle, and other risk factors to make a more informed decision about CVD risk [91,92]. Table 2 (Ref. [93–114]) lists *In-vitro* biomarkers that can be identified in the serum and plasma of asymptomatic and CVD patients. To improve diagnosis and CVD risk stratification, multivariate *genomic-based biomarkers* and multivariable prediction models have been used [93,115,116]. The prediction models assess multivariate atherosclerosis and coronary artery development indicators in circulating molecules. Cellular, biochemical, epigenetic, and/or transcriptional GBBM contributing to CVD are addressed below. ACS biomarkers include C-reactive protein (CRP) [94], a liver protein released in response to inflammation, which increases cardiovascular risk. Another study by Barwari *et al.* [95] and Barwari *et al.* [95] found plasma

LDL-cholesterol levels to be a biomarker for ACS. LDL-cholesterol is considered “bad” because it causes arterial plaque. Joshi *et al.* [96] and Cristell *et al.* [97] noted that PCSK9 regulates cholesterol metabolism and that the identified variant is associated with higher LDL-cholesterol levels and an increased risk of cardiovascular events. Pedicino *et al.* [98] and Partida *et al.* [99] identified pro-inflammatory CD4+ cells with poor CD28 expression as a biomarker for ACS. Sato *et al.* [100] and Montone *et al.* [101] found that biomarkers of ACS include a drop in the number of regulatory T lymphocytes and their ability to stop cancer cells from growing. The following rows list plaque rupture biomarkers without systemic inflammation. Kelley *et al.* [102] found inflammasome activation, while Kreiner *et al.* [103], Toldo *et al.* [104], and Omerovic *et al.* [105] found interleukins 1 and 18 and emotional disturbance-induced catecholamine release as CVD biomarkers. Repova *et al.* [106] found neutrophil activity, while Dang *et al.* [107] found macrophages or T lymphocytes as ACS biomarkers, eroding plaque. In summary, Table 2 provides a comprehensive overview of different biomarkers associated with plaque progression in patients with CVD. The table highlights the complexity of CVD and the need for personalized treatment approaches based on individual patient characteristics.

Radiogenomics Risk Predictors are valuable biomarkers used for CVD risk stratification, combining radiological imaging data and genetic information to assess an individual's CVD risk [75,117]. These predictors analyze quantitative features extracted from imaging modalities like MRI, CTA, OCT, and US, alongside genetic data, serving as specific indicators of pathological changes in the arteries [118]. Referred to as “RBBMs”, they are not mere symptoms but powerful tools for risk evaluation [119]. Numerous studies, detailed in Table 1, have explored and emphasized the significance of these risk predictors.

CAD affects major blood vessels supplying the heart muscle, primarily due to cholesterol deposits causing atherosclerosis, leading to reduced blood flow and potential heart attacks, angina, or strokes [120]. Symptoms of CVD may differ between genders, with men experiencing more chest pain and women often presenting shortness of breath, nausea, and extreme fatigue, indicating underlying heart or blood vessel issues [121]. Abnormal anatomical conditions in CVD, such as cardiomegaly, myocardial infarction, vasculitis [122], atherosclerosis, and thrombosis [123], are observable through medical imaging, physical examinations [124], or laboratory tests, providing critical insights into disease development. Studying these pathological changes is vital for understanding CVD and utilizing radiological biomarkers, to detect stenosis and other risk factors, contributing to a comprehensive comprehension of CVD and its related conditions.

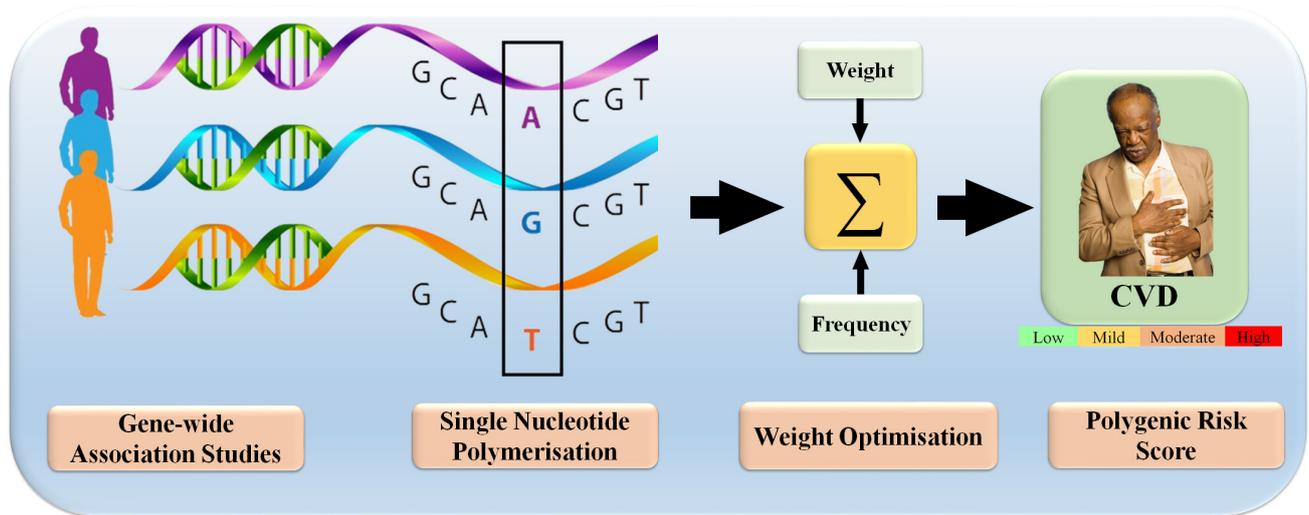


Fig. 6. Molecular data used for prediction of PRS for CVD (Original image, AtheroPoint™ LLC, Roseville, CA, USA).

Table 2. Studies show the genomics biomarkers responsible for plaque progression.

SN	Author	Disease	Phenotype	Biomarker
1	Thibaut <i>et al.</i> [93], Padua <i>et al.</i> [94]	CVD	common phenotype	C-reactive protein (CRP)
2	Barwari <i>et al.</i> [95], Cristell <i>et al.</i> [97]	CVD	common phenotype	Plasma levels of low low-density protein cholesterol (LDL-cholesterol)
3	Joshi <i>et al.</i> [96], Cristell <i>et al.</i> [97]	CVD	common phenotype	PCSK9 variant
4	Pedicino <i>et al.</i> [98], Partida <i>et al.</i> [99]	CVD	systemic inflammation and plaque rupture	CD4+ cells that are pro-inflammatory and have a poor expression of the co-stimulatory molecule CD28 on their cell surfaces
5	Sato <i>et al.</i> [100], Montone <i>et al.</i> [101]	ACS	systemic inflammation and plaque rupture	a decrease in the number of circulating regulatory T lymphocytes as well as their inhibitory function
6	Montone <i>et al.</i> [101]	CVD	systemic inflammation and plaque rupture	CD31 and protein tyrosine phosphatase N22, upstream regulatory mediators, modulate T-cell number and function.
7	Kelley <i>et al.</i> [102]	CVD	plaque rupture without systemic inflammation	Activation of Inflammasome
8	Kreiner <i>et al.</i> [103]	ACS	plaque rupture without systemic inflammation	Interleukin (IL)-1
9	Toldo <i>et al.</i> [104]	CVD	plaque rupture without systemic inflammation	Interleukin (IL)-18
10	Omerovic <i>et al.</i> [105]	CVD	plaque rupture without systemic inflammation	Catecholamine release due to emotional disturbance
11	Repova <i>et al.</i> [106]	CVD	erosion of plaque	activation of Neutrophil
12	Dang <i>et al.</i> [107]	CVD	erosion of plaque	Macrophages or T lymphocytes
13	Thota <i>et al.</i> [108]	CVD	erosion of plaque	Proteoglycans
14	Wang <i>et al.</i> [109]	ACS	erosion of plaque	Glycosaminoglycans
15	Worssam <i>et al.</i> [110]	CVD	erosion of plaque	Arterial Smooth Muscle Cells (SMCs)
16	Romo <i>et al.</i> [111]	CVD	erosion of plaque	Monocyte HYAL2 expression increased.
17	Pinheiro-de-Sousa <i>et al.</i> [112]	CVD	erosion of plaque	up regulation of Endothelial cell CD44
18	Chong <i>et al.</i> [113]	CVD	plaque in the absence of thrombus	Vasospasm
19	Shimokawa <i>et al.</i> [114]	CVD	plaque in the absence of thrombus	Rho-kinase activity

ACS, Acute Coronary syndrome.

4.2 AI Genomics-Based Composite Risk Score for CVD Risk Stratification

The medical imaging field has noted the progress made in ML and DL [125–128]. Deep neural networks (DNNs), a subset of DL, work like the human brain [39,117,129]. AI has been used in recent studies to figure out the risk of CVD using RBBM [11,12,38,130–134] and GBBM [33,135,136] frameworks. DL is becoming more popular because (i) it automatically extracts features [137], (ii) it can fuse with different ML configurations for classification [117,138], (iii) it uses UNet and Hybrid UNet-based DL strategies for segmentation [43,119], and (iv) Lastly, it gives more accurate segmentation and solo or ensemble-based classification because it can go through forward and backward propagation by reducing the loss using different kinds of loss functions [74].

4.2.1 Training and Prediction

The architecture consists of two halves. The left is the training subsystem, while the right is the prediction subsystem.

The DL training classifiers consist of one of the DL classifiers, namely, long short-term memory network (LSTM), recurrent neural network (RNN), gated recurrent units (GRU), bidirectional-LSTM (BiLSTM), bidirectional-RNN (BiRNN), and bidirectional-GRU (Bi-GRU) (presented in the following subsection).

Along with the DL classifier bank, there are supervised clinical risk labels representing ground truth (GT), such as heart failure (or high CVD risk) and stroke [130,139]. This GT representing the CAD includes computed tomography (CT) coronary score [140] or quantification of CAD lesions using intravascular ultrasound (IVUS) [141,142]. Several non-linear training-based approaches have been shown in heart disease risk stratification [12,132,134,143]. Fig. 7 shows AI-based architecture for CVD risk assessment.

4.2.2 Deep Learning Classifier Banks

The RNN [144], BiRNN [145], LSTM [146], BiLSTM [147], GRU [148], and BiGRU [149] models evaluate sequential data, such as Electrocardiograph (ECG) [148,150], text [146], speech [151], localization of myocardial infarction [147], and handwriting [152,153]. Table 3 (Ref. [154–168]) below summarises AI-based genomics studies that make a personalized and accurate prediction of CVD. A total of 15 studies are listed in the table and described with sample size, ground truth, technology, benchmark, source description, AI type, classifier type, cross-validation technique, and performance characteristics. In the first investigation, Davies *et al.* [154] (2010) tried to predict CVD using SNP data in conjunction with ML techniques using SVM and LR. The total number of participants in the study was 2333, and the ACC and SPE parameters each attained an AUC of 0.80 and 0.78, respectively. The study was prospective.

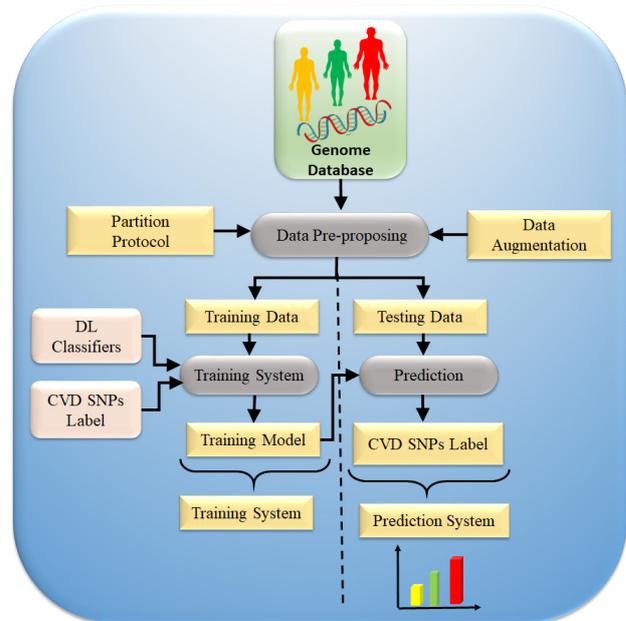


Fig. 7. AI genomics-based architecture for CVD risk assessment (Original image, AtheroPoint™ LLC, Roseville, CA, USA).

Valavanis *et al.* [155] (2010) demonstrated the ability to predict CVD using DNA data and the DL algorithm PDM-ANN. With a sample size of 63 in a retrospective study, the accuracy of the prediction was found to be 95.5%. However, Beigi *et al.* [156] (2011) used SNP data with an SVM-based ML paradigm to predict CVD. In a prospective study, the sample size was only 23, but it still reached a very high accuracy of 91%. By combining SNP data with ML algorithms like SVM, RF, and XGB, Montañez *et al.* [157] (2017) conducted a retrospective study that predicted CVD. In the study, there were 12 participants, and the SPE parameter managed to reach an AUC of 0.9.

Zhao *et al.* [158] (2019) carried out a prospective study that uses SNP data in conjunction with the DL technique known as CNN to predict CVD. The total number of participants in the trial was 490, and the AUC was 0.82. To predict dilated cardiomyopathy (DCM), Schiano *et al.* [159] (2021) used mRNA data in conjunction with the DT-based ML technique. The study has an accuracy of 0.79 with a sample size of 443. Yang *et al.* [160] (2021) carried out the study, which used SNP data and ML algorithms like SVM and RF to predict CVD. The retrospective study included 117 participants and obtained an AUC value of 0.91 for the SEN of 0.93. The study by Akbarzadeh *et al.* [161] (2022) uses DNA data and ML algorithms SVM, DT, RF, and LR to predict CVD. The prospective research study utilized a sizable sample size of 4756 participants and successfully achieved a range of performance criteria, one of which was an AUC of 0.78 for the ACC. The study, which was conducted by Kesar *et al.* [162] (2022), forecasted CVD

Table 3. AI-based genomics studies that predict CVD in a personalized and precision framework.

SN	Studies	Year	SS	GT	BM	SD	Tech	AI (ML/DL)	CT	CVP	Performance parameters					CTR
											ACC	SEN	SPE	AUC	F1	
1	Davies <i>et al.</i> [154]	2010	2333	CVD	LBBM, OBBM	SNP	GWAS	ML	SVM, LR	10K	0.61, 0.55	NR	NR	0.80, 0.78	NR	Prospective
2	Valavanis <i>et al.</i> [155]	2010	63	CVD	LBBM, OBBM	DNA	DEG	DL	PDM-ANN	3K	0.95	0.98	0.94	0.96	NR	Retrospective
3	Beigi <i>et al.</i> [156]	2011	23	CVD	LBBM, OBBM	SNP	Proteinase k	ML	SVM	10K	0.91	NR	NR	NR	NR	Prospective
4	Montañez <i>et al.</i> [157]	2017	12	CVD	LBBM, OBBM	SNP	DEG	ML	SVM, RF, XGB	10K	NR	0.88, 0.52, 0.70	0.86, 0.95, 0.82	0.90, 0.87, 0.85	NR	Retrospective
5	Zhao <i>et al.</i> [158]	2019	490	CVD	LBBM, OBBM	SNP	DEG	DL	CNN	10K	0.81	0.83	0.79	0.82	NR	Prospective
6	Schiano <i>et al.</i> [159]	2021	443	DCM	LBBM	mRNA	DEG	ML	DT	10K	0.79	NR	NR	NR	NR	Prospective
7	Yang <i>et al.</i> [160]	2021	117	CVD	LBBM, OBBM	SNP	DEG	ML	SVM, RF	10K	0.86, 0.89	NR	NR	0.91, 0.93	NR	Retrospective
8	Akbarzadeh <i>et al.</i> [161]	2022	4756	CVD	LBBM	DNA	Proteinase k	ML	SVM, DT, RF, LR	5K	0.72, 0.73, 0.74, 0.70	0.66, 0.66, 0.69, 0.67	0.78, 0.80, 0.78, 0.73	0.78, 0.77, 0.80, 0.77	NR	Prospective
9	Kesar <i>et al.</i> [162]	2022	203	CVD	LBBM, OBBM	NR	NR	ML	LR, XGB	10K	NR	NR	NR	0.75, 0.76	NR	Prospective
10	Pirruccello <i>et al.</i> [163]	2022	116	CVD	LBBM, OBBM	SNP	DEG	DL	UNet	10K	0.96	NR	NR	NR	NR	Retrospective
11	Steinfeldt <i>et al.</i> [164]	2022	395713	CVD	LBBM	NR	NR	DL	CNN	10K	0.78	NR	0.81	NR	NR	Prospective
12	Lee <i>et al.</i> [165]	2022	283	CVD	LBBM	SNP	DEG	ML	LR	10K	0.81	0.79	0.83	NR	NR	Retrospective
13	Libiseller-Egger <i>et al.</i> [166]	2022	34432	CVD	LBBM, OBBM	SNP	GWAS	DL	SVM, LR	5K	0.76	0.81	0.84	0.81	NR	Prospective
14	Kang <i>et al.</i> [167]	2023	17044	AMI	LBBM	mRNA and miRNA	DEG	ML	SVM, RF, DT	10K	0.81, 0.85, 0.81	0.79, 0.89, 0.77	0.84, 0.82, 0.86	0.92, 0.96, 0.88	NR	Retrospective
15	Venkat <i>et al.</i> [168]	2023	82	CVD	LBBM, OBBM	SNP	DEG	ML	RF	5K	0.80	NR	NR	NR	NR	Prospective

SN, serial number; SS, Sample size; GT, Ground Truth; Tech, Technique; BM, Benchmark; LBBM, Lab-base biomarkers; OBBM, Office base biomarkers; SD, Source description; AI, Artificial Intelligence; CT, classifier type; CVP, Cross-validation protocol; CTR, Clinical trials; ACC, Accuracy; SEN, Sensitivity; SPE, Specificity; AUC, Area under the curve; ML, Machine Learning; DL, Deep Learning; CNN, Convolution neural network; PDM, parameter decreasing method; ANN, Artificial neural network; PDM, parameter decreasing method; DEG, Differential expression gene; SVM, Support vector machine; RF, Random forest; DT, Decision tree; NR, Not Reported; DCM, Dilated cardiomyopathy; AMI, Acute myocardial infarction.

using both LBBM and OBBM; however, the data types were not stated. The research had a total of 203 participants as its sample size, and it managed to get an AUC of 0.75 and an F1 score of 0.76. The research was prospective in scope.

Overall, these studies demonstrate the potential of AI-based genomics approaches to predict CVD accurately and provide personalized and precise care for patients. However, more studies are needed to validate these approaches' effectiveness and assess their impact on clinical practice.

5. Explainable AI, Reliability Stability, and Survival Analysis of Model for CVD Risk Stratification in Joint Cloud and Pharmaceutical Framework

This section discusses using explainable AI, reliability stability, and survival analysis techniques to design and develop the CVD risk stratification in a joint cloud and pharmaceutical framework. It examines the benefits and limitations of these techniques and provides examples of successful implementations. Section 5.1 focuses on the importance of explainability in AI-based decision-making in the pharmaceutical paradigm. It discusses different techniques to ensure explainability, provides examples of use cases, and examines potential benefits and limitations.

Section 5.2 discusses the use of cloud-based solutions for AI in the pharmaceutical industry, including the benefits of scalability, flexibility, and cost-effectiveness. It also examines potential challenges and limitations, such as data security and privacy concerns, and provides case studies of successful implementations. Subsection 5.3 explains the use of statistical methods to analyze the reliability and accuracy of AI prediction models in the pharmaceutical industry. It provides an overview of common statistical techniques, different types of AI prediction models, and case studies of successful applications. Lastly, Subsection 5.4 focuses on applying AI-based survival analysis in the pharmaceutical industry. It examines different types of AI-based survival analysis models, their benefits, and the importance of interpretability and explainability. It also provides case studies of successful applications.

5.1 Explainable AI-Based Decision-Making in Pharmaceutical Model

In the past, AI models were considered "black boxes", meaning that it was unknown what specific patterns in the input data would result in the desired output. To put it another way, even if a classification algorithm is nearly perfect, humans must still determine what circumstances led to the categorisation [169]. The lack of transparency in model decisions becomes problematic when a model is trained to make accurate predictions based on features that are irrelevant to the situation at hand, and, as a result, it lacks generalization for that dataset [170]. Fig. 8 (Ref. [171]) shows the eight customizable DL processes: (i) DL training, (ii) quality assurance (QA), (iii) installation, (iv) de-

ployment, (v) prediction, (vi) cross-validation-based testing (A/B test), (vii) monitoring, and (viii) debugging. These processes are made possible by incorporating the feedback loop in XAI. Incorporating XAI enhances its usability, increasing demand for such systems and generating higher revenue [172]. Moreover, it offers greater stability to the AI system, thus extending the lifespan of the product design. XAI strategies expose sophisticated model decision patterns [173]. XAI can provide new information about a dataset and the disease by revealing input variables' predictive importance, including risk factors, traits, and protein expression levels. However, models like principal component analysis (PCA), LR, and Cox linear regression use model parameters to determine feature relevance [174].

The average importance of features across samples is determined using feature analysis [175]. Training models to distinguish across classes can be expanded to numerous classes, providing insights such as specific patient groups [176]. XAI clinical power stems from strategies that explain patient decisions. Fig. 9 illustrates the clinical decision system concept employing XAI. If the AI model predicts a patient's risk, the doctor can inquire about the model's output for clinical, imaging, or molecular features route databases and gene set enrichment estimates can uncover risk variables and molecular disease pathways. This information can help clinicians choose better treatment plans. Furthermore, by understanding the decision process, the physician will be able to judge the accuracy of the predictions. Explainability has thus been recommended as an ethical requirement for prospective clinical decision systems [177]. This section describes various XAI techniques and summarises medical and clinical applications for patient evaluation [8,42,43,153].

Explainable Modeling

XAI can help interpret the results of a clinical Pharma Mode, such as the diseases like CVD. An ML model was trained in Pharma Mode to predict the risk of CVD based on clinical and demographic variables. Local interpretable model-agnostic explanations (LIME) work by training a local linear model to approximate the behavior of the ML model in the neighbourhood of a specific instance. The local model can be used to identify which features strongly influence the predicted outcome for that instance. The equation for the local linear model is:

$$f(x') = w_0 + w_1 * x'_1 + w_2 * x'_2 + \dots + w_n * x'_n \quad (1)$$

where, x' is a modified version of the original input x , and w_0, w_1, \dots, w_n are the weights of the linear model. LIME uses a technique called feature perturbation to generate modified instances x' that are similar to the original instance but have one or more features changed. The local model is trained on a set of perturbed instances and their corresponding predictions, and the weights are learned us-

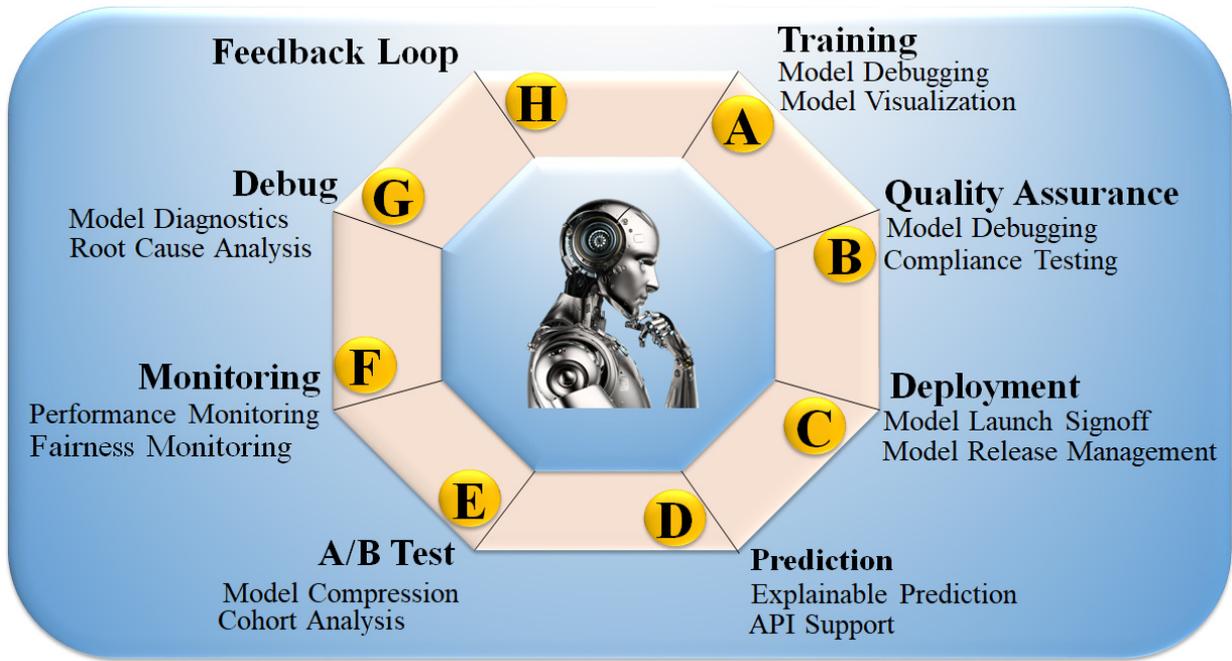


Fig. 8. Eight aspects of XAI [171].

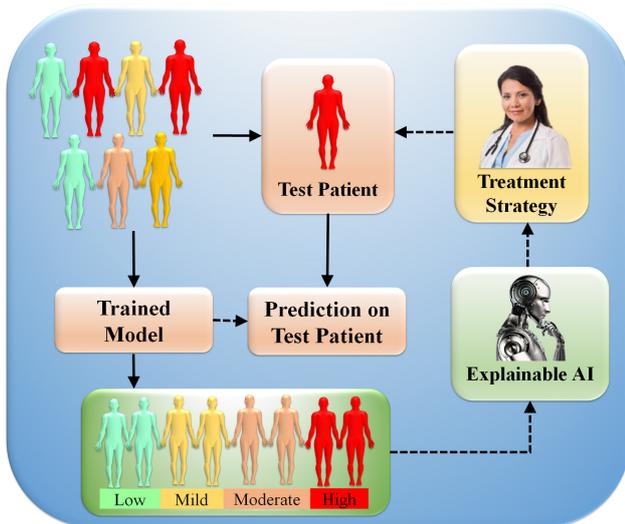


Fig. 9. Clinical features decisions system using XAI. AI models are trained using clinical, imaging, or multi-omics data into different classes (low, mild, moderate, and high). The trained algorithm predicts (prediction blocks) patient disease or symptom risk. Lastly, the XAI presents decision patterns to help the doctor evaluate the forecast and plan treatment (Original image, Athero-Point™ LLC, Roseville, CA, USA).

ing linear regression. On the other hand, Shapley additive explanations (SHAP) use a game-theoretic approach to assign a contribution score to each feature in the model. The contribution score represents the degree to which each feature contributes to the difference between the model's and average predictions across all possible feature combinations. The equation for the SHAP value of a feature i is:

$$\phi_i(x) = \left(\frac{1}{M}\right) * \sum m_j 1^M [f(x_j) - E[f(z_j)] * h_i(z_j)] \quad (2)$$

where x is the instance to be explained, M is the number of feature combinations, f is the ML model, $E[f(z_j)]$ is the expected value of f over all feature combinations that include feature i , and h_i is a function that measures the difference between the prediction of the model with and without feature i for a given instance z_j . The SHAP value of a feature i represents the average contribution of that feature to the difference between the model's prediction for x and the average prediction for all possible feature combinations. In the context of the CVD Pharma Mode, LIME and SHAP techniques can be used to identify which clinical and demographic features are most important for predicting the risk of CVD and to explain how the model arrives at its predictions for individual patients. This information can help physicians make more informed decisions about patient care and identify areas where further research is needed.

5.2 Cloud-based Explainable AI in Pharmaceutical Model

Cloud-based XAI is an approach that allows researchers and healthcare professionals to access powerful ML/DL models and tools for data analysis and prediction without needing specialized hardware or software. In the context of predicting CVD, cloud-based XAI can provide an efficient and cost-effective way to analyze large amounts of data and generate accurate predictions. Cloud-based XAI relies on cloud computing technology, which involves using remote servers to store and process data rather than relying on local resources [43,72,178,179]. Fig. 10 shows a

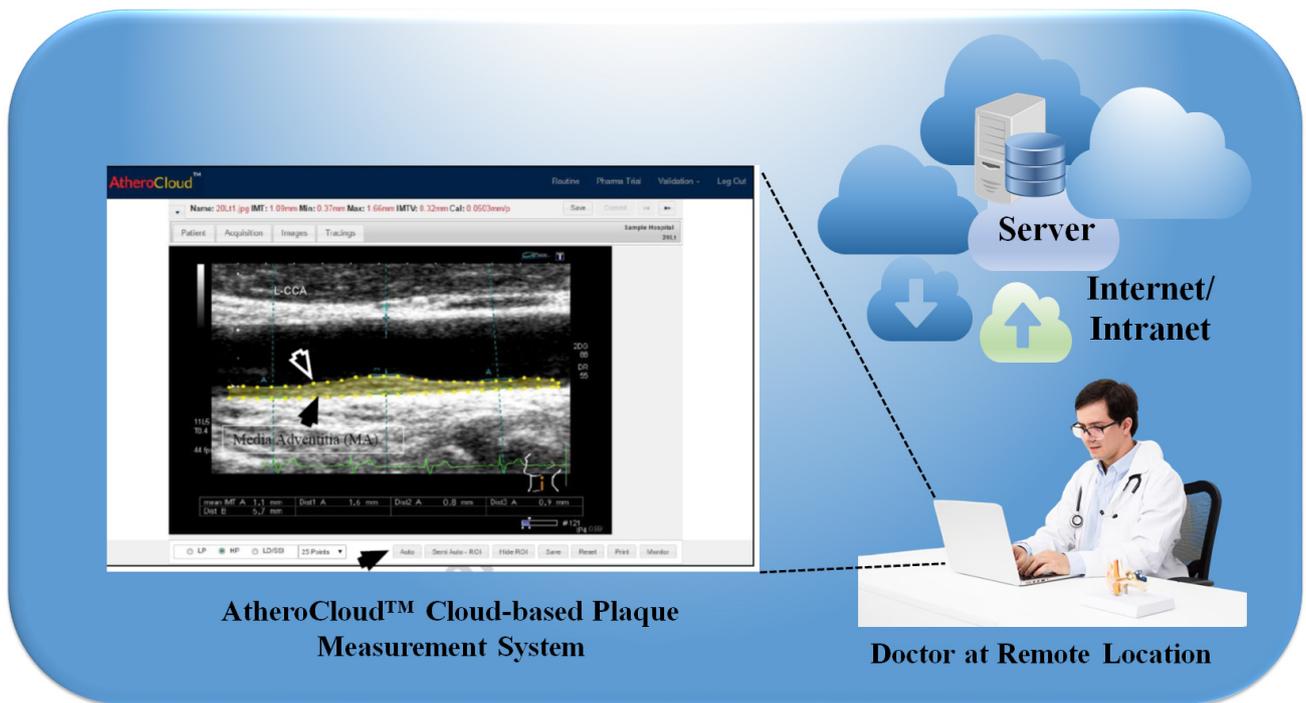


Fig. 10. AtheroCloud™ system depicts a typical daily routine. A yellow color fills the plaque region, representing the total plaque area after the image has been loaded in the Routine mode and the “Auto Trace” button has been clicked (Original image, AtheroPoint™ LLC, Roseville, CA, USA).

cloud-based XAI system. By leveraging cloud-based infrastructure, researchers can access powerful computing resources and AI models that can process vast amounts of data quickly and efficiently.

To build a cloud-based XAI system for predicting CVD researchers can follow a few steps: (i) Feature selection: Feature selection is the process of identifying the most important features contributing to predicting CVD. This can be accomplished through the use of statistical approaches such as regression analysis or machine learning/deep learning algorithms that automatically choose the most relevant features. (ii) Model interpretability: The model can be made more interpretable using algorithms that explain individual predictions, such as LIME and SHAP. These algorithms provide feature importance scores and highlight the most important features for a specific prediction. (iii) Data visualization: Data visualization can be utilized to explore data and uncover patterns and relationships among features. Visualization tools such as scatter plots, heatmaps, and box plots can help researchers identify outliers and correlations that may be useful for predicting CVD. (iv) Cloud-based infrastructure: Cloud-based infrastructure can be used to store and process large amounts of data, making it possible to build more complex and accurate models.

Cloud-based AI platforms such as Amazon Web Services (AWS) and Google Cloud Platform (GCP) provide powerful tools for building and deploying ML/DL models [180]. (v) Collaboration: Collaboration is essential for developing accurate and reliable models for CVD pre-

diction. Cloud-based XAI platforms enable researchers to share data and models, collaborate on model development, and work together to identify new insights and approaches [181]. Cloud-based XAI has several advantages over traditional on-premises solutions. First, researchers can access powerful computing resources without needing specialized hardware or software. Second, it provides a scalable and flexible platform that can be easily adapted to meet changing healthcare needs. Finally, it enables researchers and healthcare professionals to collaborate and share data and models, leading to better and more accurate predictions for CVD and other health conditions.

5.3 Explainable AI Using Heatmaps

Heatmaps in Explainable AI work by highlighting the regions of input data that significantly influence the model’s output. For image-based tasks, such as object detection or medical image analysis, heatmaps visually depict the importance of different pixels or regions within the input image. The intensity of colors in the heatmap indicates the magnitude of the model’s focus on particular areas [182]. The generation of heatmaps often involves techniques like Gradient-weighted Class Activation Mapping (Grad-CAM) and Guided Backpropagation. Grad-CAM computes the gradients of the target class with respect to the final convolutional layer’s feature maps. These gradients are then global-average-pooled to obtain the heatmap, which highlights the relevant regions in the image. Guided Backpropagation, on the other hand, is used to ensure that only mean-

ingful features are highlighted in the heatmap by preventing the model from backpropagating through unimportant regions [183]. By interpreting heatmaps, researchers, domain experts, and end-users gain valuable insights into why a specific decision was made by the AI model. For instance, in medical diagnosis, heatmaps can help doctors understand which regions of an X-ray or MRI scan contributed most to the AI model's identification of a certain condition [184].

Skandha *et al.* [138] proposed the first of its kind method to characterize and classify the carotid plaque using an optimized transfer learning approach and SuriNet (a class of Atheromatic™ 2.0 TL). Eleven Atheromatic™ models were implemented, and the best AUC was 0.961 ($p < 0.0001$) from MobileNet and 0.927 ($p < 0.0001$) from SuriNet. We validated the performance using grayscale median, fractal dimension, higher-order spectra, and spatial heatmaps. TL showed equal and comparable performance to deep learning. The Atheromatic™ 2.0 TL model showed a performance improvement of 12.9% over Atheromatic™ 1.0 ML (AtheroPoint™, Roseville, CA, USA) compared with the previous. Moreover, the Atheromatic™ 2.0 TL model displayed an outstanding 12.9% performance improvement over the previous Atheromatic™ 1.0ML (AtheroPoint™, Roseville, CA, USA), which was based on traditional machine learning techniques. Notably, the system's validity was established using a widely accepted dataset, reinforcing the robustness and reliability of the findings. This study sets a significant milestone in understanding carotid plaque characteristics, opening new avenues for enhanced diagnosis and treatment in the field of carotid artery disease.

In conclusion, heatmaps are a crucial tool in the toolkit of Explainable AI, offering visual interpretations of AI model decisions and making complex AI systems more transparent and interpretable. As AI continues to impact various aspects of our lives, XAI using heatmaps will play an instrumental role in building responsible and trustworthy AI applications.

5.4 Statistical Analysis of Artificial Intelligence Prediction Models

The statistical analysis involved the presentation of continuous variables as mean \pm standard deviation. The normal distribution of continuous variables was verified using the Kolmogorov-Smirnov test [185]. The independent samples *t*-test or Mann-Whitney U test was used to compare continuous data, while the chi-square test or Fisher's exact test was used for categorical variables, as appropriate [186]. For comparisons involving multiple groups, one-way analysis of variance (ANOVA) or Kruskal-Wallis H test with Bonferroni test was used, as appropriate [187]. Pearson *r* and Spearman rho coefficient were used for correlation assessment, depending on the nature of the data [188].

Multivariable linear regression analysis assessed the association between left atrium (LA) function parameters and myocardial scar size/location [118]. The regression

models included demographic characteristics, traditional cardiovascular risk factors, and Late gadolinium enhancement (LGE) location/size as covariates. To avoid collinearity, Spearman correlation coefficients were used to test for correlations between continuous variables, and variables with $r > 0.50$ were excluded from the same multivariable model [189]. A *p*-value < 0.05 was considered statistically significant. The analysis was performed using IBM SPSS Statistics version 22 (SPSS Inc., Chicago, IL, USA) [190].

5.5 Artificial Intelligence-Based Survival Analysis

AI-based survival analysis is a cutting-edge technique used to predict the risk of CVD [134]. Using huge amounts of medical data, AI algorithms may estimate the chance of an individual having CVD based on parameters such as age, gender, blood pressure, cholesterol levels, and lifestyle patterns [129]. This approach can give physicians valuable insights into patient health and help them create personalized treatment plans for each individual [191].

By utilizing AI-based survival analysis, doctors can also identify high-risk individuals who may require closer monitoring or more aggressive treatment to prevent the development of CVD [192]. AI technology can revolutionize the healthcare industry by improving the accuracy of CVD diagnosis and treatment, leading to better patient outcomes and improved overall public health [69,193].

6. Critical Discussions

The ML/DL system needs to overcome critical concerns like bias, explainability, ergonomic design, and affordability to ensure the safety and effectiveness of the medical product, such as CVD risk stratification.

6.1 Principal Findings

This is the first study of its kind (a) that combines radiomics and genomic biomarkers to detect the severity of CVD and stroke risk precisely, and (b) an explainable XAI-based composite risk CVD/Stroke model using DL can predict with precision in a preventive and personalized (aiP³) framework benefiting pharmaceutical paradigm. Using these two hypotheses, we demonstrated that CVD and stroke risk severity could be determined using RBBM and GBBM biomarkers in the DL framework. Such models can be considered "personalized medicine frameworks". One significant advancement is the inclusion of carotid imaging and CVD genetic indicators in the DL framework for CVD risk classification. A set of six recommendations for accurate, robust, real-time CVD risk assessment utilizing combined RBBM and GBBM were offered. The study proposed model having significant potential such as (a) radiomics and genomic biomarkers have a strong correlation and can be used to detect the severity of CVD and stroke precisely, and (b) The proposed review suggests a unique, unbiased, and XAI model (AtheroEdge™ 4.0) that can predict the composite risk of CVD/Stroke using

Table 4. Benchmarking table for CVD risk using multivariate biomarkers.

K0	K1	K2	K3	K4	K5	K6	K7	K8	K9	K10	K11	K12	K13	K14	K15	K16	K17
1	Krittanawong <i>et al.</i> [194]	2017	31	✓	✓	✗	✓	✓	✗	✓	✓	✓	NR	✗	✗	✗	✗
2	Arena <i>et al.</i> [195]	2018	202	✓	✓	✗	✓	✗	✗	✓	✗	✓	NR	✗	✗	✗	✗
3	Krittanawong <i>et al.</i> [27]	2018	88	✓	✓	✗	✓	✗	✗	✓	✗	✓	DL	✗	✗	✗	✗
4	Jamthikar <i>et al.</i> [143]	2019	110	✓	✓	✓	✗	✗	✗	✓	✓	✗	HDL	✗	✗	✗	✗
5	Saba <i>et al.</i> [199]	2019	125	✓	✓	✓	✗	✗	✗	✓	✓	✗	DL	✗	✗	✗	✗
6	Dainis <i>et al.</i> [41]	2019	83	✓	✓	✗	✓	✗	✗	✓	✗	✓	DL	✗	✗	✗	✗
7	Gruson <i>et al.</i> [201]	2020	42	✓	✓	✗	✓	✓	✗	✓	✗	✓	HDL	✗	✗	✗	✗
8	Alimadadi <i>et al.</i> [197]	2020	56	✓	✓	✗	✓	✗	✗	✓	✗	✓	ML	✗	✗	✗	✗
9	Saba <i>et al.</i> [198]	2020	69	✓	✓	✓	✗	✗	✗	✓	✓	✗	ML	✗	✗	✓	✗
10	Westerlund <i>et al.</i> [196]	2021	167	✓	✓	✗	✓	✗	✗	✓	✗	✓	DL	✗	✗	✗	✗
11	Schiano <i>et al.</i> [159]	2021	29	✓	✓	✗	✓	✓	✗	✓	✗	✓	ML	✗	✗	✗	✗
12	Jain <i>et al.</i> [119]	2022	67	✓	✓	✓	✗	✗	✗	✗	✓	✗	ML	✗	✗	✗	✗
13	Staub <i>et al.</i> [200]	2022	25	✓	✓	✓	✗	✗	✗	✗	✓	✗	NR	✗	✗	✗	✗
14	Jain <i>et al.</i> [75]	2022	85	✓	✓	✓	✗	✗	✗	✓	✓	✗	DL	✗	✗	✓	✓
15	Saba <i>et al.</i> (Proposed)	2023	214	✓	✓	✓	✓	✓	✓	✓	✓	✓	DL	✗	✗	✓	✓

K0: Serial Number, K1: Studies, K2: Year, K3: References, K4: OBBM, K5: LBBM, K6: RBBM, K7: GBBM, K8: PBBM, K9: EBBM, K10: Preventive, K11: Prediction, K12: Personalized, K13: AI Type, K14: FDA discussion, K15: Clinical Setting, K16: Risk of Bias, K17: AI explainability. CVD, Cardiovascular Disease; DL, Deep Learning; ML, Machine Learning; HDL, Hybrid deep learning; NR, Not reported.

radiogenomics in the pharmaceutical paradigm. The proposed model required less time than the traditional model to stratify CVD/stroke risk, saving thousands of hours using phrmamode.

AtheroCloud™ can be utilized in either the (a) “Routine” mode or the (b) “Pharma” trial mode. Both the batch of carotid ultrasound scans and individual scans are automatically processed in real-time in the Routine mode and Pharma trial mode, respectively, during the patient visit. The system supports large databases, from gigabytes to terabytes, and can operate in batch mode, processing as many as 10,000 images simultaneously.

6.2 Benchmarking

Table 4 (Ref. [27,41,75,119,143,159,194–201]) displays the benchmarking studies. It has 17 attributes, namely, K0: Serial Number, K1: Studies, K2: Year, K3: References, K4: OBBM, K5: LBBM, K6: RBBM, K7: GBBM, K8: PBBM, K9: EBBM, K10: Preventive, K11: Prediction, K12: Personalized, K13: AI Type, K14: FDA discussion, K15: Clinical Setting, K16: Risk of bias; K17: AI explainability. Our observations showed that there were only eight studies [27,41,159,194–197] that discussed the role of GBBM in CVD using DL, while the remaining studies predicted CVD using RBBM [75,119,143,198–200,202,203]. However, all the studies mentioned the role of OBBM and LBBM in CVD risk. Five studies adopted DL technologies [27,41,75,196,198,199], while eight studies used ML [11,131,197,202], and two studies used HDL [143,201]. Only four studies discussed the risk of bias (RoB) [75,143,202]. Except for the proposed study, no other study addressed clinical settings, AI explainability, and fusion of GBBM and RBBM.

6.3 The Role of AI Bias during Designs

Evaluating bias in AI models has gained much greater significance in recent years [204,205]. Earlier computer-aided diagnosis techniques showed a lack of bias in evaluations [206]. To reduce bias, a large sample size, appropriate clinical testing, the incorporation of comorbidities, the use of big data configurations, the usage of unseen data analysis, and the scientific validation of training model design are all strategies that can be utilized [140,207]. Essential phases in patient risk stratification include determining the AI RoB [191,207,208] and suitably modifying diagnostics and treatment.

6.4 The Role of Pruning-Based AI Systems

Edge devices are becoming increasingly important as cloud-based systems and the internet improve. Edge devices are extremely important when using trained AI models for future predictions or disease risk stratifications in mobile frameworks. There is a requirement to deploy compressed models since huge data models cannot be deployed on edge devices. Image-based DL models such as fully convolutional networks (FCN) or segmentation networks (SegNet) [40] can be pruned using evolutionary algorithms such as Particle Swarm Optimization (PSO), Genetic Algorithms (GA), Wolf Optimization (WO), and Differential Evolution (DE) [209]. The future of radiomics-based CVD risk stratification fused genetic-based paradigms can be compressed and deployed on edge devices for rural areas, especially in third-world nations.

6.5 Recommendations

The following are recommendations for a suggested Radiogenomics model that can be used to stratify

CVD/stroke risk. The study proposes two hypotheses: (a) radiomics and genomic biomarkers have a strong correlation and can be used to detect the severity of CVD and stroke precisely, and (b) The proposed review suggests a unique, unbiased, and XAI model (AtheroEdge™ 4.0) that can predict the composite risk of CVD/Stroke using radiogenomics in the pharmaceutical paradigm. The following recommendations are: (i) requires a clinical evaluation and scientific validation for reliable detection and CVD risk stratification, and (ii) requires hyper-parameter optimization in CVD/Stroke risk stratification. (iii) balancing the risk classes (control, low-risk, and high-risk) is the most effective way to minimize DL bias; (iv) with proper pruning and compression, DL systems can be adapted to edge devices; (v) A DL system that relies on surrogate carotid imaging can be cost-effective without compromising precision in CVD risk stratification.

6.6 Strengths, Weakness, and Extensions

This pilot review's ability to risk stratify CVD and stroke patients by integrating RBBM and GBBM was a major strength. The biomarkers generated from radiological, biochemical, and morphological complexity that demonstrated a link to CVD supported the first hypothesis. An XAI-based composite risk CVD/Stroke model using DL can predict, with precision, in a preventive and personalized (aiP³) framework benefiting the pharmaceutical paradigm. A DL approach was presented to evaluate CVD and stroke risk by integrating RBBM and GBBM. While the system is pretty straightforward, it requires optimization to eliminate the possibility of bias and generalization to account for comorbidities. Better comprehensive feature space can be tried for superior DL-based classification [210]. Ensemble-based solutions embedding PCA for best feature selection followed by recurrent neural networks are possible extensions for superior CVD/stroke risk solutions [211].

6.7 The Role Odds Ratio in Clinical Trials

In clinical trials, researchers often analyze the effectiveness of a new treatment or intervention compared to a control group. One of the essential statistical measures used in this context is the "Odds Ratio" (OR). The odds ratio helps to assess the association between an exposure (such as receiving a treatment) and an outcome (such as a positive response to the treatment) [212].

The odds ratio is calculated by taking the ratio of two odds: the odds of an event occurring in the treatment group and the odds of the same event occurring in the control group. Mathematically, it can be expressed as:

The odds ratio is calculated as follows:

$$OR = (a/b)/(c/d) \quad (3)$$

Where:

- a is the number of people in the exposed group who

have the outcome

- b is the number of people in the exposed group who do not have the outcome
- c is the number of people in the unexposed group who have the outcome
- d is the number of people in the unexposed group who do not have the outcome

The odds ratio can be used to determine if there is a significant difference in the odds of the outcome between the treatment and control groups. If the odds ratio is equal to 1, it suggests that there is no association between the treatment and the outcome, meaning the treatment has no effect. If the odds ratio is greater than 1, it indicates that the treatment is associated with a higher likelihood of the outcome. Conversely, if the odds ratio is less than 1, it implies that the treatment is associated with a lower likelihood of the outcome [213].

Researchers typically calculate the odds ratio along with a confidence interval to assess the statistical significance of the results. If the confidence interval includes the value 1, the results are considered not statistically significant, while values above or below 1 indicate a statistically significant association [214]. The odds ratio is a useful tool in clinical trials as it provides valuable information about the relative impact of a treatment compared to a control group. However, it's essential to interpret the odds ratio in the context of the study design and the specific clinical question being addressed [214]. In conclusion, the odds ratio is a critical statistical measure used in clinical trials to analyze the association between treatment and outcomes, providing valuable insights into the effectiveness of interventions.

7. Conclusions

The proposed research investigation presented two hypotheses: (i) an extensive investigation into several genomic biomarkers, namely, IL, CD31+, EPCs, and hs-CRP, which have been found to correlate most significantly with prognosis. The surrogate radiomic features such as plaque burden, plaque area, carotid intima thickness, maximum plaque height, and lumen stenosis/lumen diameter further improve the CVD risk prediction. (ii) The proposed review suggests a unique, unbiased, and XAI model (AtheroEdge™ 4.0) that can predict the composite risk of CVD/Stroke using radio genomics in the pharmaceutical paradigm. There is a strong link between the genetic and radiomic biomarkers of atherosclerosis in the carotid, coronary, and aortic arteries. A DL-based system is critical in reducing nonlinearity among multi-covariate biomarkers and outcomes. During this pilot review, various issues were considered, such as AI bias, AI pruning, and a suggestion for a cloud-based cascaded system design.

Abbreviations

ARDS, Acute respiratory distress syndrome; LGE, Late gadolinium enhancement; ASCVD, Atherosclerotic

cardiovascular disease; LIME, Local interpretable model-agnostic explanations; ANS, Autonomic nervous System; MRI, Magnetic resonance imaging; AUC, Area-under-the-curve; NR, Not reported; AI, Artificial intelligence; NPV, Negative predictive value; ACS, Acute coronary syndrome; NB, Naive bayes; BMI, Body mass index; Non-ML, Non-machine learning; CAD, Coronary artery disease; OBBM, Office-based biomarker; CAS, Coronary artery syndrome; OH, Orthostatic hypotension; CHD, Coronary heart disease; OxLDL, Oxidation of low-density lipoprotein; CT, Computed tomography; PE, Performance evaluation; CUSIP, Carotid ultrasound image phenotype; PPV, Positive predictive value; CV, Cross-validation; PCA, Principal component analysis; CVD, Cardiovascular disease; PBBM, Proteomics based bio-markers; CVE, Cardiovascular events; PRISMA, Preferred reporting items for systematic reviews and meta-analyses; CNN, Convolution neural network; PTC, Plaque tissue characterization; DL, Deep learning; RA, Rheumatoid arthritis; DM, Diabetes mellitus; RF, Random forest; DT, Decision tree; ROS, Reactive oxides stress; EC, Endothelial cell; RoB, Risk of bias; EBBM, Environment-based biomarkers; ROC, Receiver operating-characteristics; GT, Ground truth; RNN, Recurrent neural network; GBBM, Genetically based biomarkers; SCORE, Systematic coronary risk evaluation; HTN, Hypertension; SMOTE, Synthetic minority over-sampling technique; HDL, Hybrid deep learning; SVM, Support vector machine; ICAM, Intercellular adhesion molecule; SHAP, Shapley additive explanations; VCAM, Vascular cell adhesion molecule; TPA, Total plaque area; LBBM, Laboratory-based biomarker; TC, Tissue characterization; LA, left atrium; US, Ultrasound.

Author Contributions

MM: Design of the manuscript, proofreading many iterations, researching PubMed and other research sites for article search, AMJ, KIP, NNK, MM, JFF, JSS: Resources, imaging contribution and proofreading of the manuscript, MM, AMJ, LM, ERI, MMF: Design of the genomics and genetics component of the manuscript, proofreading many iterations, researching PubMed and other research sites for article search, JSS, VR, VV, MKK, NS: Proofreading and guidance of cardiology components of the manuscript, JSS, AN, NNK: The vision of cardiac risk assessment and proofreading the manuscript, final approval of the manuscript, MKK, LS: Design and support of radiology components such as CT and carotid ultrasound, JRL, SC, MMF, MAM: Proofreading and guidance of cardiology imaging components of the manuscript, JRL, VV, KIP ZR, ERI: Proofreading and guidance of cardiology and genomics components, MM, JSS: Design and solid proofreading of the manuscript, especially the Phramamode component, revising it critically for important intellectual content, and final approval of the manuscript, SC, VR, MKK ERI, MMF: clinical trial and proofreading of the manuscript, JSS: Principal Investigator-design, proofreading of the manuscript

and management. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

Dr. Suri and Dr. Maindarkar is with AtheroPoint™ LLC, Roseville, CA, USA, which does cardiovascular and stroke imaging. The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.31083/j.fbl2810248>.

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