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REVIEW

# Cardiovascular risk assessment in patients with rheumatoid arthritis using carotid ultrasound B-mode imaging

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## Abstract

Rheumatoid arthritis (RA) is a systemic chronic inflammatory disease that affects synovial joints and has various extra-articular manifestations, including atherosclerotic cardiovascular disease (CVD). Patients with RA experience a higher risk of CVD, leading to increased morbidity and mortality. Inflammation is a common phenomenon in RA and CVD. The pathophysiological association between these diseases is still not clear, and, thus, the risk assessment and detection of CVD in such patients is of clinical importance. Recently, artificial intelligence (AI) has gained prominence in advancing healthcare and, therefore, may further help to investigate the RA-CVD association. There are three aims of this review: (1) to summarize the three pathophysiological pathways that link RA to CVD; (2) to identify several traditional and carotid ultrasound image-based CVD risk calculators useful for RA patients, and (3) to understand the role of artificial intelligence in CVD risk assessment in RA patients. Our search strategy involves extensively searches in PubMed and Web of Science databases using search terms associated with CVD risk assessment in RA patients. A total of 120 peer-reviewed articles were screened for this review. We conclude that (a) two of the three pathways directly affect the atherosclerotic process, leading to heart injury, (b) carotid ultrasound image-based calculators have shown superior performance compared with conventional calculators, and (c) AI-based technologies in CVD risk assessment in RA patients are aggressively being adapted for routine practice of RA patients.

**Keywords** Arthritis · Rheumatoid · Atherosclerosis · Cardiovascular disease · Inflammation · Carotid artery diseases · Carotid intima-media thickness · Risk assessment

## Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease that not affects only synovial joints but also has several extra-articular involvements, including those related to the skin, eyes, heart, lungs, kidneys, and other organs [1, 2]. It affects ~ 1% of the global population, with a higher prevalence in females when compared with males [3, 4]. Cardiovascular disease (CVD) is a common manifestation in RA patients with a two- to three-fold higher risk of cardiovascular events and mortality compared with a normal population [5]. However, this increased risk is not entirely explained by conventional risk factors [6]. Current statistically derived CVD risk calculators use conventional risk factors alone [7–9], are not suitable for RA patients, and they either underestimate or overestimate the risk [10–12]. This may be because of the paradoxical behavior of some of the conventional risk factors such as body mass index, low-density lipoprotein, high-density lipoprotein, and total cholesterol in RA [13, 14]. Despite this lack of clarity, the guidelines by the European League Against Rheumatism (EULAR) recommend aggressive control of these conventional risk factors [15, 16]. Recent attempts were made to improve the CVD risk assessment in the RA population, including the development of "RA-specific risk factors" in the CVD risk calculators [17–20]. However, such calculators could not provide adequate improvement in risk

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prediction and reportedly still underestimated or overestimated CVD risk in RA patients [21, 22].

To provide a better CVD risk assessment in RA, a pathophysiological association between these diseases should be understood, as this would help in refining CVD risk predictors in RA patients [23]. Atherosclerosis, a common phenomenon in RA [24, 25], can be adequately monitored using imaging modalities such as magnetic resonance imaging [26], computed tomography [27], optical coherence tomography [28], and ultrasound [29]. Each of these imaging modalities offers unique information about morphological variations in atherosclerotic plaque. Ultrasound imaging, specifically in carotid arteries, is a comparatively low-cost, non-invasive, radiation-free, and easy-to-use imaging modality that is widely adopted in preventive cardiovascular and clinical vascular practices [29, 30]. The image-based phenotypes of carotid ultrasound, such as carotid intima-media thickness (cIMT) and carotid plaque, are considered surrogate markers of coronary artery disease and have been used for preventive CVD risk assessments in several studies [31–34]. These image-based phenotypes indicate the morphological variations in the atherosclerotic plaque and are associated with the inflammatory markers of RA [35–38]. Patients with RA have elevated cIMT and have more plaque area (PA) when compared with non-RA patients [39–41]. Thus, the inclusion of these image-based phenotypes in risk prediction models may improve the CVD risk assessments of RA patients. Recent studies have combined the effect of these image-based phenotypes with conventional risk factors, including pro-inflammatory markers like erythrocyte sedimentation rate (ESR), to perform CVD risk assessment [42–44]. Such integrated risk calculators have demonstrated better CVD risk stratification when compared to traditional CVD risk calculators in non-RA patients [42, 43, 45].

Besides these statistically derived CVD risk calculators, artificial intelligence (AI)-based techniques are also penetrating several medical imaging and risk assessment applications [46–54]. AI-based algorithms such as machine learning (ML) methods provide a better CVD risk assessment when compared with statistically derived conventional risk calculators [51, 55, 56]. So far, AI algorithms have been used for CVD risk assessment in the non-RA population, and their potential still needs to be evaluated in RA cohorts. However, AI is well adapted for RA screening and diagnosis [57–60]. This review provides an insight into how the AI-based algorithms can be used for CVD risk assessment in RA patients. There are three aims of this review: (1) to summarize the pathophysiological pathways that link RA with CVD; (2) to identify several traditional and carotid ultrasound image-based CVD risk calculators for RA patients, and (3) to provide an understanding of the role of artificial intelligence in CVD risk assessment in RA patients.

## Search strategy

Figure 1 shows a flow diagram indicating the search strategy for this narrative review. To write a comprehensive narrative review, it is essential to select at least two credible databases that provide high-quality peer-reviewed articles [61]. This review is the outcome of several searches in the PubMed and Web of Science databases using keywords such as "cardiovascular diseases" AND "risk assessment" AND "rheumatoid arthritis," "carotid atherosclerosis" AND "rheumatoid arthritis," "non-invasive imaging" AND "rheumatoid arthritis," "carotid ultrasound" AND "rheumatoid arthritis," "carotid intima-media thickness" OR "carotid plaque" AND "inflammatory markers," "carotid atherosclerosis" AND "erythrocyte sedimentation rate" OR "C reactive protein," "machine learning" AND "rheumatoid arthritis," and "machine learning" AND "cardiovascular risk assessment" AND "rheumatoid arthritis." The availability of all these keywords in the abstract and the full text was investigated to select the relevant articles. Peer-reviewed articles published in the last 10 years were then given priority. Citations from the published articles were also shortlisted for this review. All these articles were subsequently filtered by the expert co-authors to select only those that met the objectives of this review, leading to 120 articles.

## Pathophysiology of RA leading to CVD

The pathophysiological association between RA and CVD can be explained in two stages: (1) the role of traditional risk factors, and (2) direct vascular damage. Inflammation plays a pivotal role in both of these stages [24].

### The role of traditional risk factors in the pathophysiology of RA-driven atherosclerotic CVD

The right-hand panel of Fig. 2 explains the pathophysiological association between RA and CVD via four pathways [I(a)–I(d)] governed by traditional risk factors such as hypertension, proatherogenic dyslipidemia, insulin resistance, and obesity. Patients with RA are generally found with pro-inflammatory cytokines such as interleukin (IL) 1, IL-6, and tumor necrosis factor α (TNF-α) [62]. These pro-inflammatory cytokines are found in the synovium, which triggers a systemic inflammatory response, and may result in damage to the vascular endothelial cells [62]. Nitric oxide (NO) and cyclooxygenase-1 are two essential components required

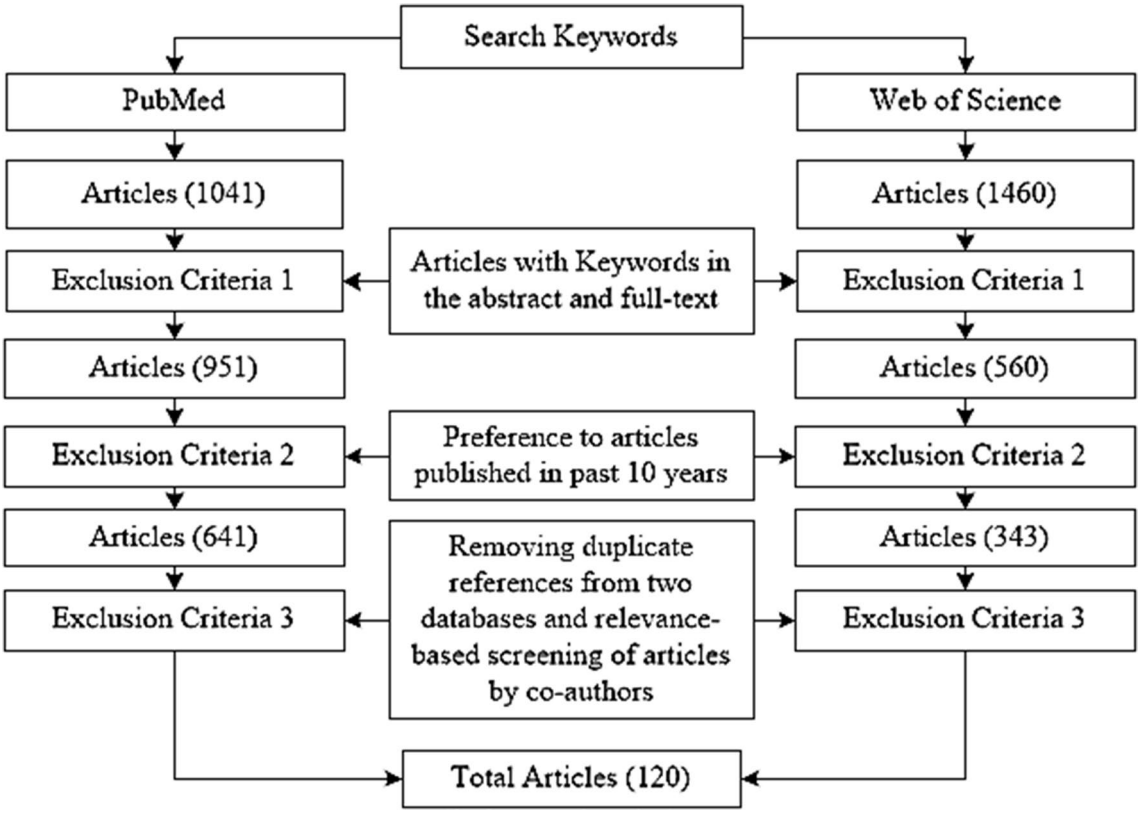


**Fig. 1** Flow diagram for the search strategy

to maintain the healthy endothelium, which is inhibited by TNF-α and IL-6, thereby resulting in endothelial cell damage [23, 62]. Inhibiting endothelial NO leads to arterial stiffness [63] and is further associated with an increase in peripheral vascular resistance (PVR) [64], thus leading to hypertension in RA patients. Additionally, several medications used to treat RA, such as disease-modifying antirheumatic drugs (DMARDs) leflunomide and cyclosporine, glucocorticoids, nonsteroidal anti-inflammatory drugs (NSAIDs), and cyclooxygenase II inhibitors (Cox IBs) may also be involved in the development of hypertension in RA patients [65, 66].

Another pathophysiological link between RA and CVD is proatherogenic dyslipidemia [67]. Nearly 55%–65% of RA patients have proatherogenic dyslipidemia [68]. In non-RA patients, increased CVD risk is associated with elevated levels of low-density cholesterol (LDL-c), total cholesterol, and reduced high-density lipoprotein cholesterol (HDL-c). However, in RA patients, low levels of total cholesterol (TC), low levels of LDL-c, and suppressed levels of HDL-c have been reported. This condition is known as "the lipid paradox" [14]. Highly suppressed HDL levels in RA patients are "proatherogenic" [14]. Furthermore, RA patients show high atherogenic index levels despite low lipid levels. The atherogenic index is calculated as a ratio of TC: HDL-c, and it may vary according to their levels [14]. Apolipoprotein B (Apo B) is a major apolipoprotein in LDL, and several studies have indicated an increase in the ratio of Apo B: Apo A in RA patients [14]. A combination of low TC, LDL-c, and suppressed HDL-c levels with a high atherogenic index and a high ApoB:ApoA ratio behaves as proatherogenic dyslipidemia [14, 69]. Long-standing proatherogenic dyslipidemia causes atherosclerosis and, eventually, CVD.

*Rheumatoid cachexia* is another important RA-specific characteristic that increases CVD risk [70]. It is characterized by significantly increased adiposity and reduced muscle mass while one maintains their bodyweight [71]. The pathophysiology [shown in "pathway-I (c)"] behind *R. cachexia* can be explained in two ways: (1) It is characterized by the reduction of muscle mass that is largely due to increased inflammatory cytokines (particularly TNF-α) by activating the transcriptional nuclear factor-kappa B cells (NF-kB) pathway and promoting the ubiquitin pathway, which causes catabolism/proteolysis (muscle protein breakdown) [72, 73]. (2) Central obesity or abdominal obesity is present in 20–57% of women and 80–90% of men. This causes visceral adiposity in RA, which has an additional adverse impact on CVD [74]. On the other hand, increased adiposity also induces the production of inflammatory cytokines in RA, which further worsens this

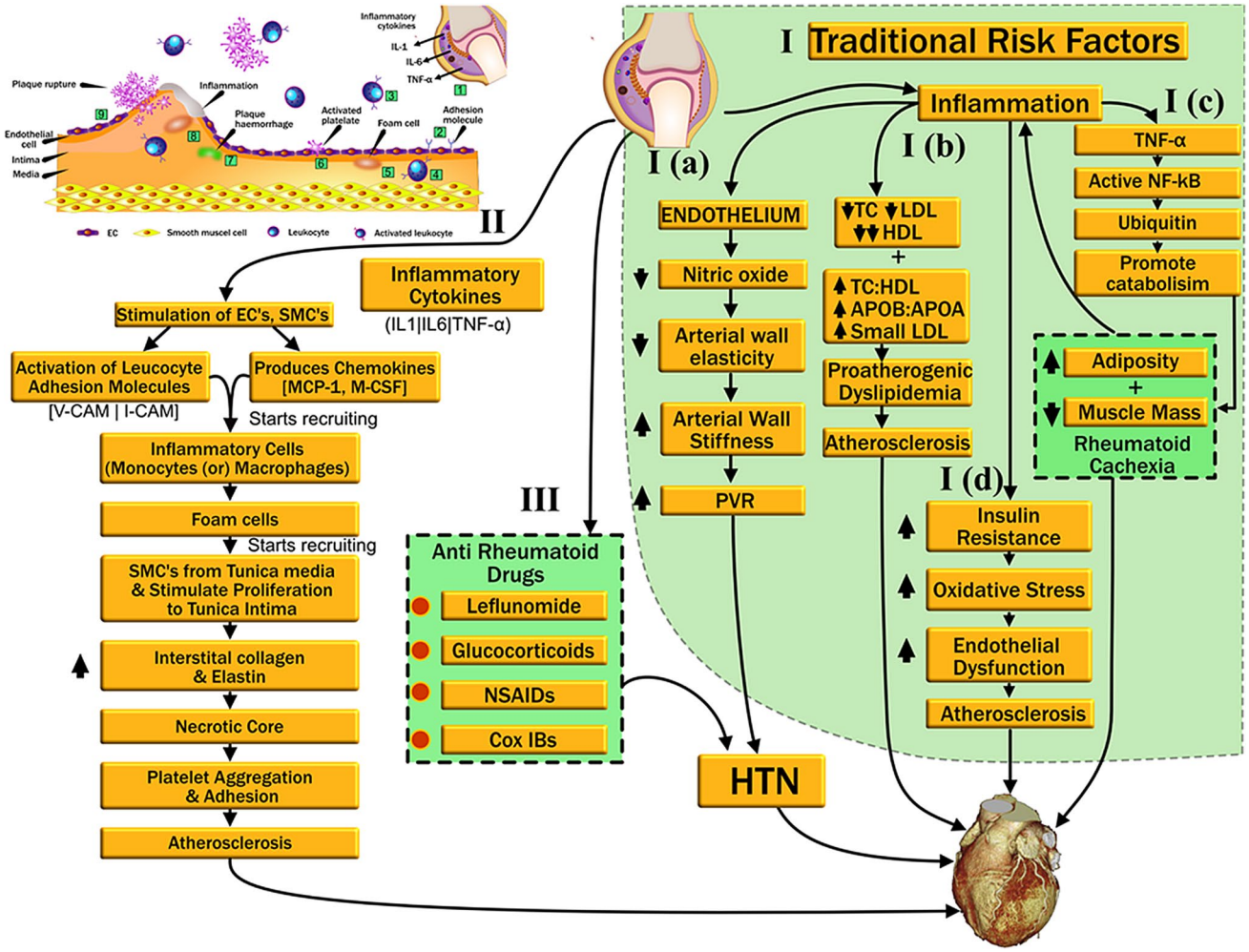


**Fig. 2** Pathophysiological association between rheumatoid arthritis and cardiovascular disease. *IL1* interleukin 1, *IL6* interleukin 6, *TNF-α* tumor necrosis factor α, *EC* endothelial cells, *SMC* smooth muscle cells, *MCP-1* monocyte chemoattractant protein 1, *M-CSF* macrophage colony-stimulating factor, *V-CAM* vascular cell adhesion molecule, *I-CAM* intercellular adhesion molecule, *NSAIDs* nonsteroidal anti-inflammatory drugs, *Cox-IBs* cyclo-oxygenase inhibitors, *HTN* hypertension, *PVR* peripheral vascular resistance, *TC* total cholesterol, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *APOB* apolipoprotein B, *APOA* apolipoprotein A, *NF-kB* nuclear factor-kappa B cells

scenario [75]. This syndrome may be explained in the triad of increased adiposity reduced muscle mass and low body mass index (BMI).

Epidemiological studies have suggested a strong association between insulin resistance (IR), metabolic syndrome, and RA [76, 77] [shown in "pathway-I (d)" in the dark green-dotted box]. Inflammation plays a crucial role in these three conditions [78]. In patients with RA, IR serves as an independent prognostic risk factor that signifies the presence of subclinical atherosclerosis; it is determined by carotid intimal thickness (cIMT) and is measured by carotid ultrasonography [79]. Longstanding inflammation due to RA promotes oxidative stress, endothelial dysfunction, and atherosclerosis in this population [24].

## Progression of atherosclerosis and direct vessel damage in RA

In RA, the activation of T-cells and mast cells increases the production of pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α. These pro-inflammatory cytokines stimulate endothelial cells (ECs) and smooth muscle cells (SMCs) in subendothelium [80] (1) by expressing cell adhesion molecules such as vascular cell adhesion molecule 1 (VCAM) and the "intercellular adhesion molecule" (ICAM) [80] and (2) by producing chemokines, including monocyte chemoattractant protein (MCP) and macrophage colony-stimulating factor (M-CSF). The activation of endothelial cells allows the migration of LDL-c into the sub-endothelial layer, where

it becomes oxidized and triggers the inflammatory response for the recruitment of immune cells such as T lymphocytes and monocytes in the intimal layer. Once they enter the intimal layer, monocytes are transformed into macrophages, and they then take up the oxidized LDL-c to become foam cells. The completion of this complex process then leads to the formation of atherosclerotic plaque. Macrophages also trigger the migration of smooth muscle cells from tunica media to tunica intima and initiate their proliferation. The SMCs form a thin fibrous cap to prevent the encroachment of atherosclerotic plaque towards the lumen. However, over time, pro-inflammatory cytokines, enzymes, and free radicals cause fibrous cap erosion and make the plaque vulnerable for rupture. The amplification of the inflammatory response results in the acceleration of plaque formation, eventually leading to plaque rupture and thrombotic events, which damage the blood vessels. Pathway II of Fig. 2 represents this process.

## Current conventional CVD risk prediction models for RA

Over the last decade, several CVD risk assessment calculators have been developed, very few of which are recommended by the cardiovascular risk management guidelines [9, 81, 82]. Some standard cardiovascular risk prediction algorithms are the Framingham risk score (FRS) [7], Systematic Coronary Risk Evaluation (SCORE) [8], American College of Cardiology/American Heart Association (ACC/AHA) risk score [9], World Health Organization (WHO) risk charts [83], and Reynolds's risk score (RRS) [17]. These risk calculators use traditional risk factors such as patient demographics (age, gender, ethnicity), blood biomarkers (low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and total cholesterol), behavioral markers (smoking and alcohol consumption), and physiological markers (height, weight, body mass index). All these risk calculators were initially developed for non-RA populations; therefore, when used in RA cohorts, CVD risk is substantially underestimated [10–12]. The use of traditional risk factors alone (while not considering RA-specific inflammatory markers) could be another reason for such underestimation. However, RRS included an RA-specific inflammatory marker called "high sensitivity C-reactive protein" (hs-CRP) [84] for CVD risk prediction but did not report any significant improvement in the CVD risk assessment [11]. Rajagopalan et al. [85] also reported a small improvement in area under the curve (+0.006 in females and +0.004 in males) when C reactive protein (CRP) or erythrocyte sedimentation rate (ESR) was added to the FRS.

Over the past few years, several efforts have been made to improve the cardiovascular risk assessment in RA patients. The EULAR guidelines recommended the use of a modified SCORE (mSCORE) in RA patients positive with rheumatoid factor (RF) or anticitrullinated protein antibodies (ACPA) and RA duration of more than 10 years [16, 86]. Cox et al. [19, 20] developed the QRISK2 and QRISK3 algorithms, which use the presence of RA as a CVD risk predictor (hazard ratio = 1.23, 95% confidence interval 1.19–1.28). Solomon et al. [18] also developed an RA-specific CVD risk calculator (called expanded risk score or ERS) by including RA-specific biomarkers [such as disease activity, disease duration, a modified health assessment questionnaire (HAQ) disability index, and daily prednisone use] with the traditional biomarkers used in the Cox-based model. The authors reported an improvement of ~ 4.8% in c-index when validating the risk score on the reserved dataset. Recently, Curtis et al. [87] also proposed a CVD risk prediction tool for RA patients by combining conventional and RA-specific risk factors. The authors predicted the risk of composite CVD events such as MI, stroke, and death during the follow-up period of 3 years. The area under the curve (AUC) for cardiovascular risk stratification for this model was 0.70.

All these RA-specific CVD risk scores reported a better risk assessment on the proprietary databases. Still, when compared with other risk calculators in different RA cohorts, these calculators have demonstrated mixed results [10–12]. Crowson et al. [11] reported an underestimation of CVD risk by FRS and RRS in 525 RA patients. The observed risk was twice the predicted risk. Furthermore, the authors did not report any improvement in cardiovascular risk prediction when CRP was added to their model. Arts et al. [10] investigated the roles of SCORE, FRS, RRS, and QRISK2 in 1050 RA patients. Out of these four models, SCORE, FRS, and RRS underestimated CVD risk in RA patients, whereas, the QRISK2 reported an overestimation. The AUC ranged between 0.78 and 0.80 for the four risk models. A similar study by Arts et al. [12] investigated the performance of the original, recalibrated, and improved version of SCORE calculators to predict the CVD risk in 1016 RA patients. The AUC values for these scores were 0.78 (95% CI 0.74–0.82), 0.78 (0.74–0.83), and 0.80 (0.75–0.84). All these three scores underestimated the CVD risk in RA patients. In short, even after the SCORE was redesigned using the RA-based risk factors, it did not result in an adequate CVD risk assessment. In another study by Crowson et al. [21] of 5638 RA patients, a CVD-risk prediction model was developed that reported better performance (AUC = 0.71) compared with conventional risk calculators such as FRS (AUC = 0.71), ACC/AHA (AUC = 0.72), SCORE (AUC = 0.70), and QRISK2 (AUC = 0.72). Furthermore, conventional risk calculators either overestimated or underestimated CVD risk in RA patients. Wahlin et al. [88] compared the expanded risk score, ACC/AHA risk score, and a modified version of ACC/AHA with a multiplier of 1.5 for a CVD risk assessment of

665 RA patients. The authors also reported an underestimation of CVD risk by all calculators. However, the discrimination ability was slightly better, since AUC for ERS-RA risk was 0.78 compared to AUC of 0.98 for two variants of ACC/AHA.

The overall trend of all these risk prediction algorithms, developed for general and RA cohorts, indicates a "poor CVD risk assessment" in patients with RA. One possible reason for such poor performance is the paradoxical behavior of some of the risk factors such as lipids and body mass index. Another potential reason for this outcome is the inclusion of risk factors that do not provide complete information about the CVD risk profile in RA patients [89]. Corrales et al. [89] indicated a high prevalence of carotid atherosclerosis plaque in patients with low-CVD risk. This observation demonstrated the limited ability of conventional risk factor-based algorithms to improve the CVD risk assessment process, which may be improved using imaging modalities. Therefore, there is still room to develop more accurate, automated, and reliable risk calculators for RA patients by exploring and including nontraditional risk factors such as genetic biomarkers, inflammatory biomarkers, or image-based atherosclerotic plaque phenotypes in the risk prediction algorithm.

## Carotid ultrasound atherosclerosis imaging for CVD risk assessment in RA patients

Imaging modalities are becoming essential for the visualization of atherosclerotic plaque and CVD risk assessment in RA patients [90]. Non-invasive imaging modalities such as computed tomography, magnetic resonance imaging, ultrasound, and positron emission tomography are currently used to assess carotid atherosclerosis in RA patients [26]. MRI is used to measure the plaque composition, including calcification, lipid-rich necrotic core, and fibrous cap thickness [26]. Computed tomography is generally used to determine carotid artery stenosis [27]. F-fludeoxyglucose–positron emission tomography (FDG-PET) is a nuclear imaging modality that quantifies the inflammation in carotid atherosclerotic plaque [91]. Non-invasive carotid ultrasound is a commonly adopted imaging modality that can capture morphological variations in the atherosclerotic plaque quantified using (1) carotid intima-media thickness (cIMT), (2) carotid intima-media thickness variability (IMTV), and (3) plaque area [30]. When compared with other non-invasive counterparts, carotid ultrasound is less expensive and easier to use [30, 92]. Therefore, the scope of this review is restricted to the use of carotid ultrasound for CVD risk assessment in RA patients. The automated cIMT and carotid PA are considered surrogate markers of coronary artery disease and widely used for CVD/stroke risk assessment [31–34].

Several studies have shown a high prevalence of increased cIMT and carotid plaque in RA patients [39–41]. Studies have also demonstrated the significant association between these carotid atherosclerosis biomarkers and RA-specific markers of inflammation, such as ESR, CRP, and IL-6 [35–38]. Table 1 provides some of such studies that link both carotid atherosclerosis and RA, using two sets of biomarkers (i.e., image-based phenotypes and inflammatory biomarkers). One common observation from these studies is that patients with RA show an elevated cIMT and carotid plaque area compared with non-RA cohorts (row R2–R4 of Table 1) [39, 40, 93]. This association between carotid atherosclerosis and RA also seems independent of the three carotid artery segments (common carotid artery, carotid bulb, and internal carotid artery) from where the cIMT or plaque was measured [40, 93]. However, several studies have reported more aggressive atherosclerotic plaque formation in the carotid bulb segment when compared to other arterial segments [94]. The higher plaque prevalence in the carotid bulb is a consequence of turbulent blood flow and reduced shear stress, which leads to endothelial dysfunction [95, 96]. This observation of higher plaque in a bulb has also been confirmed in RA patients [40]. Figure 3 shows carotid ultrasound scans for RA (Fig. 3a, b) and non-RA patients (Fig. 3c, d). The left-hand side panel of Fig. 3a, c shows the raw carotid ultrasound scans measured using a B-mode ultrasound scanner.

Similarly, the right-hand side panels of Fig. 3b, d show the processed scans tracking morphological variations in the carotid atherosclerotic plaque for the quantification of cIMT and plaque area. The cIMT and plaque area are both greater in RA patients than in non-RA patients.

Another important observation from Table 1 is the significant association between carotid atherosclerotic biomarkers and RA-specific inflammatory markers, such as ESR, CRP, and IL-6 [37, 97]. ESR is a relatively inexpensive measure of inflammation in RA patients—therefore, several studies have used ESR for CVD risk assessment [98–100]. Some of such studies are listed in Table 2. All these studies indicated a substantially higher CVD event rate in patients with elevated ESR levels. Besides ESR, studies have also suggested the use of other popular RA-specific inflammatory markers such as CRP, or hsCRP, and IL-6 for the improvement in the CVD risk assessment [37, 85, 101, 102]. Furthermore, these RA-specific inflammatory markers are also associated with the annual progression of cIMT [38, 97, 103–105], which is a prominent surrogate marker of cardiovascular events. In a study with 30 RA patients, Kaseem et al. [37] demonstrated the association of ESR, CRP, and IL-6 with carotid atherosclerosis, with significant odds ratios ($p < 0.05$) of 1.50, 1.90, and 1.80, respectively.

The broad usage of carotid ultrasound-based phenotypes and their significant association with RA-specific

**Table 1** Association of carotid atherosclerosis with rheumatoid arthritis and inflammatory markers

| SN | C1<br>First author (year) | C2<br>*N* | C3<br>Mean age (years) | C4<br>Image-based phenotype | C5<br>Non-image risk factors | C6<br>Results | C7<br>Summary |
|---|---|---|---|---|---|---|---|
| R1 | Rincon (2003) [35] | 204 | 59.6 (For RA) and 59.7 (For Controls) | cIMT and presence CP | ESR and CRP | cIMT associated with ESR ($r=0.16$, $p=0.004$ for) and CRP ($r=0.13$, $p=0.02$) | cIMT and presence of CP are associated with ESR and CRP. cIMT increases by 0.005 mm for every one-unit increase in ESR |
| R2 | Carotti (2007) [39] | 80 (40 with RA and 40 controls) | 59.95 ± 11.93 | cIMT and CP from CCA | TC, LDL-c, TG, BMI, RF, VAS, CRP | RA vs. Non-RA: cIMT = 0.83 ± 0.23 vs. 0.86 ± 0.22 mm and CP prevalence = 25% vs. 12.5% | Carotid atherosclerosis image-based phenotypes are significantly higher in RA patients than in the non-RA population |
| R3 | Kobayashi (2010) [40] | 393 (195 with RA and 198 controls) | 59.4 (RA) and 59.8 (controls) | cIMT and CP from CCA and ICA-bulb | HTN, BMI, DM, Smoking, FH, | RA vs. Non-RA: IMT in ICA-bulb = 1.16 vs. 1.02 mm and OR for CP = 2.41, 95% CI 1.26-4.61 | RA was associated with high severity of atherosclerosis in carotid ICA-bulb than with CCA |
| R4 | Ristić (2010) [93] | 74 (42 with RA and 32 controls) | 45.3 ± 10 (RA) and 45.2 ± 9.8 (controls) | cIMT from CCA, bifurcation, and ICA | Age, BMI, Smoking, RF, ESR, duration of RA therapy | RA vs. Non-RA: $cIMT_{CCA=}$ 0.671 vs. 0.621, $cIMT_{BIF=}$ 0.889 vs. 0.804, $cIMT_{ICA=}$ 0.577 vs. 0.535 | Carotid IMT in RA patients was higher in three artery segments (CCA, BIF, ICA) when compared to controls. Also, cIMT is negatively correlated with RA inflammation treatment |
| R5 | Kaseem (2011) [37] | 30 | 43.59 ± 7.2 | cIMT and cIMTmax | CRP, ESR, IL-6 | OR for carotid atherosclerosis: CRP = 1.90, ESR = 1.50, and IL-6 = 1.80, with $p<0.05$ | Inflammatory markers are significantly associated with carotid atherosclerosis |
| R6 | Rincon (2015) [38] | 487 | 58.2 | cIMT | ESR | OR for cIMT progression using ESR = 1.12 per 10 mm/h | ESR and ESR × CVD risk factor terms were significantly associated with cIMT progression |
| R7 | Corrales (2015) [89] | 144 | 52.1 ± 5.7 with CP and 42.4 ± 9.5 without CP | CP | Age, TC, disease-modifying agents such as DMARDs | AUC for carotid plaque prediction in RA: using age = 0.807 ($p<0.0001$) and using TC = 0.679 ($p=0.001$) | Prevalence of plaque = 37.5% wit age > 49.5 years and TC > 5.4 mmol/l. The carotid plaque in RA patients can be we well predicted using age and TC |

**Table 1** (continued)

| SN | C1 | C2 | C3 | C4 | C5 | C6 | C7 |
|---|---|---|---|---|---|---|---|
| | First author (year) | *N* | Mean age (years) | Image-based phenotype | Non-image risk factors | Results | Summary |
| R8 | Pope (2016) [36] | 31 | 63.2 ± 8.9 with plaque<br>57.1 ± 9.8 without plaque | cIMT | ESR, hsCRP | OR for carotid plaque burden using ESR = 1.148, $p = 0.028$ | Inflammatory markers such as ESR and hsCRP are used to predict the carotid plaque burden |
| R9 | Svanteson (2017) [113] | 55 | 62.2 ± 8.6 | cIMT and CP height | Age, BMI, SBP, DBP, HTN, DM, Smoking, Hyperlipidemia | OR for CAD:<br>For cIMT ≥ 0.7 mm = 4.08<br>For CP height ≥ 1.5 mm = 8.96 | Beyond the presence of CP, CP height, and cIMT are also important for predicting CAD in RA patients |

*SN* serial number, *N* number of patients, *RA* rheumatoid arthritis, *CVD* cardiovascular disease, *CAD* coronary artery disease, *cIMT* carotid intima-media thickness, *cIMTmax* maximum carotid intima-media thickness, *CP* carotid plaque, *CCA* common carotid artery, *ICA* internal carotid artery, *BIF* bifurcation, *ESR* erythrocyte sedimentation rate, *CRP* C reactive protein, *hsCRP* high sensitivity C reactive protein, *IL-6* interleukin 6, *RF* rheumatoid factor, *DMARDs* disease-modifying antirheumatic drugs, *TC* total cholesterol, *LDL-c* low-density lipoprotein cholesterol, *HDL-c* high-density lipoprotein cholesterol, *TG* triglyceride, *BMI* body mass index, *HTN* hypertension, *DM* diabetes mellitus, *FH* family history, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *OR* odds ratio, *AUC* area-under-the-curve

inflammatory markers has also enabled their inclusion in the CVD risk prediction calculators [42, 43, 54, 106]. Recently, several CVD/stroke risk prediction models have been developed that have combined the effect of conventional risk factors and the automated carotid atherosclerosis biomarkers [42, 43]. These risk prediction models reported a better performance in identifying high CVD risk patients compared with current standard-of-care risk calculators. However, such so-called integrated risk prediction models were developed for the general population. They were based on the annual progression rates of carotid atherosclerotic biomarkers and conventional risk factors [42–44]. Therefore, given the progression rates of cIMT and PA due to the RA-specific inflammatory markers, such models can be updated and might be useful for CVD risk assessment in RA patients.

## Artificial intelligence in CVD/stroke risk assessment

Artificial intelligence (AI) is expeditiously changing the landscape of the global healthcare system and assisting the healthcare workforce in clinical decision-making [107]. Machine learning (ML) and deep learning (DL) are the two common branches of AI that have broad ranges of applications in almost every medical imaging sector (e.g., classification and plaque characterization for stroke risk assessment [47], thyroid cancer characterization [48], liver cancer diagnosis [49], prostate cancer diagnosis, ovarian cancer diagnosis [53], lung cancer detection [108], brain tumor classification [50], and heart disease prediction and disease classification [51, 52, 54]). During the recent global pandemic of coronavirus diseases 2019, AI is providing promising results in the diagnosis of patients with the help of several imaging techniques such as computed tomography [109] and X-rays [110].

Since this review is on CVD/stroke risk assessment, we have summarized several studies that have used ML-based algorithms for CVD/stroke risk assessment (Table 3). All of these studies follow a supervised learning approach in which the ML-based classifier is trained to identify the correct output labels using input risk factors or features and predefined gold standards or labels. Figure 4 shows the generalized framework of supervised ML-based CVD risk assessment. In the case of CVD risk assessment, the gold standard can be (1) the primary endpoints such as presence or absence of cardiovascular events, or (2) surrogate endpoints such as cIMT, PA, and CAC score, or a combination of these risk factors [51, 52, 54]. Several types of input features can be used to train the AI-based algorithms. They can be traditional risk factors, image-based phenotypes, grayscale image features, or statistically derived features. Once the offline ML classifier is trained using these features and gold

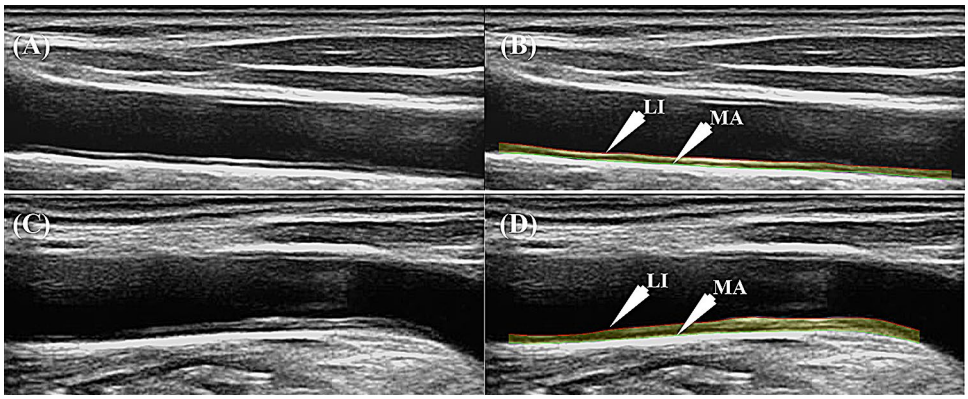


**Fig. 3** Carotid ultrasound image of the common carotid artery for control patients

standard, its coefficients are then used in the online ML system to predict the out risk labels. Online ML systems do not require a gold standard to make the final risk classification. All the studies provided in Table 3 used this approach for CVD risk assessment. Unlike ML-based algorithms, DL-based models, such as convolutional neural networks, do not require input features beforehand. Instead, such algorithms automatically learn their offline coefficients from the input image datasets [111].

Currently, AI-based techniques are used in the diagnosis of RA [57], the identification of RA disease severity [58], the classification of several RA synovial tissues [59], and mortality prediction due to RA [60]. Although ML-based algorithms are used in the RA field, no efforts have been made to assess the CVD risk in RA patients using such automated intelligence-based paradigms. ML-based algorithms have been used to perform CVD risk assessments in non-RA populations and reported a better performance in identifying high-risk CVD patients when compared with the current standard of care conventional risk calculators [51, 55, 56]. Patients with RA experience more atherosclerotic plaque in the carotid artery, which might lead to cardiovascular events [39–41]. In recent years several studies have demonstrated a better stroke risk assessment using ML-based strategies [29] and DL-based strategies [112]. Besides all these studies, attempts can be made to develop more accurate CVD risk prediction tools for RA patients using AI techniques. Figure 5 conceptualizes several components required for CVD risk assessment in RA patients. The AI-based CVD risk assessment for RA patients can be made possible by combining several types of risk factors, such as patients' demographics, physiological parameters, behavioral risk factors, image-based phenotypes, and (most importantly) RA-specific inflammatory markers. This combined set of features can be used as inputs along with the gold standard to identify what CVD risk category RA patients belong to. As such, both ML and DL-based systems can be employed to performed CVD risk assessment in patients. Because of the significant association between carotid atherosclerosis and RA, researchers can conduct a pilot study with cIMT and plaque areas as the surrogate markers for CVD risk assessment.

## Summary

In this review, we provided several pathophysiological pathways that highlight the role of cardiovascular and inflammatory risk factors in the progression of atherosclerosis and heart injury in RA patients. Furthermore, we also indicated an unmet need to look for new biomarkers to achieve a more accurate cardiovascular risk assessment in RA patients. Specifically, carotid ultrasound is a non-invasive and economical technique for preventive screening applications. The carotid atherosclerotic image-based biomarkers such as cIMT and plaque have a significant association with RA-specific inflammatory markers. Most of the current statistically derived cardiovascular risk calculators, developed for both RA and non-RA cohorts, either underestimate or overestimate the CVD risk in RA patients. Even after the inclusion of RA-specific inflammatory markers such as CRP, risk calculators reported little improvement in risk prediction. The accuracy of risk assessment can be improved using AI techniques. AI techniques are currently used for RA screening and not for CVD risk assessment in RA patients. However, they reported promising results of CVD risk assessment in non-RA cohorts. Thus, we believe that the development of AI-driven risk prediction models by combining traditional, image-based, and inflammatory risk factors is warranted to improve the CVD risk assessment in RA patients.

**Table 2** Studies indicating the role of ESR in the risk of CVD and cardiovascular events

| SN | First author (year) | *N* | FU (years) | Age | ESR (mm/h) | Events | Results | Summary |
|---|---|---|---|---|---|---|---|---|
| 1 | Andresdottir (2003) [99] | 16,673 | 20 | 51.9 ± 8.8 (men)<br>53.4 ± 9.6 (women) | Median ESR: 3 (men)<br>8 (women) | 2893 CHD and 429 deaths due to cerebrovascular events | Hazard ratio for CHD = 1.57 (men) and 1.49 (women) due to ESR | ESR is a long-term predictor of CHD in men and women |
| 2 | Natali (2003) [100] | 1995 | ~7.67 | 55 ± 10 | 8 (men) and 14 (women) | 170 | CC with atherosclerosis: 0.11, $p < 0.0001$ and OR = 1.72, $p = 0.0008$ | ESR is associated with coronary atherosclerosis and is an independent predictor of cardiac deaths |
| 3 | Danesh (2004) [114] | 6428 | 12 | 70.2 ± 9.7 | 7.4 ± 10.6 (patients)<br>6.3 ± 9.7 (controls) | 2459 CHD and MI deaths | OR for CHD due to ESR = 1.30 | CRP is moderate, and ESR is a poor predictor of CHD |
| 4 | Timmer (2005) [115] | 346 | 7.4 | 58.8 ± 108 (ESR < 15 mm/h)<br>62.3 ± 9.3 (ESR ≥ 15 mm/h) | Median ESR = 8 | 87 | The odds ratio for sudden death due to ESR = 3.3, $p < 0.01$ | Elevated ESR with hyperglycemia are the predictors of mortality due to STEMI |
| 5 | Rajagopalan (2014) [85] | 5300 | 2 | 59.7 ± 14.2 | 36.6 ± 24.6 | 328 | Hazard ratio due to high ESR or CRP = 2.05 | There was a small improvement in CVD prediction when ESR or CRP was added to the Framingham model |

*SN* serial number, *N* number of patients, *FU* follow-up, *CVD* cardiovascular disease, *CHD* coronary artery disease, *MI* myocardial infarction, *ESR* erythrocyte sedimentation rate, *CRP* C reactive protein

**Table 3** Machine learning-based CVD/stroke risk stratification in non-RA cohorts

| C1 | C2 | C3 | C4 | C5 | C6 | C7 | C8 | C9 | C10 |
|---|---|---|---|---|---|---|---|---|---|
| SN | First Author (Year) | *N* | Features types | TF | Feature Selection | Classifier type | Gold standard | PE | Benchmarking |
| R1 | Gastounioti (2015) [116] | 56 | Kinematics features | 1236 | FDR, WRS, PCA | SVM | Follow-up data labels | ACC (88%) | Against kNN, PNN, DT, DA |
| R2 | Unnikrishnan (2016) [117] | 2406 | CCVRFs | 9 | NA | SVM | Follow-up data labels | Se (68.2%), Sp (85.9%), AUC (0.71) | Against FRS |
| R3 | Venkatesh (2017) [118] | 6814 | CCVRFs, image phenotypes, and serum biomarkers | 735 | MDMST | RF, Cox, LASSO-cox, AIC-Cox backward regression | Follow-up data labels | C-Index (0.81), BS (0.083) | Against FRS and PCRS |
| R4 | Banchhor (2017) [119] | 22 | Texture-based and wall-based features | 65 | PCA | SVM | Carotid plaque burden | ACC (91.28%) AUC (0.91) | – |
| R5 | Araki (2017) [47] | 204 | Image-based texture features | 16 | Statistical Test | SVM | LD-based risk labels | ACC (NW: 95.08% & FW: 93.47%) | – |
| R6 | Weng (2017) [56] | 378,256 | CCVRFs | 30 | – | RF, LR, GBM, ANN | Follow-up data labels | AUC: 0.764 | Against PCRS |
| R7 | Kakadiaris (2018) [55] | 6459 | CCVRFs | 9 | – | SVM | Follow-up data labels | Se (86%), Sp (95%), AUC (0.92) | Against PCRS |
| R8 | Jamthikar (2019) [54] | 202 | CCVRFs and CUS Image-based features | 47 | PCA polling | RF | Carotid stenosis surrogate endpoint of CVD | AUC of ML system = 0.80 (95% CI 0.77–0.84) AUC for CCVRC = 0.68 (95% CI 0.64–0.72) | – |
| R9 | Jamthikar (2020) [51] | 202 | CCVRFs and CUS image-based features | 19 | – | SVM | Surrogate endpoint of CVD | AUC of ML system = 0.88 ($p < 0.001$) | Against 13 CCVRC |
| R10 | Jamthikar (2020) [120] | 202 | CCVRFs and CUS image-based features | 38 | Logistic regression | RF | LD as surrogate endpoint of CVD | AUC for integrated ML system = 0.99, $p < 0.001$ | – |

*SN* serial num, *N* Number of patients, *CVD* cardiovascular disease, *CUS* carotid ultrasound, *LD* lumen diameter, *LR* logistic regression, *FDR* fisher discriminant ratio, *WRS* Wilcoxon Rank-Sum, *PCA* principal component analysis, *DA* discriminant analysis, *MDMST* minimal depth of maximal subtree, *SVM* support vector machine, *GMM* Gaussian Mixture Model, *RBPNN* Radial Basis Probabilistic Neural Network, *DT* decision tree, *kNN* K-nearest neighbor, *NB* Naïve Bays, *FC* Fuzzy Classifier, *QNN* Quantum Neural Network, *MLP* Multilayer Perceptron, *RF* Random Forest, *SOM* Self Organization Map, *ANN* artificial neural network, *DWT* Discrete Wavelet Transform, *HoS* higher-order spectra, *CCVRFs* conventional cardiovascular risk factors, *ACC* accuracy, *Se* sensitivity, *Sp* specificity, *AUC* area under the curve, *BS* Brier Score, *IGR* information gain ranking, *DB* database, *CCVRC* conventional cardiovascular risk calculators, *PCRS* pooled cohort risk score, *FRS* Framingham risk score

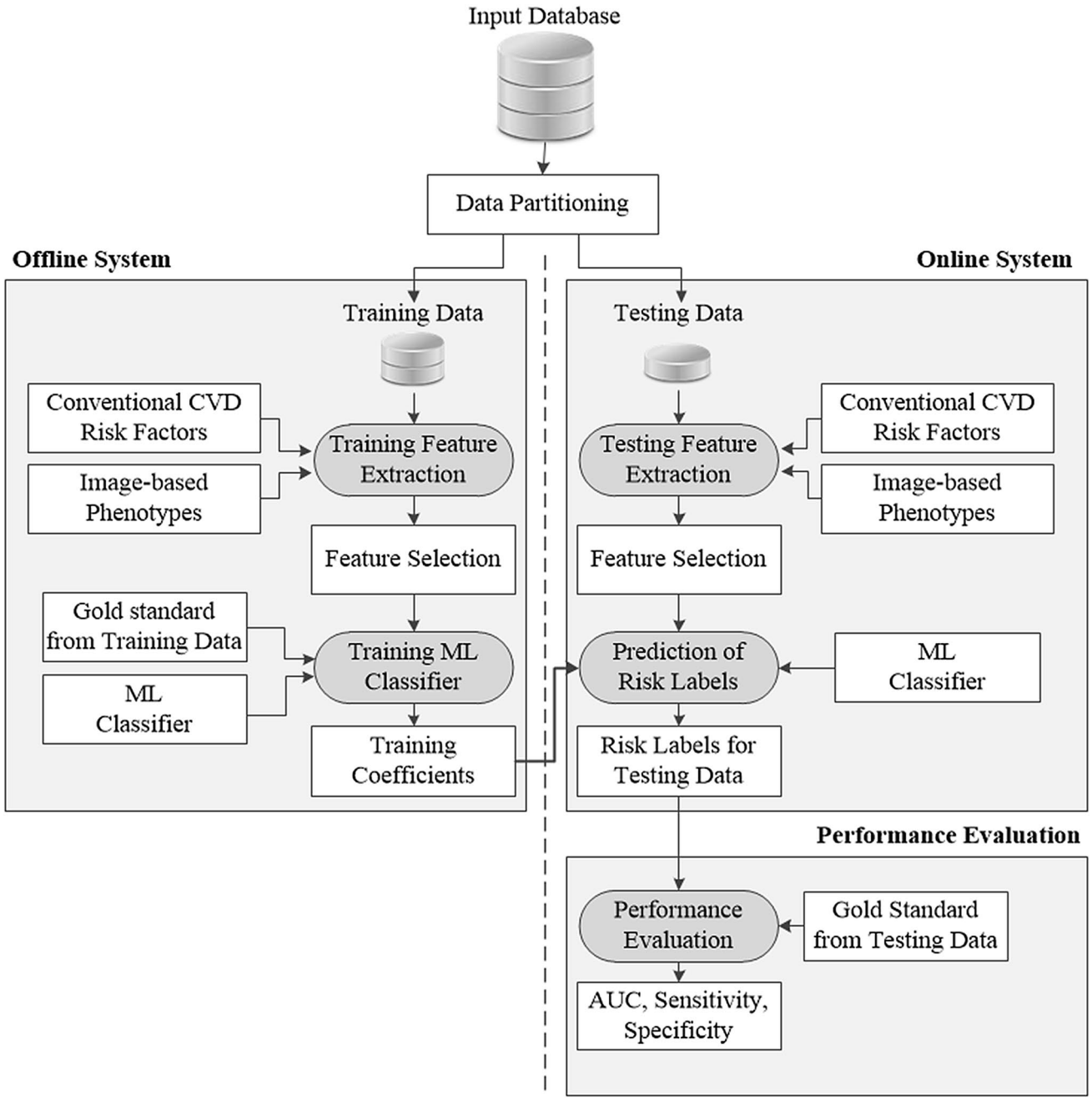


**Fig. 4** The generalized framework of supervised ML-based CVD risk assessment system. *CVD* cardiovascular disease, *ML* machine learning, *AUC* area under the curve

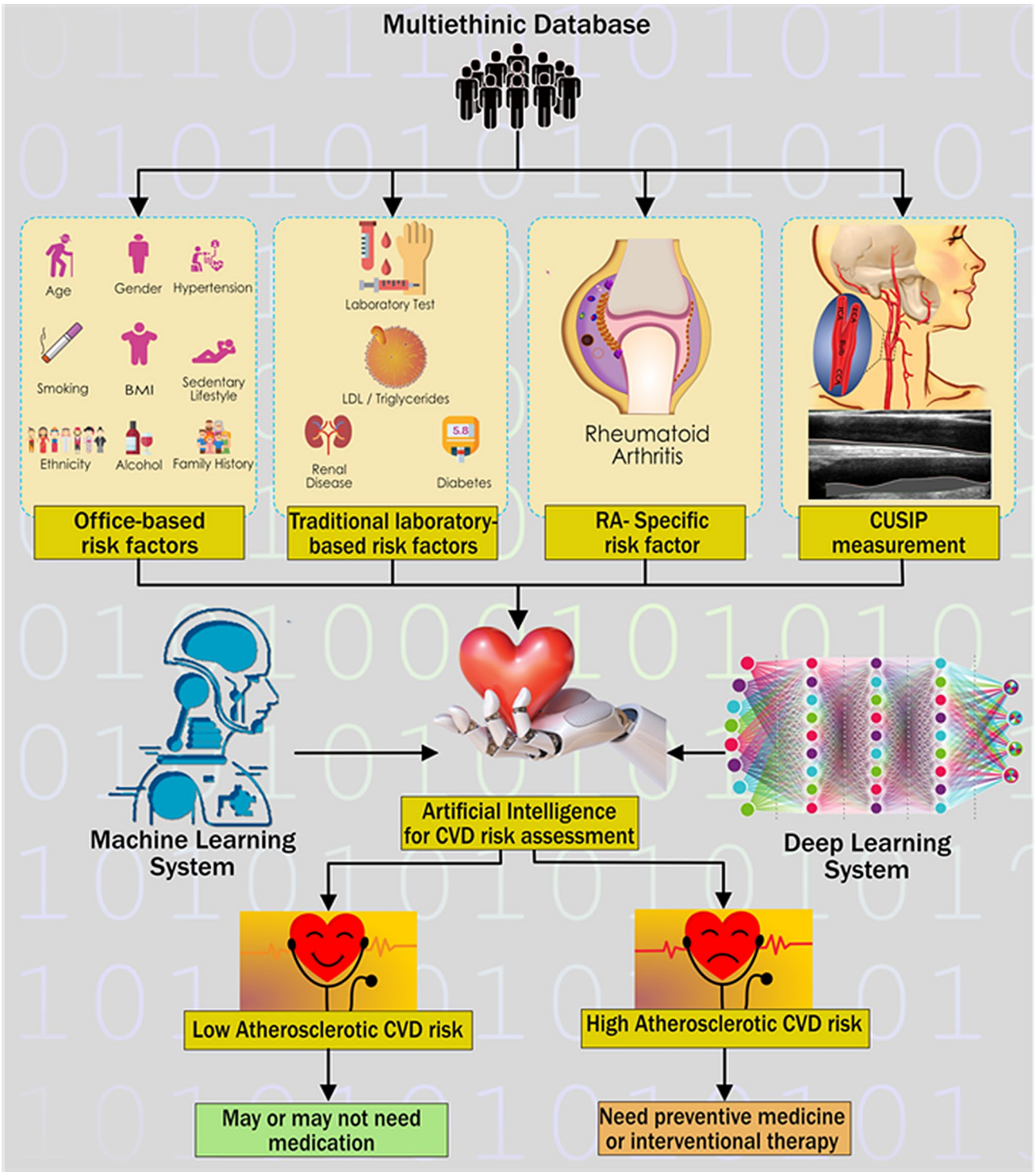


**Fig. 5** AI framework for CVD risk assessment in RA patients. *BMI* mody mass index, *LDL* low density lipoprotein, *CVD* cardiovascular disease, *RA* rheumatoid arthritis, *CUSIP* carotid ultrasound image-based phenotypes

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and guidance of cardiology components of the manuscript. NNK: The vision of cardiac risk assessment and proofreading the manuscript, final approval of the manuscript. LS: Design and support of radiology components such as CT and carotid ultrasound. SM: Proofreading and guidance of cardiology imaging components of the manuscript. JRL, GP, MM, AS, VR: Proofreading and guidance of cardiology and vascular components. GDK: Design and solid proofreading of the manuscript, especially the rheumatology component, revising it critically for important intellectual content, and final approval of the manuscript. RK: Vascular tissue characterization and proofreading of the manuscript. JSS: Principal Investigator-design, proofreading of the manuscript and management.

## Compliance with ethical standards

**Conflict of interest** The author(s) declare that they have no competing interests.

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