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REVIEW

Artificial intelligence-based preventive, personalized and precision medicine for cardiovascular disease/stroke risk assessment in rheumatoid arthritis patients: a narrative review

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Abstract

The challenges associated with diagnosing and treating cardiovascular disease (CVD)/Stroke in Rheumatoid arthritis (RA) arise from the delayed onset of symptoms. Existing clinical risk scores are inadequate in predicting cardiac events, and conventional risk factors alone do not accurately classify many individuals at risk. Several CVD biomarkers consider the multiple pathways involved in the development of atherosclerosis, which is the primary cause of CVD/Stroke in RA. To enhance the accuracy of CVD/Stroke risk assessment in the RA framework, a proposed approach involves combining genomic-based biomarkers (GBBM) derived from plasma and/or serum samples with innovative non-invasive radiomic-based biomarkers (RBBM), such as measurements of synovial fluid, plaque area, and plaque burden. This review presents two hypotheses: (i) RBBM and GBBM biomarkers exhibit a significant correlation and can precisely detect the severity of CVD/Stroke in RA patients. (ii) Artificial Intelligence (AI)-based preventive, precision, and personalized (aiP^3) CVD/Stroke risk AtheroEdge™ model (AtheroPoint™, CA, USA) that utilizes deep learning (DL) to accurately classify the risk of CVD/stroke in RA framework. The authors conducted a comprehensive search using the PRISMA technique, identifying 153 studies that assessed the features/biomarkers of RBBM and GBBM for CVD/Stroke. The study demonstrates how DL models can be integrated into the AtheroEdge™–aiP^3 framework to determine the risk of CVD/Stroke in RA patients. The findings of this review suggest that the combination of RBBM with GBBM introduces a new dimension to the assessment of CVD/Stroke risk in the RA framework. Synovial fluid levels that are higher than normal lead to an increase in the plaque burden. Additionally, the review provides recommendations for novel, unbiased, and pruned DL algorithms that can predict CVD/Stroke risk within a RA framework that is preventive, precise, and personalized.

Keywords Rheumatoid arthritis · Cardiovascular disease · Stroke · Biomarkers · Radiomics · Genomics · Deep learning · Bias · Explainable AI

Abbreviations

ARDS	Acute respiratory distress syndrome
ASCVD	Atherosclerotic cardiovascular disease
ANS	Autonomic nervous system
AUC	Area-under-the-curve
AI	Artificial intelligence
ACS	Acute coronary syndrome
BMI	Body mass index
CAD	Coronary artery disease
CAS	Coronary artery syndrome
CHD	Coronary heart disease
CT	Computed tomography
CUSIP	Carotid ultrasound image phenotype
CV	Cross-validation
CVD	Cardiovascular disease
CVE	Cardiovascular events
CNN	Convolution neural network
DL	Deep learning
DM	Diabetes mellitus
DT	Decision tree
EC	Endothelial cell

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EBBM	Environment-based biomarkers
GT	Ground truth
GBBM	Genetically based biomarkers
HTN	Hypertension
HDL	Hybrid deep learning
ICAM	Intercellular adhesion molecule
VCAM	Vascular cell adhesion molecule
LBBM	Laboratory-based biomarker
LIME	Local interpretable model-agnostic explanations
MRI	Magnetic resonance imaging
NR	Not reported
NPV	Negative predictive value
NB	Naive Bayes
Non-ML	Non-machine learning
OBBM	Office-based biomarker
OH	Orthostatic hypotension
OxLDL	Oxidation of low-density lipoprotein
PE	Performance evaluation
PPV	Positive predictive value
PCA	Principal component analysis
PBBM	Proteomics-based biomarkers
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PTC	Plaque tissue characterization
RA	Rheumatoid arthritis
RF	Random forest
ROS	Reactive oxides stress
RoB	Risk of bias
ROC	Receiver operating characteristics
RNN	Recurrent neural network
SCORE	Systematic coronary risk evaluation
SMOTE	Synthetic minority over-sampling technique
SVM	Support vector machine
SHAP	Shapley additive explanations
TPA	Total plaque area
TC	Tissue characterization
US	Ultrasound

Introduction

Rheumatoid arthritis (RA) is a persistent autoimmune disorder characterized by joint inflammation and structural impairment. It affects about one percent of the world's population [1]. The key symptoms of RA are associated with joint health, and there is accumulating evidence that RA patients are more likely to develop cardiovascular disease (CVD)/stroke, which encompasses illnesses such as atherosclerosis, heart attacks, and stroke [2–4]. Obesity, hypertension, metabolic syndrome, smoking, and abnormal lipid are the common risk factors in patients with RA leading to CVD/Stroke. According to numerous studies, there is a clear indication that carotid intima-media thickness (cIMT) is positively correlated with the duration of rheumatoid arthritis [5–7]. As a result, it has emerged as the primary cause of morbidity and mortality in RA patients [8, 9]. However, traditional CVD/Stroke risk stratifying tools, such as the Framingham Risk Score and ACC/AHA risk calculator, may not be as sufficient and clear in forecasting CVD/Stroke risk in RA patients [1, 10]. This is due to the unique underlying pathophysiology of RA, which involves chronic inflammation, immune system dysregulation, vascular complications, and bone erosion [11]. To overcome the limitations of traditional risk assessment tools, there is research scope to forecast the CVD/Stroke threat in RA patients in a personalized framework using a combination of genomic and radiomics biomarkers along with traditional biomarkers [12].

Genetic approaches involve studying an individual's Deoxyribonucleic Acid (DNAs) and Ribonucleic acid (RNAs) to identify genetic-based biomarkers (GBBM) associated with CVD/Stroke risk in patients having RA [13]. Recent studies [14, 15] have discovered several genetic variants associated with both RA and CVD, such as the HLA-DRB1 gene, which has been implicated in both diseases [16]. By analyzing the genetic data of RA patients, it is precisely identified individuals at an increased risk of developing CVD [17–19].

Several CVD/Stroke biomarkers can be analyzed using imaging modalities such as magnetic resonance imaging (MRI), computed tomography (CT), and ultrasound (US) [20], as well as nuclear imaging techniques like positron emission tomography (PET). These imaging methods are very useful in providing insightful information regarding several facets of CVD [21]. For instance, cardiac CT and MRI are useful for visualizing coronary calcification and susceptible plaque features, which reveal changes in coronary plaque morphology [22]. These imaging techniques are extremely useful when paired with CT, fluorodeoxyglucose positron emission tomography (FDG-PET), also known as FDG-PET, enables improved visualization of target lesions using a radioactive substance that accumulates in regions of active inflammation [23]. Intravascular optical coherence tomography (IVOCT) is a sophisticated imaging modality that provides accurate visualization of microstructural plaque constituents associated with an increased susceptibility to rupture [24]. The use of carotid ultrasound (CUS) is an economically efficient and non-intrusive imaging methodology employed for the assessment of asymptomatic atherosclerotic carotid plaque and the quantification of carotid intima-media thickness (cIMT) [25, 26]. CVD and stroke risk assessment in patients with RA can be significantly enhanced through the utilization of carotid ultrasound (CUS) as a diagnostic tool [7, 27].

Artificial intelligence (AI) methods utilize machine learning (ML) algorithms to analyze complex datasets of

radiological, genetics, and laboratory parameters, and generate predictions [2, 28–32]. Figure 1 illustrates a model that utilizes AI to stratify the risk of CVD and stroke in patients having RA. Numerous studies have underscored the potential of AI techniques in enhancing the forecasting of CVD and stroke risk for patients having RA [1, 2, 10]. These algorithms continuously learn from data, refining their predictive capabilities over time [33].

Integrating office-based biomarkers (OBBM), lab-based biomarkers (LBBM), radiomics-based biomarkers (RBBM), and genomics-based biomarkers (GBBM) using AI techniques can further enhance CVD/Stroke risk assessment in RA patients [34, 35]. This can lead to more accurate risk prediction models that incorporate genetic and clinical data. By accurately identifying high-risk RA patients, healthcare providers can implement more efficient CVD/Stroke prevention strategies tailored to the individual's genetic profile.

In this study, we explore combining genetic and AI platforms for the severity detection of CVD/Stroke in RA patients. Presented study reviews the current state of knowledge regarding the genetic basis of RA and CVD/Stroke and discusses the potential of AI approaches for improving CVD/Stroke risk severity in patients having RA. This study also highlights recent studies that have combined genetics in the AI paradigm for CVD/Stroke risk forecasting in RA patients and discuss the implications of these findings for clinical practice. Ultimately, such as integration of genetic in AI framework can potentially improve CVD/Stroke risk prognosis and management in RA patients, reducing the burden of CVD/Stroke in this vulnerable population.

Search strategy and statistical distribution

The search strategy for identifying relevant studies for the severity forecasting of CVD/Stroke in RA patients using combined genetic and AI platforms involves a comprehensive and systematic approach [4]. First, we identified relevant databases, including PubMed, Embase, Web of Science, and Scopus. We constructed our search query by using appropriate Medical Subject Headings (MeSH) and keywords related to RA, CVD/Stroke, genetics, and AI. The search query was tailored to the specific requirements of each database and included Boolean operators, such as "AND," "OR," and "NOT," to ensure comprehensive coverage of the relevant literature. Next, we screened the titles and abstracts of the retrieved studies to identify relevant studies that meet our inclusion criteria. Our inclusion criteria included studies that use combined genetic and AI approaches for the severity detection of CVD/Stroke in RA patients. We excluded studies that do not meet our inclusion criteria, such as studies that are not published in English or not peer-reviewed. After screening the titles and abstracts, we reviewed the potentially relevant studies' full texts to determine their inclusion eligibility. To ensure the selection of high-quality studies for our review, we applied specific inclusion and exclusion criteria. Additionally, we conducted a thorough manual search of the reference lists in the included studies to identify any additional relevant research (Fig. 2).

Finally, we extracted relevant data from the included studies, including study design, sample size, population characteristics, genetic markers studied, ML/DL

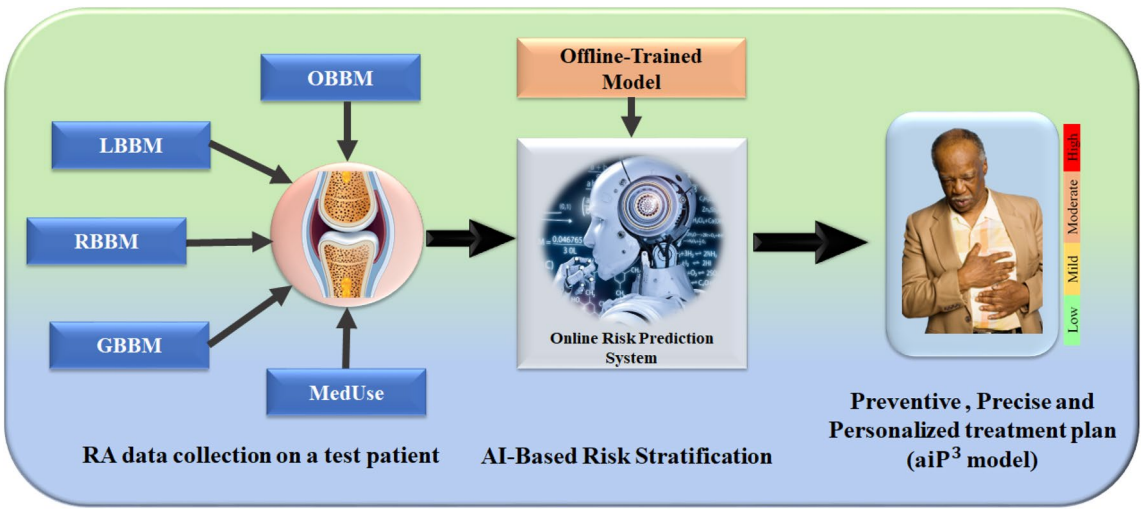

Fig. 1 The aiP3 model offers an integrated approach to manage and treat both RA and CVD. *OBBM* office-based biomarker, *LBBM* laboratory-based biomarker, *RBBM* radiomics-based biomarker, *GBBM* genomics-based biomarker, *PBBM* proteomics-based biomarker, *PRS* polygenic risk score, *aiP*^{3} AI for preventive, precision, and personalized system (Original image, Courtesy AtheroPoint™ LLC, Roseville, CA, USA)

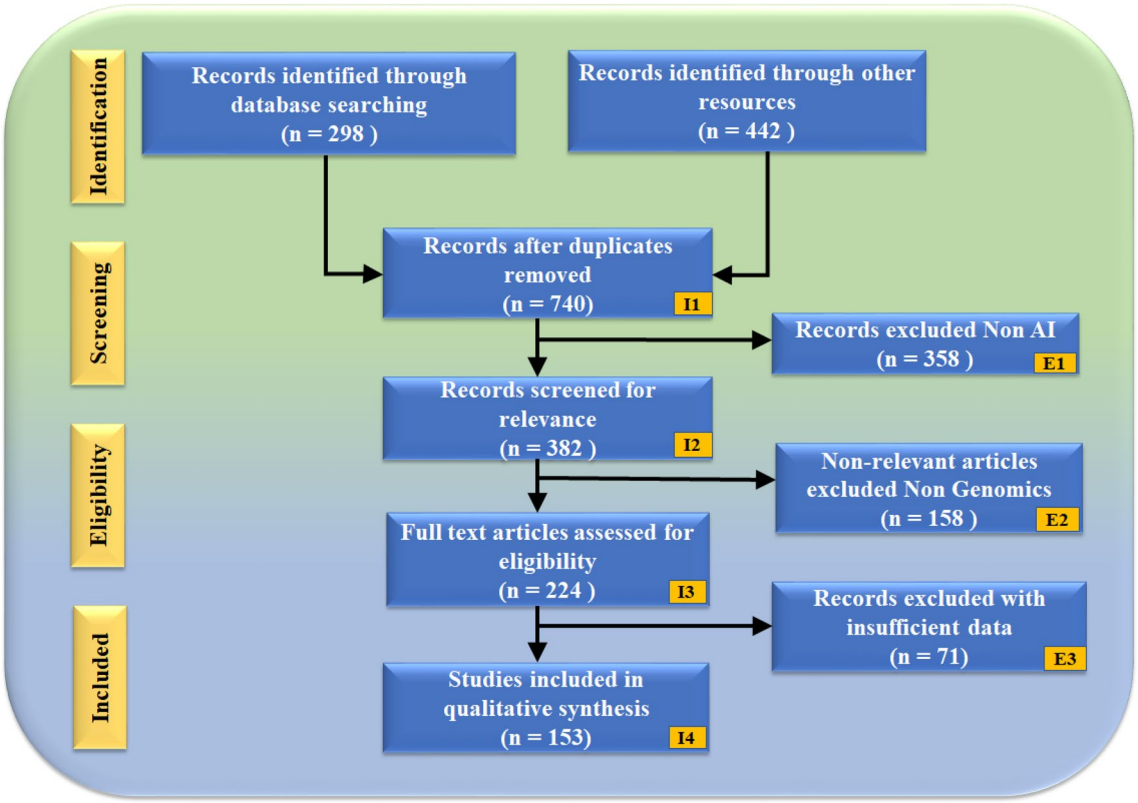

Fig. 2 PRISMA model for study selection. *I* included, *E* excluded

algorithms used, and outcomes. We then performed a meta-analysis or a narrative synthesis of the data, depending on the nature and quality of the included studies.

Statistical distribution

Figure 3 in the presented article illustrates the distribution of studies conducted in RA, genomics, CVD, Stroke, and AI domains. Figure 3A shows that studies, 29 focus on integrating RA, genomics, and CVD, aiming to understand the genetic factors associated with both conditions. Additionally, 18 studies explore the intersection of RA, CVD, Stroke, and AI, investigating the application of AI methodologies, particularly ML algorithms, to analyze data and detect patterns related to RA and CVD/Stroke. Another set of 16 studies examines the integration of RA, genomics, and AI, aiming to gain a deeper understanding of the genetic basis of RA through AI techniques applied to genomic information. Furthermore, three studies explore the cumulative influence of RA, genomics, CVD, Stroke, and AI.

Figure 3B indicates several studies utilizing RA, CVD, Stroke, AI, and genomics as variables from 2019 to 2023. The number of studies has increased, indicating a promising interest in RA research. Figure 3C reveals different AI techniques in RA studies, with ML used in 21 studies, DL in 12 studies, and HDL in 4 studies. ML appears to be the most commonly employed technique in RA research. Figure 3D showcases the performance metrics used in the studies, including ACC, SEN, SPE, AUC, MCC, NPV, and F1. ACC is the most frequently reported metric (16 studies), while F1 is the least commonly reported (2 studies).

Our search strategy for detecting CVD/Stroke severity in RA patients using combined genetic and AI platforms will be comprehensive, systematic, and based on predefined inclusion and exclusion criteria. The study aims to ensure the validity and reliability of the presented findings.

Biological link

Growing evidence suggests that various pathophysiological factors may contribute to the link between RA and atherosclerosis. Also, several genes have been identified that are involved in both diseases, suggesting a shared genetic basis. Subsection "Rheumatoid Arthritis induced Atherosclerosis" below addresses RA-induced atherosclerosis, and subsection "Shared genes for Rheumatoid Arthritis and Atherosclerosis" discusses the shared genes responsible for developing RA and CVD diseases.

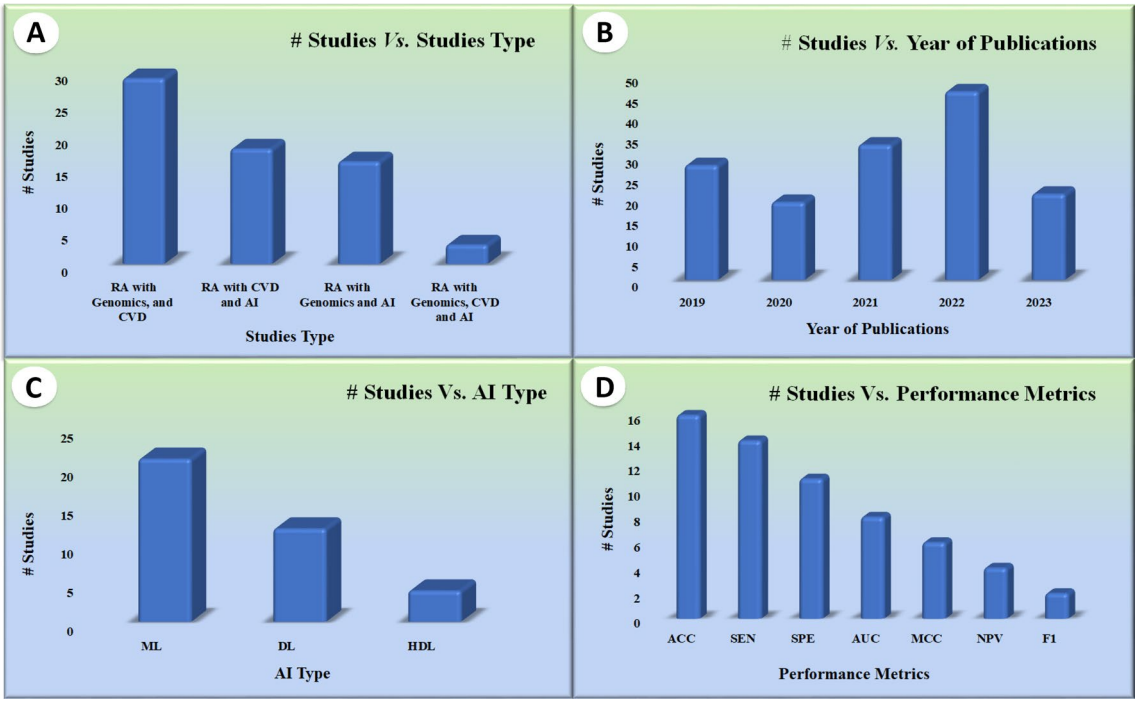

Fig. 3 Statistical analysis of various studies involved in RA and CVD/Stroke. *ML* machine learning, *DL* deep learning, *HDL* hybrid deep learning, *ACC* accuracy, *SEN* sensitivity, *SPE* specificity, *AUC* area under the curve, *MCC* Mathew coefficient, *NPV* negative positive value, *F1* F1-score, *AI* artificial intelligence, and *RA* rheumatoid arthritis, and *CVD* cardiovascular disease

Rheumatoid arthritis-induced atherosclerosis

The connection between atherosclerosis and RA is closely associated with inflammation [36]. According to a study by Skeoch et al. [37], RA patients tend to experience a faster accumulation of plaque in their blood vessel walls. Inflammatory cytokines, primarily found in the synovial membrane, have widespread effects throughout the body, leading to blood vessel inflammation and damage to endothelial cells [38]. It is important to note that tumor necrosis factor-alpha (TNF-α) and Interleukin-6 (IL-6) exhibit impact, as they impede endothelial function by inhibiting the formation of nitric oxide and cyclooxygenase-1. These two enzymes are essential for keeping a healthy endothelial layer [39]. The shared genetic and environmental factors in RA and atherosclerosis environment are responsible for endothelial dysfunction [40].

The expansion of endothelial cells facilitates the penetration of low-density lipoprotein cholesterol (LDL-C) across the lumen-intima boundary and into the subendothelial layer, where they go through oxidation [41]. This phenomenon enhances the permeability of endothelial cells, thereby facilitating the infiltration of immune cells such as T lymphocytes and monocytes into the intimal layer. Monocytes transform into macrophages within the intimal layer and engulf oxidized LDL-C, forming foam cells [42]. Subsequently, macrophages secrete pro-inflammatory cytokines, such as IL-6 and TNF-α, which serve to recruit additional monocytes to the intimal layer [43].

However, macrophages undergo a crucial role in promoting the migration and proliferation of smooth muscle cells (SMCs) within the intima, forming a protective fibrous barrier to prevent plaque infiltration into the lumen [44]. T helper cells and macrophages produce pro-inflammatory cytokines, free radicals, and enzymes, causing erosion of the fibrous cap [45] and increasing the vulnerability of atherosclerotic plaque, as documented in previous studies [46, 47]. TNF-α, in particular, has been shown to worsen LDL-C oxidation, with higher levels observed in individuals with RA compared to those without the condition [48, 49]. Furthermore, the pro-inflammatory cytokine TNF-α induces an increase in the expression of adhesion molecules on the surface of endothelial cells, thereby augmenting the process of monocyte and macrophage recruitment [50]. This inflammatory cascade ultimately leads to plaque development, rupture, and thrombotic events in atherosclerosis. Figure 4 illustrates the biochemical relationship between RA and CVD.

Amyloidosis is a serious complication linked to RA, where amyloid fibrils are deposited on various organ tissues. This condition increases the likelihood of developing atherosclerosis and CVD [51, 52]

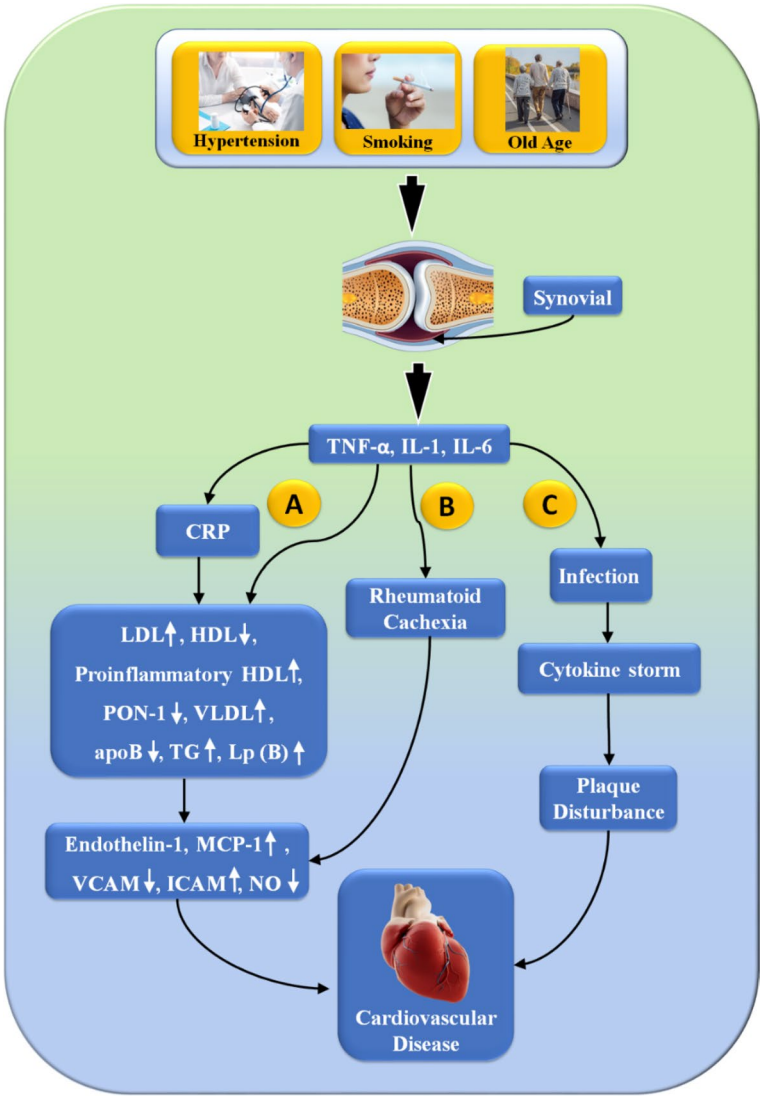

Fig. 4 The biological link between RA and CVD. *TNF-α* tumor necrosis factor-alpha, *IL-6* interleukin-6, *LDL-C* low-density lipoprotein cholesterol, *HDL* high-density lipoprotein, *SMCs* smooth muscle cells, *MCP-1* monocyte chemoattractant protein-1, *PON-1* paraoxonase 1, *VCAM* vascular cell adhesion molecule, *ICAM* intercellular adhesion molecule, *VLDL* very low-density lipoprotein, *apB* apolipoprotein B, *TG* triglycerides, *CRP* C-reactive protein, Heart image: courtesy of AtheroPoint™, Roseville, CA, USA

Shared genes for rheumatoid arthritis and atherosclerosis

The genetic basis for the link between RA and atherosclerosis is complex and involves multiple genes [53]. Here, we discuss the prominent combined genes responsible for both diseases, and several genes have been identified as being involved in both RA and atherosclerosis.

- **TNF-α:** TNF-α is a cytokine that plays a central role in RA's inflammation development [54]. Elevated levels of TNF-α have also been associated with the development of atherosclerosis [55]. Genetic variations in the TNF-α gene have been linked with an elevated risk of both diseases [56].
- **HLA-DRB1:** The human leukocyte antigen (HLA) complex is a group of genes that help regulate the immune system [57]. HLA-DRB1 has been strongly linked with the progression of RA. Studies have also suggested that genetic variations in HLA-DRB1 have contributed to the progression of atherosclerosis [7, 58].
- **APOE:** Apolipoprotein E (APOE) is a protein involved in transporting cholesterol and other lipids in the blood [59, 60]. Genetic variations in the APOE gene have been associated with an increased risk of atherosclerosis [59]. Studies have also suggested that genetic variations in APOE may contribute to the development of RA [61].
- **MMP-3:** Matrix metalloproteinase-3 (MMP-3) is an enzyme in tissue remodeling and repair [62]. Elevated levels of MMP-3 have been linked to the development of both RA and atherosclerosis [63]. Genetic variations in the MMP-3 gene have been associated with an increased risk of both diseases.
- **PADI4:** Peptidylarginine deiminase 4 (PADI4) is an enzyme involved in the citrullination of proteins, a process that is thought to contribute to the development of

RA [64]. Genetic variations in the PADI4 gene have been strongly associated with the development of RA [65]. Studies have also suggested that genetic variations in PADI4 are involved in the progression of atherosclerosis [66, 67].

It is important to note that the genetic basis for both RA and atherosclerosis is complex and involves many different genes and pathways [37]. The genes listed above are just a few examples of the genetic factors that have been implicated in both diseases. In summary, IL-6, TNF- α, LDL-C, erythrocyte sedimentation rate (ESR), fibrinogen, serum amyloid A, and secondary phospholipase, are linked to atherosclerosis and RA [68]. However, the link between RA and atherosclerosis in genomics pathways involves shared genetic factors in inflammation, lipid metabolism, and endothelial function [69]. Epigenetic modifications may also contribute to the shared genetic basis of these diseases [61]. A better understanding of these genetic and epigenetic mechanisms could lead to new therapies for both RA and atherosclerosis.

Artificial intelligence-based CVD/stroke risk stratification

Machine learning (ML) algorithms have been developed to enhance segmentation and classification [30, 70–73]. However, these methods lack automated feature extraction. In contrast, ML combined with deep learning (DL) provides a powerful framework capable of automatically generating features by leveraging underlying knowledge of radiological features and genetic features. It also offers an advanced training paradigm, enabling dynamic adjustment of the nonlinear relationship between risk factors and the desired outcome, making ML/DL a potent approach [30, 70–73]. Our team has conducted an extensive examination of different applications of DL and has taken measures to appropriately prepare and balance the data sets used for training and testing purposes [74–76]. The process involves four steps: data preparation (or preprocessing, also referred to as quality control), data partitioning, offline training using the training data, and estimation (or prediction) of CVD risk on the test data. Data preparation includes data normalization and augmentation using a SMOTE or ADASYN model (shown in Fig. 5). To aid in the process, we utilize PCA-based pooling, a statistical attribute selection technique [10, 77].

The K10 cross-validation methodology is employed for data partitioning, which creates separate training and testing sets. The model generator utilizes DL classifiers such as recurrent neural networks (RNNs) and long short-term memory (LSTM). These classifiers take risk factors (or variables) and CVD/Stroke risk as inputs to generate offline coefficients [78, 79]. The prediction paradigm utilizes the model to predict CVD/Stroke risk on the test data sets [70, 80, 81]. The process is performed in a cyclic sequence to ensure no overlap between combinations and no inclusion of test data in the training set [70, 82]. Embedded feature optimization is essential for the learning algorithm [78, 79, 83]. The online system incorporates an effective element that utilizes known reference values to calculate accuracy. The performance evaluation process involves the assessment of multiple measures, such as reliability, specificity, sensitivity, recall, precision, and *p*-value, using a cross-validation protocol. The study utilizes a methodology that combines ML and DL techniques, along with meticulous data preprocessing, appropriate data segmentation, and thorough performance evaluation. This approach aims to accurately predict the risk of CVD and stroke in individuals diagnosed with RA. Figure 5 depicts a representative ML/DL system. The process of acquiring input data involves the inclusion of diverse biomarkers, which encompasses OBBM, LBBM, carotid image-based phenotypes (CUSIP) that are classified as RBBM, medication information (MedUSE), and GBBM (Original image, Courtesy AtheroPoint™ LLC, Roseville, CA, USA).

CVD/stroke risk stratification in RA using machine learning-based classifiers

The primary goal of an ML-based classifier is to categorize received data into predetermined labels or categories [84]. In the case of predicting CVD/Stroke events, for example, the classifier utilizes input features to predict whether an event will occur or not. In this particular study, the ML-based classifier assigned patients to the low-risk or high-risk category based on their specific risk profiles. Several studies have demonstrated the successful use of ML-based plaque risk stratification, particularly utilizing the RF classifier. Jamithkar et al. [85] proposed an RF-based ML algorithm, shown in Fig. 6, which has exhibited superior predictive capacity to other ML algorithms [86, 87]. Hence, the researchers chose this study's RF classifier for risk stratification [88].

CVD/stroke risk stratification using deep learning classifiers

Recurrent Neural Networks (RNNs) are a type of neural network that was first discussed by Rumelhart et al. [89]. RNNs are powerful at getting close to unknown, non-linear dynamical systems [90, 91]. But training an RNN can encounter challenges such as disappearing gradient issues, which can make the model less stable, and thus need to be optimized [92]. To get around these challenges, a hybrid design, shown in Fig. 7, is suggested. The design is made up of one RNN unit activated by a Rectified Linear Unit (ReLU) and four

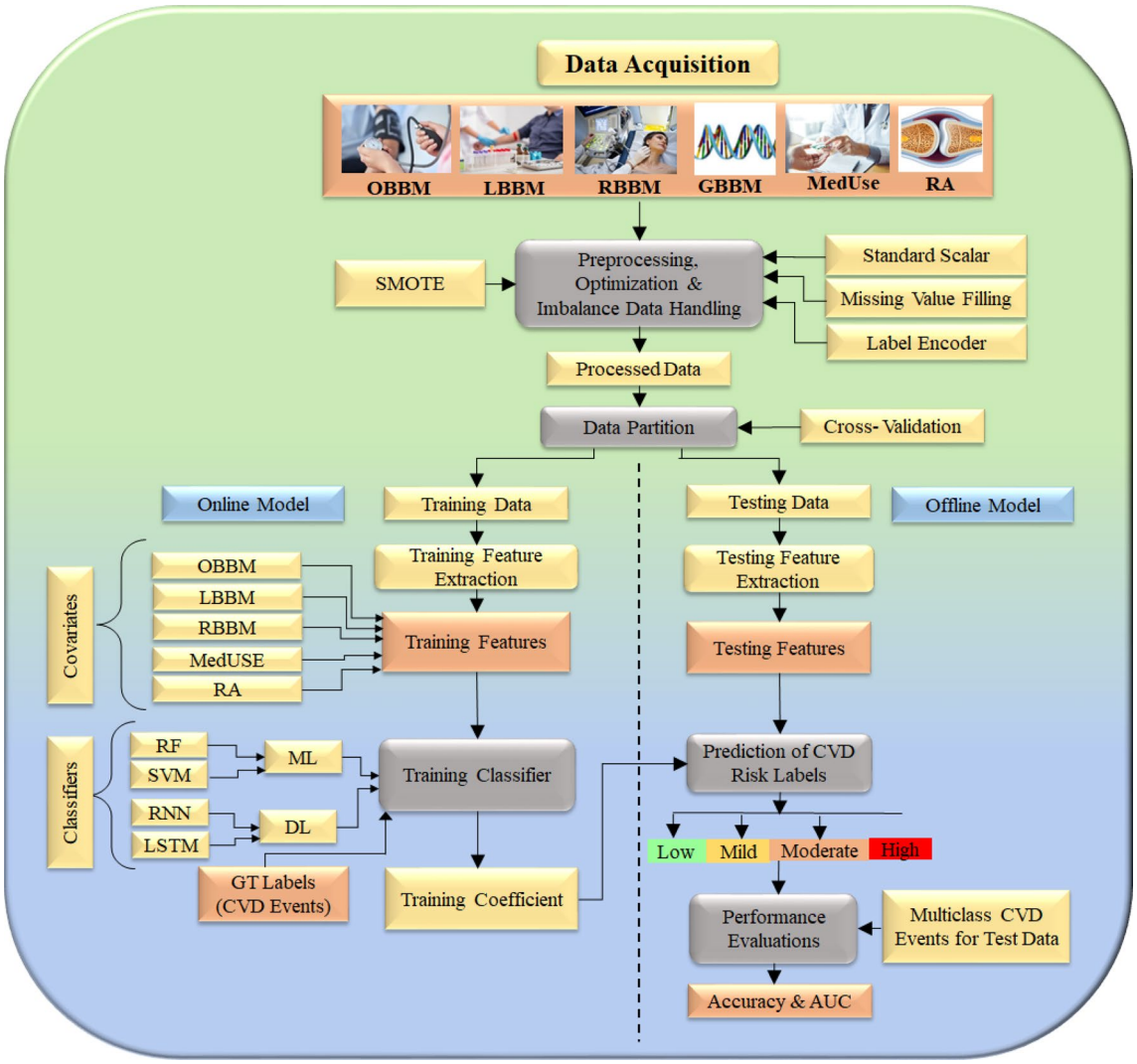

Fig. 5 A typical ML/DL system for RA patients' CVD/Stroke risk stratification. *OBBM* office-based biomarker, *LBBM* laboratory-based biomarker, *RBBM* radiomics-based biomarker, *GBBM* genomics-based biomarker, *PBBM* proteomics-based biomarker, *MedUse* medication, *RA* rheumatoid arthritis, *RF* random forest, *SVM* support vector machine, *RNN* recurrent neural networks, *LSTM* long-short-term memory, *CVD* cardiovascular disease (Original image, Courtesy AtheroPoint™ LLC, Roseville, CA, USA)

thick layers stacked on top. The thick layers in the middle possess 64, 32, and 8 nodes, respectively. The SoftMax function turns on four nodes in the output layer. The Adaptive Moment Estimation (ADAM) method is used to train the model. The categorical cross-entropy loss (CEL) is used as the loss function. The end goal is to train a complete model that can predict a patient's atherosclerosis risk based on their test features. Figure 8 shows an outline of how the RNN model is put together.

LSTM classifier

Long-Short-Term Memory (LSTM) is a specific type of DL algorithm that holds the potential for forecasting the risk of CVD or stroke [77]. LSTM is particularly advantageous in dealing with the challenge of long-term dependency, which is crucial for capturing temporal patterns and relationships in sequential data. Figure 8 illustrates the LSTM architecture and its ability to handle long-term dependencies effectively. Unlike other models, LSTM naturally tends to remember information for extended periods without much effort. The structure of an LSTM consists of a series of repeating modules in an RNN fashion. In basic RNNs, these modules often yield similar results to a single Tanh layer. However, the LSTM algorithm exhibits a distinctive capability to analyse a wide range of data points, encompassing individual observations. The cell serves as the principal unit accountable for conserving values at irregular intervals, and the transfer of data within and outside of the cell is regulated by three gates [94–96]. The LSTM architecture consists of four completely

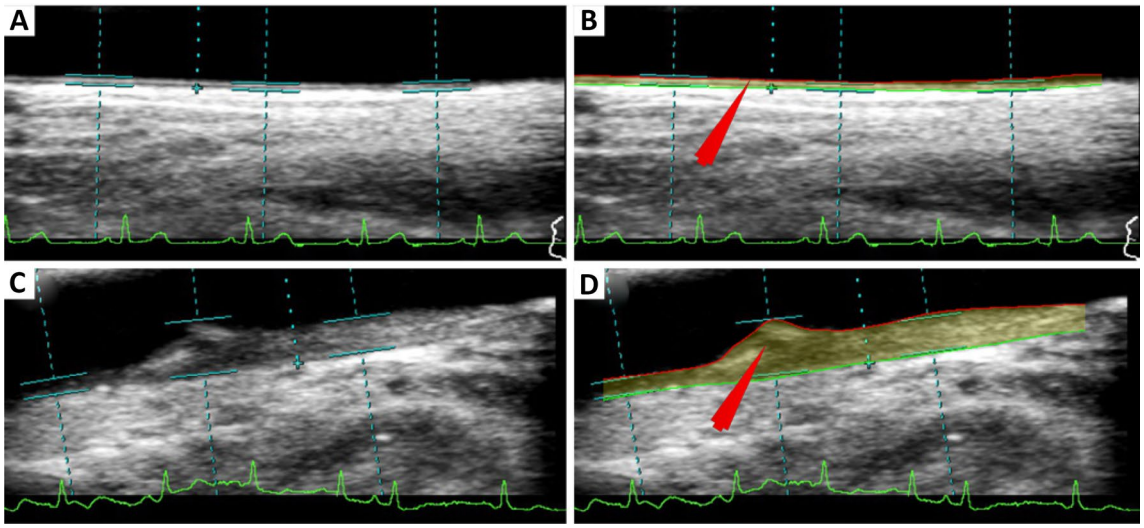

Fig. 6 CVD risk stratification relies on the utilization of an automatic AtheroRisk-ML Integrated system. Row 1, consisting of elements **A** and **B**, is characterized by a low level of risk, while Row 2, comprising elements **C** and **D**, is associated with a high level of risk [88]

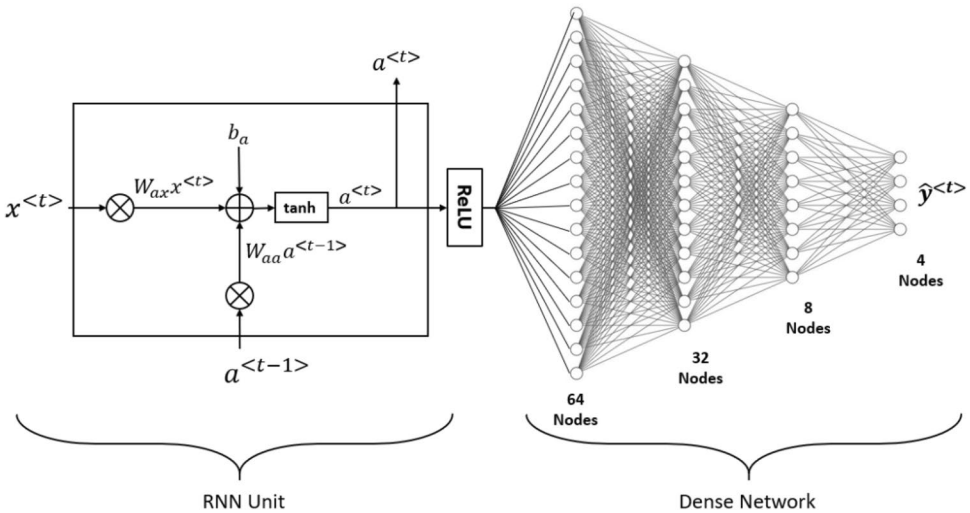

Fig. 7 The overall architecture for RNN [93]

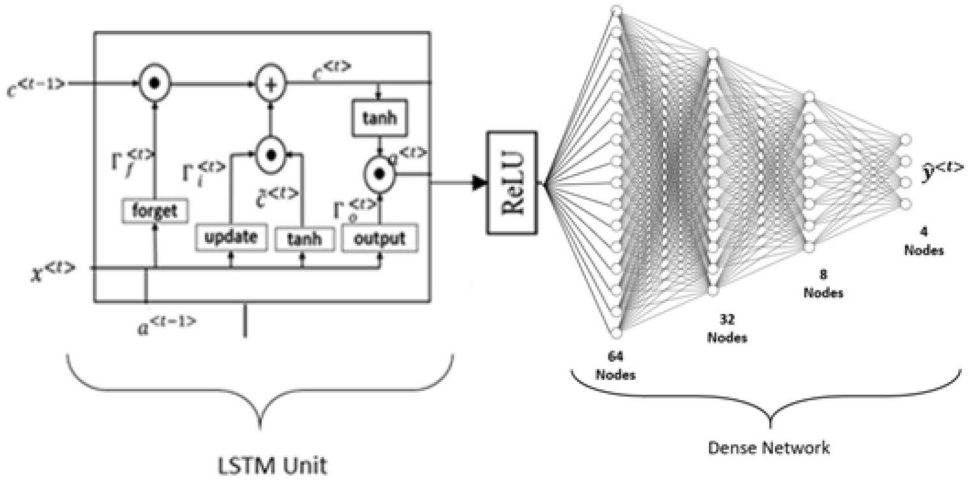

Fig. 8 The basic model of LSTM architecture [93]

interconnected layers that are stacked sequentially. The use of a stacked design allows for the efficient capture and utilization of long-term associations present within the data, thereby catching the potential of alternative methods [97]. One frequently encountered obstacle in LSTM models is the issue of overfitting, which poses a significant challenge in terms of effectively addressing it through the conventional dropout strategy. The regularisation technique known as a dropout is implemented by eliminating data and recurrent connections to the LSTM units throughout stimulation and weight updating in the training process. The implementation of dropouts in LSTM models may pose certain challenges. To address this issue, the researchers in the present study chose to employ weight initialization using a small value [77].

Critical discussion

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

Principal findings

Best to our knowledge, this is the first study of its kind (a) that combines radiomics and genomic biomarkers to detect the risk of CVD/stroke precisely in RA and (b) that introduces a proposed ai$\mathbf{P}^3$ risk model based on a preventive, predictive, and personalized approach that uses DL to classify CVD and stroke risk more accurately in RA. Using these two hypotheses, we demonstrated that CVD and stroke risk severity in RA could be determined using RBBM and GBBM biomarkers in the DL framework. Such models can be considered "personalized medicine frameworks". One of the major innovations is to ensure that cBUS imaging, RA, and CVD genomic biomarkers are jointly used in the DL framework for CVD risk stratification in RA patients. A set of six recommendations were provided for accurate, robust, real-time CVD risk stratification using combined RBBM and GBBM in RA patients.

Benchmarking

The benchmarking studies mentioned in Table 1 consist of 17 attributes that are identified by the letter 'B' followed by a number. The first attribute, B0, refers to the serial number assigned to each study. The second attribute, B1, represents the name of the studies, while B2 represents the year of publication. The third attribute, B3, indicates the references used in the studies. The remaining 14 attributes, B4 through B17, are related to using different types of AI studies in CVD risk prediction in RA patients. B4 through B9 represent six different types of AI-based biomarkers for CVD, including OBBM, LBBM, RBBM, GBBM, and environmental-based biomarkers (EBBM).

Table 1 Benchmarking table for CVD risk using multivariate biomarkers

B0	B1	B2	B3	B4	B5	B6	B7	B8	B9	B10	B11	B12	B13	B14	B15	B16	B17
1	Kataria et al. [98]	2017	24	✓	✓	✓	✗	✗	✗	✓	✓	✗	ML	✗	✗	✗	✗
2	Jamthikar et al. [99]	2019	54	✓	✓	✓	✗	✗	✗	✓	✓	✗	ML	✗	✗	✓	✗
3	Kim et al. [117]	2019	99	✓	✓	✗	✓	✗	✗	✓	✗	✓	ML	✗	✗	✗	✗
4	Khanna et al. [2]	2019	150	✓	✓	✗	✓	✗	✗	✓	✗	✓	DL	✗	✗	✗	✗
5	Stoel et al. [118]	2020	50	✓	✓	✗	✓	✗	✗	✓	✗	✓	NR	✗	✗	✗	✗
6	Jamthikar et al. [71]	2020	120	✓	✓	✓	✗	✗	✗	✓	✓	✗	HDL	✗	✗	✗	✗
7	Manrique et al. [101]	2020	31	✓	✓	✓	✗	✗	✗	✓	✓	✗	ML	✗	✗	✗	✗
8	Jamshidi et al. [102]	2020	85	✓	✓	✓	✗	✗	✗	✓	✓	✗	ML	✗	✗	✓	✗
9	Song et al. [103]	2021	42	✓	✓	✓	✗	✗	✗	✓	✓	✗	DL	✗	✗	✗	✗
10	Soloman et al. [104]	2021	92	✓	✓	✗	✓	✗	✗	✓	✗	✓	DL	✗	✗	✗	✗
11	Konstantonis et al. [10]	2021	29	✓	✓	✗	✓	✓	✗	✓	✗	✓	ML	✗	✗	✗	✗
12	McMaster et al. [106]	2022	95	✓	✓	✗	✓	✗	✗	✓	✗	✓	DL	✗	✗	✗	✗
13	Navarini et al. [105]	2022	39	✓	✓	✓	✗	✗	✗	✓	✓	✗	ML	✗	✗	✓	✗
14	Hugle et al. [119]	2022	55	✓	✓	✗	✓	✓	✗	✓	✓	✓	NR	✗	✗	✗	✗
15	Madrid-García et al. [120]	2023	168	✓	✓	✗	✓	✓	✗	✓	✗	✓	HDL	✗	✗	✗	✗
16	Al-Maini et al. (Proposed)	2023	152	✓	✓	✓	✓	✓	✓	✓	✓	✓	DL	✗	✗	✓	✓

B0 serial Number, *B1* studies, *B2* year, *B3* references, *B4* OBBM, *B5* LBBM, *B6* RBBM, *B7* GBBM, *B8* PBBM, *B9* EBBM, *B10* preventive, *B11* prediction, *B12* personalized, *B13* AI type, *B14* FDA discussion, *B15* clinical setting, *B16* risk of bias, *B17* AI explainability, *CVD* cardiovascular disease, *DL* deep learning, *ML* machine learning, *HDL* hybrid deep learning, *NR* not reported

The study by Kataria et al. [98] explains the adoption of digital technology in healthcare has been rapidly increasing, and it is believed to have the potential to bring about significant changes, improve the quality of care, and make healthcare accessible to people worldwide. However, to fully establish the role of digital health in patient care, there is a need for more data, efficacy studies, and objective results. Similarly, Jamthikar et al. [99] conducted another study utilizing ML techniques for CVD risk stratification in patients having RA. The presented study highlights two of the three pathways directly affect atherosclerosis, which damages the heart. Carotid ultrasound image-based calculators outperform standard calculators.

AI-based CVD risk stratification in RA patients is also becoming more common. In contrast, Khanna et al. [2] employed a concise overview of the development of RA and its connection to carotid atherosclerosis, as observed through B-mode ultrasound imaging. It highlights the limitations of conventional risk scores and explores the potential of ML-based tissue analysis in addressing these gaps. Stoel et al. [97] summarizes rheumatology imaging has made use of AI for a long time. Although several of these techniques have been developed, only a fraction of them have been put into actual clinical use. Recent advances in DL, however, are anticipated to effect a revolutionary change in this regard. When combined with human picture interpretation and clinical reasoning, AI-powered by DL will improve patient care. In 2020, Jamthikar et al. [71] conducted another study with 120 participants, focusing on HDL techniques for CVD risk stratification in patients having RA suggesting that there is a notable correlation between carotid atherosclerotic image-based biomarkers, such as carotid intima-media thickness (cIMT) and plaque, and specific inflammatory markers specific to RA. Conventional image processing solutions such as fast marching methods using level sets for segmentation of the vascular plaque can be incorporated for speed and robustness [100]. Manrique et al. [101] comment on the integration of digital technologies into rheumatology healthcare is poised to become a growing trend in the future. There is a wide range of devices available that can be seamlessly incorporated into everyday products, providing a personalized and continuous approach to patient care. Jamshidi et al. [102] employed ML techniques for CVD risk stratification in RA patients, emphasizing the applicability for preventive purposes.

However, none of the authors mentioned the applicability of their approach for preventive and predictive purposes. Unfortunately, the study did not provide information on the FDA discussion, clinical setting, risk of bias, or AI explainability. [103–106]. Our proposed study utilizes 152 references and uses DL techniques for CVD risk stratification in RA patients. The authors reported using DL for preventive, predictive, and personalized purposes. Additionally, they mentioned the FDA discussion and reported that AI explainability was discussed. However, the clinical setting and risk of bias were not mentioned.

A short note on platelet function, complete blood count, and diagnostic methods

Several parameters, including platelet count, can evaluate platelet function and activity, mean platelet volume (MPV), platelet RNA, and protein [107, 108]. As an important component of hemostasis and thrombosis, platelets play a critical role in various CVDs [109]. Abnormalities in their function have been responsible for an increased risk of CVD and adverse cardiovascular events [110, 111]. Elevated levels of platelet count, MPV, platelet RNA, and protein have been associated with an increased risk of CVD [112, 113].

Furthermore, hematological parameters, including hemoglobin (Hb) concentration, red blood cell (RBC) count, mean corpuscular volume (MCV), and hematocrit (Hct), are commonly assessed through complete blood count (CBC) analyses [114], and mean corpuscular hemoglobin concentration (MCHC), are routinely used to assess blood cell counts and morphology [115, 116].

Abnormalities in these indices have been associated with various CVDs, such as anemia, ischemic heart disease, and stroke [121, 122]. The neutrophil to lymphocyte (N/L) ratio, which measures the balance between innate and adaptive immunity, has been proposed as a biomarker of inflammation and oxidative stress [112, 123]. Elevated N/L ratios have been associated with an increased risk of CVD and adverse cardiovascular events, reflecting chronic low-grade inflammation and impaired immune function [121, 124]. Therefore, platelet count, MPV, platelet RNA, protein, CBC blood indices, and N/L ratios are essential parameters for evaluating various aspects of cardiovascular health and disease [125, 126]. Abnormalities in these parameters should be closely monitored, as they may indicate an increased risk of CVD and adverse cardiovascular events [127, 128].

A short note on artificial intelligence bias

Evaluating bias in AI models has gained much greater significance in recent years [129, 130]. Earlier computer-aided diagnosis techniques showed a lack of bias in evaluations [131]. To reduce AI bias, a large sample size, appropriate clinical testing, incorporating co-morbidities, using big data configurations, using unseen data analysis, and the scientific validation of training model design are all strategies that can be utilized [28, 132]. Critical stages in patient risk classification encompass the assessment of the AI risk of bias (RoB) [28, 133, 134] and appropriately adapting diagnostic procedures and therapeutic interventions.

A short note on synovial fluid and cardiovascular disease

The synovial fluid does not directly contribute to CVD/Stroke [135]. However, conditions affecting the joints, which can be evaluated through synovial fluid analysis, can indirectly affect CVD/Stroke and related parameters such as platelet function, complete blood count (CBC), and diagnostic methods [136]. Inflammatory conditions in RA can induce systemic inflammation, which can influence platelet function [137]. Joint inflammation releases pro-inflammatory mediators and cytokines, activating platelets and potentially promoting platelet aggregation and thrombosis. Consequently, individuals with joint-related inflammatory diseases may exhibit abnormalities in platelet function [138]. Additionally, inflammatory joint diseases can impact CBC parameters [139].

Chronic inflammation associated with certain joint conditions can result in anemia, and elevated levels of inflammatory markers like C-reactive protein (CRP) can affect CBC results [140]. Synovial fluid analysis, primarily performed for diagnosing joint-related conditions, can indirectly provide insights into potential associations with CVD/Stroke [140]. The analysis may reveal increased levels of inflammatory markers, such as cytokines, indicating systemic inflammation linked to the development and progression of CVD/Stroke in RA [141]. Moreover, imaging techniques like magnetic resonance imaging (MRI), and low-cost ultrasound can assess joint damage and inflammation, providing information on the extent of joint involvement [142]. Left untreated, joint inflammation can contribute to systemic inflammation, potentially increasing the risk of CVD/Stroke.

The role of pruning-based DL systems

The growing importance of edge devices is attributed to the continuous advancements in systems based on the cloud and internet connectivity [143]. Edge devices are of significant importance, especially in the context of mobile frameworks for predicting future outcomes or stratifying disease risks [144]. Nevertheless, the implementation of extensive data models on edge devices is not feasible, thereby requiring the implementation of compressed models [145]. To tackle this particular challenge, it is possible to employ image-based DL models, including fully convolutional networks (FCN) or segmentation networks (SegNet) [146], and optimize them through the utilization of evolutionary algorithms, such as Particle Swarm Optimization (PSO), Genetic Algorithms (GA), Wolf optimization (WO), and Differential Evolution (DE)) [147]. The utilization of compression techniques enables the compression and efficient deployment of RBBM-based CVD risk stratification models that are integrated with GBBM. This deployment is particularly advantageous for rural areas and third-world nations [148].

The role of artificial intelligence explainability

Understanding the inner workings of AI's "black box" is a pivotal aspect of AI. Healthcare providers are more inclined to comprehend the concept of the "black box" if they can interpret and scrutinize the outcomes [149]. The utilization of tools such as Local Interpretable Model-Agnostic Explanations (LIME) and Shapley Additive Explanations (SHAP) has bolstered the credibility of AI models within the medical community. These tools offer valuable insights into intricate disorders [150, 151]. Additionally, carotid lesions and other abnormalities can be visualized using techniques such as GradCAM, GradCAM + , or GradCAM + + [75]. These interpretability tools open doors for broader acceptance of AI models in the medical field, ultimately leading to improvements and cost-effectiveness [152] stratification.

Recommendations

Following are guidelines for a proposed AI model that can be used for CVD/stroke risk identification in RA. 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 in RA patients precisely, and (b) introduces a proposed (ai$\mathbf{P^3}$) risk model that uses DL to classify CVD and stroke risk in RA patient more accurately. The following recommendations are: (i) requires a clinical evaluation and scientific validation for reliable detection and CVD risk stratification in RA, and (ii) requires hyperparameter optimization in CVD/Stroke risk stratification in RA. (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 in RA.

Strengths, weakness, and extensions

One of the major strengths of this pilot review was its ability to risk stratify patients with CVD/Stroke by integrating RBBM and GBBM. The biomarkers derived from radiological, biochemical, and morphological complexity supported the first hypothesis, establishing a clear connection between CVD/Stroke and RA.

To evaluate CVD/Stroke in RA, a DL approach was proposed and presented, integrating RBBM and GBBM biomarkers. While the system is relatively straightforward, there is room for optimization to eliminate potential biases and improve generalization, particularly when considering

co-morbidities. Exploring a more comprehensive feature space could be attempted to achieve superior DL-based classification. This involves considering a wider range of biomarkers and imaging features to enhance the predictive accuracy of the DL models [79]. Furthermore, ensemble-based solutions incorporating principal component analysis (PCA) for optimal feature selection, followed by RNNs, could be potential extensions to achieve superior CVD/stroke risk solutions in RA [78]. Ensemble methods combine multiple models to improve performance and can enhance the robustness and accuracy of the risk prediction models.

The most informative biomarkers can be identified by incorporating PCA for feature selection, reducing redundancy and noise in the data. RNNs, which are well-suited for sequential data analysis, could capture temporal dependencies and improve the prediction of CVD/stroke assessment in the RA environment over time. Stochastic models can be incorporated for image-based feature extraction to improve the robustness of the system [153]. These proposed extensions and optimizations can potentially enhance the precision and effectiveness of CVD/stroke risk assessment in RA. Refining the DL models and incorporating more comprehensive feature spaces can achieve more accurate and reliable risk assessment for CVD/Stroke in RA patients. Further research and validation are necessary to explore these avenues and assess their impact on improving the classification and prediction of CVD and stroke risk assessment in RA.

Conclusion

Diagnosing and treating CVD/Stroke in RA poses challenges due to delayed symptom onset and inadequate predictive clinical risk scores. To enhance CVD/Stroke risk assessment in RA, a proposed approach combines GBBM derived from plasma or serum samples with innovative non-invasive RBBM, including synovial fluid, plaque area, and plaque burden measurements. These biomarkers consider multiple pathways in atherosclerosis development, the primary cause of CVD/Stroke in RA.

This review presents two hypotheses: (i) RBBM and GBBM biomarkers exhibit a significant correlation and can accurately detect CVD/Stroke severity assessment in RA patients, and (ii) an AI-based preventive, precision, and personalized (ai$\mathbf{P}^3$) CVD/Stroke risk model utilizing DL can precisely classify CVD/Stroke risk in the RA framework. The study demonstrates how DL models can be integrated into the ai$\mathbf{P}^3$ framework to determine the risk assessment of CVD/Stroke in RA patients using RBBM and GBBM biomarkers. The findings of this review suggest that the combination of RBBM with GBBM introduces a new dimension to the assessment of CVD/Stroke risk in the RA framework. Higher levels of synovial fluid are associated with increased plaque burden. Furthermore, the review recommends novel, unbiased, and pruned DL algorithms that can accurately predict CVD/Stroke risk within a preventive, precise, and personalized RA framework.

In summary, integrating RBBM and GBBM biomarkers and advanced DL algorithms offers promising avenues for improving CVD/Stroke risk assessment and management in RA patients. Further research and validation of these approaches are needed to enhance the precision and effectiveness of preventive strategies in this high-risk population.

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Declarations

Conflict of interest All authors are full-time employees at their indicated affiliation institutions, which are public universities and hospitals. None of the authors received fees, bonuses or other benefits for the work described in the manuscript.

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