frontiers | Research Topics

Cardiovascular comorbidities in inflammatory rheumatic diseases

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Published in
Frontiers in Medicine
Frontiers in Immunology

ISSN 1664-8714
ISBN 978-2-8325-7212-2
DOI 10.3389/978-2-8325-7212-2

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Cardiovascular comorbidities in inflammatory rheumatic diseases

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Citation

Triantafyllias, K., Colina, M., Misra, D. P., eds. (2025). *Cardiovascular comorbidities in inflammatory rheumatic diseases*. Lausanne: Frontiers Media SA.

doi: 10.3389/978-2-8325-7212-2

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frontiers | Frontiers in Medicine

TYPE Editorial
PUBLISHED 17 November 2025
DOI 10.3389/fmed.2025.1724208

OPEN ACCESS

EDITED AND REVIEWED BY
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RECEIVED 13 October 2025
ACCEPTED 27 October 2025
PUBLISHED 17 November 2025

CITATION
Triantafyllias K, Colina M and Misra DP (2025) Editorial: Cardiovascular comorbidities in inflammatory rheumatic diseases.
Front. Med. 12:1724208.
doi: 10.3389/fmed.2025.1724208

Editorial: Cardiovascular comorbidities in inflammatory rheumatic diseases

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KEYWORDS

cardiovascular disease, cerebrovascular disease, rheumatoid arthritis, psoriatic arthritis, giant cell arteritis, gout, Sjögren's disease (SD)

Editorial on the Research Topic
Cardiovascular comorbidities in inflammatory rheumatic diseases

The survival in patients with autoimmune rheumatic diseases (ARDs) has markedly improved with the advent of better therapies, including biologic and targeted synthetic disease-modifying antirheumatic drugs (DMARDs), over the past two decades. In this context, the identification and management of comorbidities is increasingly recognized as a critical intervention toward improving the overall quality of life and prolonging survival further in these diseases. Cardiovascular (CV) comorbidity is a major cause of morbidity and mortality overall, and specifically in the context of ARDs (1, 2). The inflammatory origins of atherosclerosis are now prime targets for interventions with therapies such as canakinumab and ziltevikimab, having shown beneficial effects for CV risk (CVR) reduction in clinical trials (3, 4). CVR is uniformly increased in the ARDs, whether it be systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjögren's disease, systemic sclerosis, or systemic vasculitis (5–8). The risk factors driving CV comorbidity can be classified as disease-related (e.g., antiphospholipid antibodies), treatment-related (e.g., tofacitinib or glucocorticoids), or traditional risk factors such as smoking or diabetes mellitus whose prevalence is also higher in patients with rheumatic diseases (5). Imaging to detect subclinical atherosclerosis (ultrasound, coronary artery calcium detected using computed tomography, fluorodeoxyglucose positron emission tomography) or subclinical cardiac pathology [cardiac magnetic resonance imaging (MRI)] is also increasingly being used to diagnose early and stratify CV disease in rheumatic diseases (5).

In this article collection, original research and review articles provide novel insights into CV risk, disease mechanisms, and biomarkers across a spectrum of inflammatory rheumatic diseases. A Norwegian registry study of 1,821 RA patients diagnosed from 1972 to 2013 found an overall decline in stroke rates over time (Alsing et al.). However, men diagnosed after 2007 continued to have an excess stroke risk, whereas women did not, highlighting sex-specific differences in this context. In 120 RA patients undergoing coronary angiography, a nomogram combining LDL-C, Th17 cells, IL-17, and traditional CVR factors accurately predicted obstructive coronary artery disease (AUC = 0.974 in training and 0.896 in validation cohorts) (Wang et al.). Elevated CRP, Th17, and IL-17

levels in affected patients may further support the strong link between immune dysregulation and increased CVR in RA. In two studies examining CV biomarkers in RA, both inflammatory and renal indicators were shown to have important prognostic value (Liu et al.; Bin et al.). The first, involving 1,314 RA patients, found that elevated CBC-derived markers (systemic inflammatory response index, neutrophil-to-lymphocyte ratio, and monocyte-to-lymphocyte ratio) were independently associated with higher all-cause mortality (Liu et al.). The second, including 1,363 RA patients, identified the urine albumin-to-creatinine ratio as an independent predictor of all-cause and CV mortality, outperforming estimated glomerular filtration rate (Bin et al.). In a multi-ethnic cohort of 276 RA patients, the Haptoglobin (Hp) 2-2 genotype was independently associated with an increased risk of CV disease. According to the authors, the Hp 2-2 genotype could thus serve as a potential biomarker for improved CVR prediction in RA (Xu et al.).

The included review works in this Research Topic cover a broad spectrum of topics, ranging from CV imaging biomarkers to the interactions between immunosuppressive therapies and CVR. For instance, Sturm et al. analyzed the diagnostic value of ocular vascular markers (e.g., retinal vessel analysis, Optical Coherence Tomography Angiography, retrobulbar color Doppler) in patients with ARDs (Sturm et al.). Key findings included retinal arterial narrowing, venular widening, reduced capillary density, and ophthalmic vessel abnormalities, which were partially linked to systemic inflammation and traditional CVR factors. Moreover, Vitale et al. explored the role of cardiac MRI in systemic sclerosis, providing a comprehensive evaluation of its capabilities. The study highlighted MRI's ability to detect key cardiac abnormalities, including myocardial inflammation, fibrosis, microvascular dysfunction, and right ventricular strain, while also discussing its potential value as a prognostic CV tool (Vitale et al.). Heart failure with preserved ejection fraction (HFpEF) is common, and patients with ARDs face a higher risk due to inflammation, oxidative stress, endothelial dysfunction, and metabolic disturbances (9). The work of Xu et al. highlights the H2FPEF score for early risk assessment and supports interventions, such as SGLT2 inhibitors, to target disease-specific pathways and prevent HFpEF progression (Xu et al.,"Autoimmune inflammation as a key risk factor for heart failure with preserved ejection fraction (HFpEF). The different types of inflammation driving to HFpEF"; in press). In a further review focusing on the IL-6 receptor–targeting monoclonal antibody tocilizumab, the drug demonstrated sustained efficacy and a favorable safety profile in RA, with no increased CVR compared to other RA therapies. These findings reinforce tocilizumab as a key treatment option, particularly for patients with an inadequate response to methotrexate or TNF-inhibitors (Parisi et al.). The link of psoriasis to a significantly increased risk of CV disease, driven by systemic inflammation and a high prevalence of cardiometabolic comorbidities, is well-established (10). As highlighted by Barbarroja et al., apremilast provides a dual-action approach by targeting both inflammation and metabolic dysfunction, offering potential to reduce CVR and improve overall health in these patients (Barbarroja et al.). In a large retrospective study of 2,249 patients with giant cell arteritis and 3,906 patients with polymyalgia rheumatica, use of the antidepressants venlafaxine and sertraline was associated with a higher risk of CV events compared to nonusers (Zhang et al.). These findings, confirmed by both multivariate logistic regression and Cox regression analyses, suggest that the use of selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors may increase CVR in this patient population. A retrospective study of 292 gout patients found that tophi, higher power Doppler signals, and frequent flares independently predicted carotid plaque vulnerability (Fang et al.). A random forest model combining these gout-specific factors with traditional CVR showed excellent predictive accuracy (C-index = 0.997), highlighting the role of crystal-driven inflammation in vascular injury and the value of integrated risk assessment. Interestingly, in a retrospective study of 49 Sjögren's-disease patients and 27 matched controls, no differences in endothelial function, measured by reactive hyperaemia index using peripheral arterial tonometry (EndoPAT®), were observed between the groups. The only factor associated with impaired endothelial function was higher body mass index. The authors concluded that EndoPAT may not be sensitive for detecting Sjögren's-specific vascular changes, highlighting the need for alternative markers in this specific patient group (Tapken et al.).

To summarize, this article collection highlights the increased risk of CV disease and potential biomarkers in psoriatic arthritis, RA, Sjögren's disease, systemic sclerosis and Giant Cell Arteritis. Articles also delineate the role of cardiac MRI and ultrasound for detecting subclinical CV pathology in inflammatory rheumatic diseases. The role of therapies such as apremilast on modulating CVR has also been explored. The editors hope this article collection serves as a nidus to promote further translational research on CVR in rheumatic diseases.

Author contributions

KT: Methodology, Data curation, Project administration, Conceptualization, Investigation, Writing – original draft, Formal analysis, Writing – review & editing. MC: Writing – review & editing. DM: Formal analysis, Data curation, Project administration, Methodology, Writing – review & editing, Investigation, Conceptualization, Writing – original draft.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

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frontiers | Frontiers in Immunology

TYPE Review
PUBLISHED 07 August 2024
DOI 10.3389/fimmu.2024.1459185

OPEN ACCESS

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RECEIVED 03 July 2024
ACCEPTED 25 July 2024
PUBLISHED 07 August 2024

CITATION
Barbarroja N, López-Medina C, Escudero-Contreras A and Arias-de la Rosa I (2024) Clinical and molecular insights into cardiovascular disease in psoriatic patients and the potential protective role of apremilast.
Front. Immunol. 15:1459185.
doi: 10.3389/fimmu.2024.1459185

Clinical and molecular insights into cardiovascular disease in psoriatic patients and the potential protective role of apremilast

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Psoriatic disease, encompassing both psoriasis (Pso) and psoriatic arthritis (PsA), is closely intertwined with a significantly elevated risk of developing cardiovascular diseases. This connection is further compounded by a higher prevalence of cardiometabolic comorbidities, including type 2 diabetes, obesity, insulin resistance, arterial hypertension, and dysregulated lipid profiles. These comorbidities exceed the rates seen in the general population and compound the potential for increased mortality among those living with this condition. Recognizing the heightened cardiometabolic risk inherent in psoriatic disease necessitates a fundamental shift in the treatment paradigm. It is no longer sufficient to focus solely on mitigating inflammation. Instead, there is an urgent need to address and effectively manage the metabolic parameters that have a substantial impact on cardiovascular health. Within this context, apremilast emerges as a pivotal treatment option for psoriatic disease. What sets apremilast apart is its dual-action potential, addressing not only inflammation but also the critical metabolic parameters. This comprehensive treatment approach opens up new opportunities to improve the well-being of people living with psoriatic disease. This review delves into the multifaceted aspects involved in the development of cardiovascular disease and its intricate association with psoriatic disease. We then provide an in-depth exploration of the pleiotropic effects of apremilast, highlighting its potential to simultaneously mitigate metabolic complications and inflammation in individuals affected by these conditions.

KEYWORDS

apremilast, cardiometabolic comorbidities, cardiovascular disease, psoriatic arthritis, psoriasis, psoriatic disease

1 Introduction

Psoriasis (Pso), is a persistent inflammatory skin condition, exhibiting autoimmune pathogenic features and a heightened susceptibility to immune-mediated genetic factors. The prevalence of the disorder aligns with its degree of severity. While commonly known as psoriasis vulgaris, it is also denoted as plaque-type psoriasis, characterized by patchy manifestations on the extremities. The chronic plaque form prevails in around 90% of patients, manifesting clinical features such as well-defined, erythematous patches that are partially pruritic and covered in silvery scaling (1). Around 30% of patients with Pso will develop arthritis at any time over their lives. Individuals with Psoriatic Arthritis (PsA), categorized under the umbrella of Spondyloarthritis, often experience impaired function and reduced quality of life. Typically, psoriasis precedes arthritis by about 10 years, although in 20% of cases, both occur simultaneously or PsA develops first (2). Diagnosis relies on clinical and imaging features across five domains: psoriasis, peripheral joint disease, axial disease, enthesitis, and dactylitis. Rheumatoid factor tests are usually negative in 95% of PsA patients, while about 25% are HLA-B27-positive. Notably, PsA is characterized by bone and cartilage destruction and pathological new bone formation (3).

PsA and Pso have been extensively linked to various coexisting conditions, including obesity, type 2 diabetes, arterial hypertension, metabolic syndrome, fatty liver, and an increased risk of cardiovascular (CV) events (3–5). Multiple studies have evidenced the heightened prevalence of cardiovascular disease (CVD) risk factors in PsA when compared to Pso, indicating a potential contribution of inflammatory joint disease to cardiovascular morbidity (6). However, additional studies are imperative to establish definitively the extent of association between PsA, Pso, and CVD (7). On the other hand, we observed that patients with PsA have a higher prevalence of CVD comorbidities compared to those with other types of inflammatory arthritis. These comorbidities include an elevated ApoB/ApoA ratio, increased atherogenic risks, obesity, insulin resistance (IR), hyperlipidemia, arterial hypertension, and type 2 diabetes mellitus (8). Furthermore, there is a research gap concerning the impact of various treatments on CVD in Psoriatic Disease. Nevertheless, studies have provided support for the potential positive effect of Apremilast on CVD associated with PsA (9). This review aims to describe the relationship between CVD comorbidities and Psoriatic Disease and to evaluate the impact of Apremilast, a phosphodiesterase-4 inhibitor, from both clinical and molecular perspectives. To accomplish this, a rigorous selection process was implemented, which involved searching for original research articles and review publications written in English. The databases PubMed, Web of Science, and Scopus were utilized, using keywords such as “CVD”, “Cardiovascular Disease,” “Psoriatic Arthritis”, “Psoriasis”, “Psoriatic Disease”, “Apremilast”, or “anti-PDE4”.

2 Enhancers of cardiometabolic risk factors

2.1 Obesity

Obesity is conventionally characterized as the presence of excessive body fat that negatively impacts health. In clinical settings, it is typically evaluated using the body mass index (BMI= kg/m2) (10). Despite significant progress in combating CVD, obesity remains a modifiable risk factor that has not been adequately addressed. Lifestyle changes and pharmacotherapy have not effectively tackled obesity, unlike other risk factors such as hypertension, dyslipidemia, T2DM, and smoking. Beyond GLP-1 inhibitors for obesity management, pharmacotherapy has not successfully addressed this condition. Research suggests that the increased CVD risk associated with a high BMI or elevated waist circumference is largely mediated by changes in intermediate risk factors such as atherogenic dyslipidemia, hypertension, and T2DM (11). Numerous studies have examined the connection between obesity and adverse CV events (12). Physicians have effective medications targeting lipids, blood pressure, and glycemic control, backed by strong evidence from large trials. However, upstream causes like high-risk adiposity may not be prioritized as treatment targets. Addressing excessive adiposity, a major contributor to elevated lipids, blood pressure, and glucose levels, could substantially reduce CVD risk (13).

Moreover, Virtue and Vidal-Puig introduced a hypothesis positing that each individual might have an inherent limit to the expandability of their adipose tissue. As one gains weight, there reaches a point where their adipose tissue can no longer accommodate additional lipids. Beyond this threshold, there is an increased flux of lipids to non-adipose organs, initiating the deposition of ectopic lipids. The build-up of lipids in cells such as myocytes, hepatocytes, and beta cells subsequently trigger adverse effects, including IR and apoptosis, which can have detrimental effects on overall health (14). Considering these insights, it becomes evident that one can be obese without being IR. In alignment with this notion, our group demonstrated that individuals with obesity who do not exhibit IR do not manifest the inflammation levels on their adipose tissue typically associated with obese patients who do have IR. This suggests that the critical link between adipose tissue expansion and the accompanying metabolic complications may be the degree of inflammation in the adipose tissue (15). Taking into account this hypothesis, targeting “dysfunctional” adipose tissue might be the right way to reduce the collateral downside effects such as IR, diabetes, hypertension or dyslipidaemia.

2.2 Diabetes mellitus and hyperglycemia

Diabetes mellitus is a chronic condition characterized by persistently high blood glucose levels and is classified into two

main subtypes: type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). T1DM is considered an autoimmune disease, wherein the body's immune system attacks and destroys beta cells in the pancreas, leading to insulin deficiency. In contrast, the role of autoimmunity in the development of T2DM is not as well-defined and remains less clear (16). Moreover, atherosclerosis is a prevalent characteristic among individuals with diabetes mellitus and is responsible for severe macrovascular complications, including coronary artery disease (CAD), stroke, and peripheral vascular disease (17). Prior research has consistently associated patients with T1DM with elevated rates of coronary calcification and increased mortality ratios related to CAD (18, 19). On the other hand, T2DM continues to be associated with CVD as the primary cause of death globally. While there has been a decline in mortality due to aggressive treatments, the growing number of diabetic patients, especially among younger and elderly populations, raises significant concerns (20).

In T1DM, hyperglycemia typically develops rapidly without preceding IR. Over time, prolonged hyperglycemia in T1DM leads to an increase in IR (21). In contrast, T2DM manifests with IR for years before noticeable hyperglycemia, resulting in a gradual rise in blood sugar levels. The presence of IR in both T1DM and T2DM complicates isolating the effects of hyperglycemia alone on CVD and its risk factors (22). However, sustained hyperglycemia, regardless of diabetes type, is known to contribute to various complications, including cardiovascular issues.

2.3 Insulin resistance

IR occurs when insulin loses its normal effects in vital metabolic tissues such as adipose tissue, skeletal muscle, or liver. A significant meta-analysis involving 516,325 patients revealed that the homeostatic model assessment (HOMA) was a superior predictor of CVD events in adults without T2DM compared to fasting glucose or insulin (23). However, fasting insulin, a classic marker of IR, has also shown associations with CVD events in individuals without T2DM, independent of other risk factors (24). Notably, IR plays a critical role in promoting atherosclerosis, particularly at the arterial wall level. It affects macrophages and endothelial cells, contributing to both the initiation of atherosclerosis (atherogenesis) and the progression of clinically significant advanced plaques (25). Understanding the impact of IR on atherosclerosis can provide valuable insights for better managing cardiovascular health and preventing related complications.

2.4 Arterial hypertension

Hypertension, often referred to as systemic arterial hypertension, is a medical condition characterized by a persistent elevation in blood pressure (BP) within the systemic arteries. BP is typically expressed as a ratio of systolic BP (the pressure exerted on arterial walls during heart contractions) to diastolic BP (the pressure during heart relaxation) (26). This complex condition is influenced by various facets of the cardiovascular system, including blood volume, cardiac output (the volume of blood pumped by the heart per minute), and the complex balance of arterial tone, which is impacted by both intravascular volume and neurohormonal systems. The regulation of healthy BP levels involves a sophisticated interplay among components within an integrated neurohumoral system. This system encompasses the renin-angiotensin-aldosterone system, the roles played by natriuretic peptides and the endothelium, the sympathetic nervous system, and the immune system. Any malfunction or disruption of these factors, within any of these systems, can directly or indirectly lead to increases in mean BP, BP variability, or both, over time. Consequently, this can result in damage to target organs, such as left ventricular hypertrophy and chronic kidney disease, and contribute to adverse outcomes in CVD (27).

2.5 Dysregulated lipid profile and fatty liver disease

Dyslipidemias can be classified into two main categories: genetically determined types, referred to as primary or familial dyslipidemias, and those arising as secondary consequences of underlying conditions like diabetes mellitus, obesity, or an unhealthy lifestyle—this secondary group being more prevalent. Among these conditions, heightened plasma LDL-cholesterol levels emerge as significant risk factors for CVD. Dyslipidemias entail deviations from the normal plasma lipid profile, often linked to various clinical conditions. The most common form is hypercholesterolemia, characterized by elevated cholesterol levels, closely associated with an increased CVD risk. Furthermore, atherogenic dyslipidemia, characterized by elevated triglyceride levels, diminished HDL-cholesterol levels, and the presence of low-density lipoproteins (LDL) particles, is notably prevalent among patients with diabetes or metabolic syndrome. This particular dyslipidemia profile significantly heightens their CVD risk.

However, dyslipidemias manifest in diverse forms, including hypertriglyceridemia, associated with severe conditions such as non-alcoholic fatty liver disease (NAFLD) (28). Moreover, the interplay between CVD and hepatic damage extends beyond adipose tissue dysfunction. It encompasses various mechanisms, including the dysregulation of lipid metabolism, where the liver plays a pivotal role. Dyslipidemias associated with CVD and hepatic damage often involve altered hepatic lipid synthesis, uptake, and secretion. Additionally, NAFLD, a prevalent hepatic condition in the context of metabolic syndrome, further complicates this relationship. NAFLD not only contributes to dyslipidemia but also serves as a source of systemic inflammation, which can exacerbate CVD risk (29). This interplay is not limited to CVD and hepatic damage alone; it extends to a network of mediators that bridge the two systems. Inflammation and oxidative stress, for instance, act as crucial mediators in both cardiovascular diseases and liver disorders. These factors can initiate and perpetuate a cycle of damage, promoting systemic inflammation and vascular dysfunction. Additionally, the influence of hemodynamic changes, neurohormonal activation, and immune system responses further

underscores the bidirectional relationship between these two vital organ systems. Understanding and managing these multifaceted interactions is crucial for effectively addressing the complex comorbidities that arise in the context of CVD and hepatic disease (30).

2.6 Endothelial dysfunction and atherosclerosis

The endothelium plays a crucial role in regulating vascular tone through the synthesis and release of various endothelium-derived relaxing factors, including vasodilator prostaglandins, nitric oxide (NO), and endothelium-dependent hyperpolarization (EDH) factors, as well as endothelium-derived contracting factors (31, 32). Endothelial dysfunction typically results from reduced production or impaired action of endothelium-derived relaxing factors and can represent an initial stage in the development of cardiovascular disease (31).

Specifically, endothelial dysfunction stands as a firmly established response to CV risk factors, taking precedence in the intricate path toward atherosclerosis. Its involvement in lesion formation encompasses a spectrum of mechanisms, ranging from the early to late stages of atherosclerosis. This involvement manifests through the up-regulation of adhesion molecules, heightened secretion of chemokines, increased adherence of leukocytes, augmented cell permeability, amplified oxidation of low-density lipoprotein, activation of platelets, production of cytokines, and the proliferation and migration of vascular smooth muscle cells. This interplay underscores the pivotal role of endothelial dysfunction in shaping the atherosclerotic landscape, illuminating the various molecular and cellular processes that contribute to atherosclerosis (33). This has led to a significant focus on evaluating endothelial function in clinical settings due to its role as an excellent surrogate marker for predicting CV events in humans. For example, impaired flow-mediated dilation of the brachial artery or a reduced digital reactive hyperemia index, as evaluated using peripheral arterial tonometry, has been linked to future CV events in individuals with coronary artery disease (34–36). These results indicate the potential value of assessing endothelial function in peripheral vascular beds as a valuable tool for predicting future CV events.

2.7 Inflammation

For nearly a century, cholesterol has held the position of being the primary instigator in the development of atherosclerosis. This conviction dates back to the early 1900s when researchers first identified cholesterol within arterial lesions in their experiments with animal models. This discovery has since become an indisputable testament to the role of genetic and environmental factors in contributing to atherosclerotic disease (37). In the late 1800s, inflammatory cells were first observed in atherosclerotic lesions, but only recently have we understood their crucial role in disease progression (38). This newfound understanding firmly establishes inflammation as central to both the onset and advancement of plaque formation. Endothelial injury, abnormal lipid metabolism, and hemodynamic stress are pivotal factors in early atherosclerosis. Flow-mediated inflammatory changes within endothelial cells are recognized in this process (39). Advanced atherosclerosis sees a significant influx of macrophages and inflammatory cytokines, leading to plaque destabilization and events like rupture and thrombosis (40, 41). The combined effects of proinflammatory signals within the plaque not only intensify inflammation but also impede tissue regeneration, crucial for maintaining mechanical stability (42). Proinflammatory mediators released by both immune cells and vascular endothelial cells sustain local inflammation, contributing to lesion progression (43). The revelation of the contributions made by both the innate and adaptive immune systems to atherogenesis has advanced our understanding of lesion development. This insight has also paved the way for novel therapeutic avenues aimed at alleviating the burden of vascular disease (44). However, it is crucial to acknowledge that chronic inflammatory disorders often coexist with additional metabolic comorbidities (45). In light of these complexities, a comprehensive therapeutic strategy must be devised to holistically address the cardiovascular risk in patients grappling with both chronic inflammatory disorders and associated metabolic complications.

3 CVD risk in psoriatic disease

The incidence of CVD is markedly elevated in individuals with inflammatory arthritis. CVD represents the primary cause of mortality in patients with psoriatic disease. Additionally, individuals with psoriatic disease exhibit a higher prevalence of traditional cardiovascular risk factors compared to the general population, exacerbating their overall cardiovascular risk (46). Patients with Pso or PsA face a higher likelihood of being overweight or obese in comparison to the general population and even when compared to individuals with other inflammatory conditions (8, 47, 48).

Studies show a strong link between these factors and NAFLD development, highlighting the pathophysiological connection between Psoriatic disease and CV comorbidities, including NAFLD. Psoriatic disease patients have a higher NAFLD prevalence than the general population (29). Additionally, the relationship between weight and Pso becomes more intriguing when abdominal obesity is considered. Multiple studies have uncovered a substantial connection between increased abdominal obesity and the presence of Pso, hinting at a possible link between weight gain and the development of this skin disorder (49). In a comprehensive 14-year study, researchers closely tracked BMI, weight changes, and central obesity indicators. Their findings revealed a persistent, strengthening link between BMI and susceptibility to PsA (50).

Moreover, PsA patients exhibit endothelial dysfunction, even without clinical evident CVD or traditional CVD risk factors (51). Furthermore, irrespective of traditional CVD risk factors, patients with PsA show a high prevalence of macrovascular disease. This is

evidenced by increased carotid intima-media thickness, when compared to healthy individuals. This suggests that PsA inherently predisposes patients to cardiovascular issues beyond the influence of typical risk factors (52).

Numerous studies consistently reveal a higher prevalence of T2DM among patients with psoriatic disease compared to the general population (8, 53). In addition, individuals with PsA often present with elevated fasting glucose levels, contrasting with those suffering from RA (48). Remarkably, the severity of PsA, denoted by joint erosions, osteolysis, and sacroiliitis, has been associated with the presence of IR (54). Moreover, Pso itself is linked to an increased prevalence and incidence of T2DM, with a particularly strong correlation in severe Pso cases (55). In parallel, Psoriatic patients frequently exhibit an altered lipid profile characterized by reduced levels of high-density lipoproteins (HDL), elevated triglyceride levels (48, 53), and heightened levels of proteins associated with LDL, such as apolipoprotein B (Apo-B), when compared to healthy individuals (56). Notably, levels of Apo-B and Apo-A are positively and negatively correlated, respectively (56). In addition, some studies have proposed that PsA patients exhibit more pronounced lipid abnormalities compared to those with Pso alone (57). However, a recent investigation revealed no significant disparities between PsA and Pso patients in terms of cardiovascular risk factors. This includes metrics such as dyslipidemia (37% vs. 32%), hypertension (36% vs. 31%), T2DM (13% vs. 14%), and hyperuricemia (32% vs. 37%) (7). Interestingly, the study conducted by Husted et al. reported hypertension as the most prevalent comorbidity in PsA (37.1%), surpassing the incidence in patients with Psoriasis alone (20%). This evidence underscores the relationship between Psoriatic disease and an elevated risk of metabolic syndrome (MetS) (58). The components of MetS, such as central obesity, hypertension, IR, and dyslipidemia, are notably prevalent in PsA patients, ranging from 24% to 58% (59). MetS consistently emerges as a significant concern in various studies of PsA patients and is intricately linked to disease severity (53, 54), more than in cases of Psoriasis alone (60). Furthermore, the prevalence of MetS is notably higher in PsA than in Pso alone (61), even exceeding the prevalence in RA (47). A comprehensive review and meta-analysis found that the pooled prevalence of MetS was substantially higher in PsA compared to Pso (62).

Furthermore, systemic inflammation, as measured by C-reactive protein (CRP), has been correlated with lower levels of HDL and higher levels of triglycerides in the context of PsA (56, 63). In addition, persistent inflammation based on CRP over the previous 5 years has shown a significant association with the development of IR in PsA (56). This observation underscores the link between chronic inflammation and metabolic dysfunction in PsA, with broader implications for CVD. In PsA, inflammation arises from both skin/joint and adiposity patterns, highlighting its multifaceted nature. Adiposity also significantly influences CVD risk by contributing to a metabolic phenotype linked to increased cardiovascular complications (64).

The complex relationship between chronic inflammation, metabolic factors, and cardiovascular health in psoriatic disease highlights its complexity and emphasizes the necessity of a holistic approach for understanding and managing these conditions. Comprehensive care strategies should address both inflammation and metabolic health to optimize patient outcomes (Figure 1A).

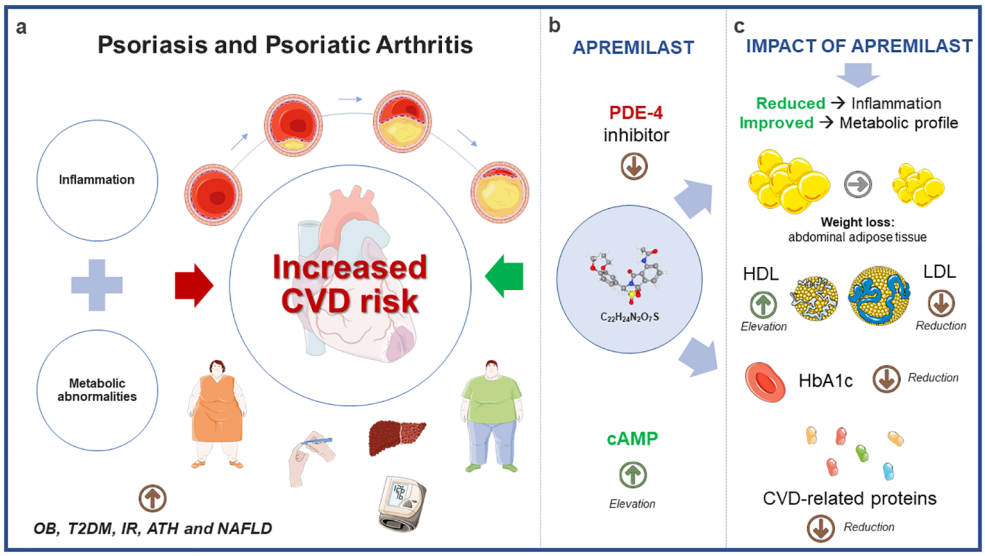

FIGURE 1
Potential impact of apremilast on cardiometabolic comorbidities associated with psoriatic disease. **(A)** The convergence of clinical characteristics in Psoriatic Disease, encompassing inflammatory patterns and metabolic irregularities, amplifies the susceptibility to cardiovascular disease. **(B)** Apremilast, by inhibiting PDE-4 and consequently elevating cAMP levels, exerts influence not only on the inflammatory profile but also on metabolic parameters. **(C)** Findings from interventional and observational studies underscore the significant effects of apremilast within the metabolic context, including weight reduction, modulation of lipid profiles, lowered HbA1c levels, and notable changes in CVD-associated proteins. Annotated names: CVD, cardiovascular disease; OB, Obesity; T2DM, Type 2 Diabetes Mellitus; IR, Insulin Resistance; ATH, Arterial Hypertension; NAFLD, Non-Alcoholic Fatty Liver Disease; PDE-4, Phosphodiesterase-4; cAMP, Cyclic Adenosine 3′, 5′-monophostate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HbA1c, Glycated hemoglobin.

4 Cyclic adenosine monophosphate and phosphodiesterase 4

One limitation of current biologic agents is their inability to directly target intracellular signaling pathways. These agents primarily act on extracellular receptors and proteins, influencing cell activity and immune signaling at the extracellular level, such as TNF inhibitors (65). However, the inability to directly target intracellular signaling pathways poses a challenge in fully intervening in complex cellular processes underlying Pso and PsA. In this sense, intracellular signaling in various cell types, including myeloid, lymphoid, and inflammatory cells, is governed by crucial "second messengers" like cAMP. The levels of intracellular cAMP are determined by the interplay between adenylylcyclases, primarily activated by G-protein coupled receptors, and phosphodiesterases (PDEs). These PDEs, expressed in a tissue-specific manner, are classified into 11 distinct families (66, 67). Interestingly, the reduction of intracellular cAMP facilitates the activity of PDE-4, resulting in an increase in inflammatory mediators and a decrease in anti-inflammatory molecules. On the contrary, inhibiting PDE-4 leads to elevated intracellular cAMP levels, which, in turn, blocks pro-inflammatory cytokines. This dynamic interplay between intracellular cAMP and PDE-4 activity plays a crucial role in modulating the inflammatory response (68).

As our comprehension of the intricate links between PDE-4 dysregulation and metabolic disorders advances, it underscores the potential importance of targeting PDE-4 as a therapeutic approach to alleviate the metabolic dysregulation and associated complications seen in T2DM and IR. The significance of PDE-4 extends to metabolic health, impacting adipocyte function, glucose regulation, hypertension, stroke, and non-alcoholic steatohepatitis. Its broad influence across metabolic domains underscores its potential as a therapeutic target for addressing metabolic disorders (69).

5 Effect of apremilast on the CVD profile in psoriatic disease

In this context, apremilast (C22H24N2O7S) emerges as a novel orally available small molecule that specifically targets PDE-4. Through its precise inhibition of this enzyme, apremilast effectively raises intracellular cAMP levels (Figure 1B). This action results in a partial suppression of several proinflammatory mediators while simultaneously promoting the production of certain anti-inflammatory mediators. Notably, these effects are more pronounced within the realm of innate immunity when compared to adaptive immunity. In addition, Apremilast boasts a low risk of serious infections and a favorable safety profile in clinical studies, offering an alternative to long-term systemic therapies, which often face issues like adverse events, safety concerns, diminishing efficacy, and injection-based administration (70).

In 2014, during the 16th week of the PALACE 1 trial, mean weight changes of -1.29 ± 3.4 kg at 20 mg and -0.97 ± 2.8 kg at 30 mg of apremilast were observed in PsA patients compared to a change of 0.19 ± 2.6 kg in the placebo group (71). Subsequently, the ESTEEM1 trial in 2015 reported a weight loss of 1.4 ± 2.08 kg in psoriasis patients, with 19% experiencing a weight loss greater than 5% (72). Around the same time, the ESTEEM2 trial noted that 20% of patients with moderate to severe plaque psoriasis exhibited a weight loss of over 5% (73). The subsequent PALACE2 trial revealed more than 5% weight loss in 17% of PsA patients on 20 mg and 14.8% on 30 mg of apremilast (74). The PALACE3 trial showed PsA patients experiencing a mean weight change of -0.05 kg (placebo), -1.2 kg (20 mg), and -1.2 kg (30 mg) (75). In 2017, a phase 2b trial in Japan revealed weight loss in 11.6% of psoriasis patients on 20 mg and 14.2% on 30 mg of apremilast (76). In 2018, the ACTIVE trial uncovered a mean weight loss of 1.20 kg at the 52-week mark in biological-naïve PsA patients, with 15.7% experiencing more than 5% weight loss (77). Additionally, the PALACE4 trial observed a higher mean BMI in PsA patients with high disease activity at week 52 (78). Recent findings from a nonrandomized clinical trial suggest that apremilast is associated with favorable impacts on cardiometabolic biomarkers and reductions in visceral and subcutaneous fat (79). These trials collectively underscore apremilast's potential for weight reduction and broader implications for mitigating cardiovascular complications.

In 2020, Mazzilli et al. made a notable observation, showing that diabetic patients with Pso and PsA achieved superior outcomes in terms of the extent and severity of Pso when compared to their non-diabetic counterparts. The treatment not only lowered cholesterol levels in both diabetic and non-diabetic Pso/PsA patients but also led to reductions in glucose levels (80). Next, Feldmand and co-investigators compared Pso patients with and without metabolic conditions newly initiating a biological or apremilast treatment. Interestingly, nearly half of the patients discontinued their index medication over 24 months, and patients with metabolic conditions had higher discontinuation rates than those without in all treatment cohorts except apremilast (81). In addition, in our previous research, we thoroughly examined the effects of apremilast and methotrexate treatments on a cohort of PsA patients with diverse cardiometabolic profiles. Remarkably, our results unveiled that only apremilast, or the combination of apremilast and methotrexate, led to a significant reduction in disease activity among PsA patients with more prominent metabolic complications, in contrast to methotrexate monotherapy. This reduction in disease activity was not only concurrent with a decrease in body mass index but also with an improvement in IR state (56). Parallely, Ferguson et al. reported weight loss primarily in subcutaneous fat and an improvement in psoriatic disease activity, further supporting the potential benefits of apremilast in addressing PsA and related metabolic issues (82).

In a substantial cohort of patients with Pso and PsA, Orroth et al. categorized individuals into two groups based on their diabetes status: a non-diabetic group and a pre-diabetic or T2DM group. Remarkably, they observed that after six months of apremilast treatment, both weight and HbA1c levels demonstrated significant reductions, irrespective of diabetes status. Furthermore, HDL levels exhibited significant increases in patients without diabetes (83). Conversely, within this cohort of 8250 Pso/PsA patients, 26.9% were classified as obese, and 33.5% as severely

obese. Interestingly, following six months of apremilast treatment, a significant reduction in weight was observed, independent of the degree of obesity. Additionally, HbA1c levels were notably reduced in Pso/PsA patients with severe obesity (84).

Data derived from the pooled analysis of five randomized, placebo-controlled, phase 3 studies, including PALACE 1-4 and ACTIVE, unveiled significant reductions in LDL cholesterol levels, particularly in patients with the highest pre-treatment levels. Additionally, this analysis indicated significant weight loss and a decrease in the rates of obesity and overweight, along with reduced HbA1c levels in patients with pre-diabetes or T2DM (85).

The SPROUT study showed that apremilast was effective and safe over 16 weeks in pediatric patients with plaque psoriasis. A significantly higher proportion achieved a Physician Global Assessment response and a ≥75% reduction in PASI scores compared to placebo, regardless of age, weight, or disease severity. Notably, younger and lower-weight patients had higher response rates (86). In addition, Guerra et al. specifically analyzed the effects of apremilast on lipid profile and weight over a one-year period. Their study demonstrated a significant reduction in weight and triglycerides at 24 and 52 weeks, as well as a significant increase in HDL levels at 52 weeks. These findings suggest that apremilast may have a positive impact on both weight management and lipid profile in individuals with moderate to severe psoriasis over the medium to long term (87). These studies represent pioneering investigations conducted in real-world clinical practice, offering valuable insights into the alterations of cardiometabolic variables following the initiation of apremilast therapy within a sizable cohort of patients suffering from Pso and PsA (Figure 1C). The extensive worldwide influence of apremilast on metabolic profiles is concisely outlined in Table 1.

TABLE 1 Impact of apremilast on the comprehensive metabolic profile of psoriatic patients.

Year	Study type	Conditions	Size	Effect of apremilast	Time	Ref.
2024	Observational: real world evidence	Pso	n=20	Weight loss, reduced triglyceride levels, and increased HDL levels.	12, 24, 52 weeks	(87)
2024	Interventional: Clinical trial (SPROUT)	Pso	n=245	Apremilast demonstrated a significantly higher rate of patients achieving PGA response and ≥75% reduction in PASI compared to placebo, irrespective of baseline age, weight, or disease severity.	16 weeks	(86)
2023	Interventional: pool of 5 clinical trial (PALACE 1-4 and ACTIVE)	Pso/PsA	N=781	Reduction in LDL cholesterol levels.	52 weeks	(85)
				Weight loss, decrease in rates of obesity and overweight.		
				Reduced HbA1c levels in pre-diabetes or T2DM patients.		
2022	Observational: real world evidence	Pso/PsA	n=8487	Weight loss.	6 months	(83)
				Reduced HbA1c levels in pre-diabetes or T2DM patients.		
				Increased HDL-cholesterol in non-diabetic patients.		
2022	Observational: real world evidence	Pso/PsA	n=8250	Weight loss independent of the degree of obesity (obese or severe obesity).	6 months	(84)
				Reduced HbA1c levels in patients with severe obesity.		
2022	Observational: real world evidence-molecular study	PsA	n=30	Decreased body mass index and insulin resistance state.	6 months	(56)
				A decrease is noted in 17 CVD-related proteins, previously identified as being altered in the plasma of PsA patients when compared to healthy donors.		
2022	Interventional: VIP-A Phase 4 clinical trial	Pso	n=70	A sustained 5% to 6% decrease in subcutaneous and visceral fat was observed after 16 weeks of treatment, and this reduction persisted through the 52-week period.	52 weeks	(79)
				Changes in cardiometabolic biomarkers related to lipoprotein characterization, inflammation and glucose metabolism.		

(Continued)

TABLE 1 Continued

Year	Study type	Conditions	Size	Effect of apremilast	Time	Ref.
2022	Interventional: PALACE4 Phase 3 clinical trial	PsA	n=175	Higher body mass index at baseline in high disease activity patients.	52 weeks	(78)
2021	Interventional: IMAPA clinical trial	Pso/PsA	n=60	Weight loss, particularly the reduction of total abdominal fat, primarily targeting subcutaneous adipose tissue.	6 months	(82)
2021	Observational: real world evidence	Pso	n=7773	Less discontinuation of the treatment with apremilast in Pso patients with metabolic condition (compared to Secukinumab, Adalimumab, Ustekinumab and Etanercept).	48 months	(81)
2020	Observational: real world evidence	Pso/PsA	n=113	Lowered total cholesterol levels in both diabetic and non-diabetic Pso/PsA patients, accompanied by decreased glucose levels.	52 weeks	(80)
2018	Interventional: ACTIVE Phase 3B clinical trial	PsA	n=219	Weight loss (15.7% of patients experiencing more than 5% weight loss).	52 weeks	(77)
2017	Interventional: Japanese Phase 2B clinical trial	Pso	n=254	Weight loss:11.6% Pso patients treated with 20mg and 14.2% Pso patients treated with 30mg.	68 weeks	(76)
2016	Interventional: PALACE 3 Phase 3 clinical trial	Pso/PsA	n=505	Weight loss exceeding 5% in 14% (20mg) and 16% (30mg).	52 weeks	(75)
2016	Interventional: PALACE 2 Phase 3 clinical trial	PsA	n=484	Weight loss exceeding 5% in 17% (20mg) and 14.8% (30mg).	52 weeks	(74)
2015	Interventional: ESTEEM 2 Phase 3 clinical trial	Pso	n=413	Weight loss exceeding 5% in 20.2% of Pso patients (30mg).	52 weeks	(73)
2015	Interventional: ESTEEM 1 Phase 3 clinical trial	Pso	n=844	Weight loss exceeding 5% in 19% of Pso patients (30mg).	52 weeks	(72)
2014	Interventional: PALACE 1 Phase 3 clinical trial	PsA	n=504	In comparison to the placebo group, which exhibited a mean weight change of 0.19 ± 2.6 kg, patients with PsA demonstrated a weight change of -1.29 ± 3.4 kg at 20 mg and -0.97 ± 2.8 kg at 30 mg of apremilast.	24 weeks	(71)

Annotated names. Pso, Psoriasis; PsA, Psoriatic Arthritis; PGA, Physician Global Assessment; HDL, High Density Lipoproteins; LDL, Low Density Lipoproteins; HbA1c, glycosylated haemoglobin; T2DM, Type 2 Diabetes Mellitus; CVD, Cardiovascular Disease; PALACE, Psoriatic Arthritis Long-term Assessment of Clinical Efficacy; ACTIVE, Assessing Apremilast Monotherapy in a Clinical Trial of BIologic-NaïVE Patients With Psoriatic Arthritis; VIP-A, Vascular Inflammation in Psoriasis-Apremilast; IMAPA, The Immune Metabolic Associations in Psoriatic Arthritis; ESTEEM, The Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis.

6 Molecular insights into apremilast impact on CVD

We identified 33 CVD-related proteins, including adipocytokines, associated with PsA at a molecular level. These proteins significantly differed in PsA patients compared to healthy controls, indicating a link between PsA and CVD characteristics. In PsA patients with varying levels of CVD comorbidities (dysregulated lipid profile, obesity, IR, hypertension, and metabolic syndrome) treated with apremilast (alone or with methotrexate), a distinct molecular profile emerged. This profile included elevated levels of proteins like CD-163, FABP-4, RARRES-2, and others in patients with multiple CVD comorbidities. Notably, this molecular profile significantly reduced with apremilast monotherapy, outperforming its combination with methotrexate or methotrexate alone after six months (week 24). These findings highlight apremilast's potential in mitigating CVD-related markers in PsA patients with multiple metabolic comorbidities (56). Conversely, at week 16 with apremilast, favorable changes in cardiometabolic biomarkers were observed, including reductions in IL-1β, fetuin A, valine, leucine, and isoleucine. By week 52, additional improvements included reduced levels of ferritin, cholesterol efflux capacity, β-hydroxybutyrate, acetone, and ketone bodies, along with increased apolipoprotein A levels (80).

On a different note, Wang and colleagues delved into the *in vitro* effects of apremilast within the context of atherosclerosis. They employed oxidized low-density-lipoprotein (ox-LDL) to simulate the atherosclerotic microenvironment in a model of human aortic endothelial cells (HAECs). Notably, apremilast demonstrated the ability to reduce the expression of key ox-LDL scavenging receptors and inflammatory cytokines, including IL-6, TNF-α, and IL-8. In addition, apremilast effectively inhibited the attachment of monocytes to HAECs, primarily attributed to the reduction of chemokine monocyte chemotactic protein 1 (MCP-1) and the cellular adhesion molecule vascular cell adhesion molecule 1 (VCAM-1). These effects were mediated through the modulation of Krüppel-like factor 6 (KLF-6) expression, which was downregulated in response to ox-LDL via the c-Jun N-terminal Kinase (JNK) pathway (88). Besides, Otto and colleagues have presented compelling evidence regarding the potential anti-inflammatory effects of apremilast, focusing on human umbilical

vein endothelial cells (HUVEC). In their study, HUVECs were exposed to TNF-α, both in the presence and absence of apremilast. Intriguingly, apremilast was found to induce a significant reduction in the secretion of pro-inflammatory mediators, including GM-CSF, CCL-2, and CXCL-10. Their investigation expanded to assess the impact of apremilast on IL-17A-induced endothelial inflammation. Significantly, apremilast effectively reduced the secretion of IL-6 and CCL-2. Additionally, apremilast demonstrated the ability to suppress adhesion molecules like VCAM-1 and E-selectin, highlighting its capacity to inhibit the adhesion of monocytic cells to activated endothelial cells, consequently impeding monocytic trans-endothelial migration. Moreover, apremilast exhibited a notable reduction in MMP-9 expression, a key player in the recruitment of inflammatory cells into the vessel wall among activated monocytic cells (89). In a recent study by Fukasawa et al., the concentrations of multiple cytokines were simultaneously and longitudinally measured at weeks 4, 16, and 24 in 20 Japanese patients with psoriasis. The study demonstrated a reduction in several serum inflammatory cytokines (IL-1β, IL-6, IL-17A, IL-17F, IL-17C, IL-21, IL-22, IL-23, IL-36γ, TGF-β1, and TNF-α) and an increase in inhibitory cytokines (IL-10 and IL-35) (90). These findings concentrate on the examination of vascular endothelial cells and present intriguing results that establish a foundation for the potential cardiovascular protective effects of apremilast treatment (Table 2). Nonetheless, further targeted studies would be essential to investigate the role of other metabolic cell types, such as hepatocytes or adipocytes,

TABLE 2 Exploring the molecular dimensions of apremilast's effects on CVD.

Study type	Conditions	Sample/Cell type	Effect of apremilast	Ref.
Observational: real world evidence- molecular study	PsA patients	Blood-based biomarkers: circulating CVD-plasma levels	A decrease is noted in CD-163, FABP-4, RARRES-2, CCL-15, MMP-3, vWF, GDF-15, TPA, TIMP-4, TR-AP, IL-2RA, CTSD, CNTN-1, GAL-3, LTBR, OPG and NT-proBNP at 6 months, previously identified as being altered in the plasma of PsA patients when compared to healthy donors.	(56)
Interventional: VIP-A Phase 4 clinical trial	Pso patients	Blood-based biomarkers: circulating plasma and serum levels	Changes in cardiometabolic biomarkers related to lipoprotein characterization, inflammation and glucose metabolism.	(79)
			At week 16, there was a reduction in IL-1β, valine, leucine, and feutin A, along with a decrease in branched-chain amino acids. By week 52, a decline was observed in ferritin, β-hydroxybutyrate, acetone, and ketone bodies, accompanied by an increase in apolipoprotein A-1.	
Molecular study	*In vitro:* gene and protein expression	Human aortic endothelial cells (HAECs) and U937 monocytic cells	Apremilast exhibited the capacity to decrease the expression of crucial receptors involved in oxidized ox-LDL scavenging, along with a reduction in inflammatory cytokines such as IL-6, TNF-α, and IL-8 upon stimulation with ox-LDL.	(88)
			Apremilast successfully hindered the attachment of monocytes to HAECs, primarily due to the diminished levels of MCP-1 and VCAM-1.	
Molecular study	*In vitro: gene and protein expression*	Human umbilical vein endothelial cells (HUVEC) and THP1 monocytic cells	Apremilast effectively inhibited the TNF-α-induced expression and secretion of crucial pro-inflammatory factors in both endothelial and monocytic cells. These factors encompass GM-CSF, CXCL-10, CCL-2, VCAM-1, E-selectin, and MMP-9.	(89)
			Apremilast diminished the adhesion of THP-1 cells to activated HUVECs and the Transwell Endothelial Migration in response to TNF-α.	
			Apremilast inhibited the activation of NFκB and MAPK signaling in activated HUVECs.	
			Apremilast decreased IL-17A-induced secretion of IL-6 and CCL2.	
Observational: real world evidence- molecular study	Pso patients	Blood-based biomarkers	Decreased levels of IL-1β, IL-6, IL-17A, IL-17F, IL-17C, IL-21, IL-22, IL-23, IL-36γ, TGF-β1, and TNF-α, alongside an elevation in inhibitory cytokines such as IL-10 and IL-35.	(90)

Annotated names. CVD, Cardiovascular Disease; PsA, Psoriatic Arthritis; Pso, Psoriasis; VIP-A, Vascular Inflammation in Psoriasis-Apremilast; CD-163, Cluster Differentiation 163; FABP-4, Fatty Acid Binding Protein 4; RARRES-2, Retinoic Acid Receptor Responder 2; CCL-15, C-C Motif Chemokine Ligand 15; MMP-3, Matrix Metallopeptidase 3; vWF, Von Willebrand Factor; GDF-15, Growth Differentiation Factor 15; TPA, Tissue Type Plasminogen Activator; TIMP-4, Tissue Inhibitor of Metalloproteinase; TR-AP, Tumor necrosis factor (TNF) receptor associated factor 2; IL-2RA, Interleukin 2 Receptor Subunit Alpha; CTSD, Cathepsin D; CNTN-1, Contactin 1; GAL-3, Galectin 3, LTBR, Lymphotoxin Beta Receptor; OPG, Osteoprotegerin; NT-proBNP, N-Terminal Prohormone Recognition Protein 1; IL-1β, Interleukin 1-beta; LDL, Low Density Lipoprotein; IL-8, Interleukin 8; MCP-1, Monocyte Chemotactic Protein 1; VCAM-1, Vascular Cell Adhesion Molecule 1; GM-CSF, Granulocyte-Macrophage Colony Stimulating Factor; CXCL-10, C-X-C Motif Chemokine Ligand 10; CCL-2, C-C Motif Chemokine Ligand 2; MMP-9, Matrix Metallopeptidase 9; NFκB, Nuclear Factor Kappa Beta; MAPK, Mitogen-Activated Protein Kinase; IL-17A, Interleukin 17A; IL-6, Interleukin 6.

particularly in the context of altered metabolic conditions associated with psoriatic disease.

7 Conclusions

1. Psoriatic disease links strongly to higher cardiovascular risk, including type 2 diabetes, obesity, IR, hypertension, and dysregulated lipids, raising mortality risk.

2. Given the increased cardiometabolic risk in psoriatic disease, treatment focus must shift to manage metabolic factors alongside inflammation.

3. Apremilast, with its dual-action potential, emerges as a pivotal treatment for psoriatic disease, addressing both inflammation and metabolic parameters, enhancing overall well-being.

Author contributions

NB: Conceptualization, Funding acquisition, Methodology, Supervision, Writing – original draft, Writing – review & editing. CL-M: Methodology, Supervision, Writing – review & editing. AE-C: Methodology, Supervision, Writing – review & editing. IA-dR: Conceptualization, Methodology, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by grants from the Instituto de Salud Carlos III (PI20/00079), co-financed by the European Union and the Andalucian Foundation of Rheumatology (FAR). NB was supported by a contract from the MINECO (RyC- 2017-23437). C-LM was supported by a contract from the Instituto de Salud Carlos III (JR21/00013).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers | Frontiers in Immunology

TYPE Original Research
PUBLISHED 19 September 2024
DOI 10.3389/fimmu.2024.1412636

OPEN ACCESS

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RECEIVED 05 April 2024
ACCEPTED 30 August 2024
PUBLISHED 19 September 2024

CITATION
Bin Z, Shen R, Wu R, Fan Y, Zhang X, Gao C, Li X and Wang C (2024) Association of urinary albumin excretion with all-cause and cardiovascular mortality among patients with rheumatoid arthritis: a national prospective study.
Front. Immunol. 15:1412636.
doi: 10.3389/fimmu.2024.1412636

Association of urinary albumin excretion with all-cause and cardiovascular mortality among patients with rheumatoid arthritis: a national prospective study

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Background: Rheumatoid arthritis (RA) patients suffering from chronic renal insufficiency tend to exhibit subtle manifestations at the beginning. Urine albumin to creatinine ratio (ACR) is a sensitive indicator for early assessment of renal function. However, it is unclear whether it serves as an independent risk factor influencing the prognosis of RA patients.

Methods: National Health and Nutrition Examination Survey (NHANES) data from 2009-2018 were included. Kaplan-Meier (K-M) curves were plotted to compare the cumulative survival probability of RA patients with different urinary albumin excretion. The association of ACR with mortality among RA patients was investigated with Cox regression model, restricted cubic spline (RCS) and stratified analyses. The prognostic efficacy of ACR and estimated glomerular filtration rate (eGFR) was evaluated by receiver operating characteristic (ROC) curves.

Results: The Cox regression model adjusted with covariates showed a 53% (HR 1.53, 95% CI 1.06-2.21) increase in all-cause mortality and a statistically non-significant increase in cardiovascular disease (CVD) mortality in RA patients with microalbuminuria (30mg/g ≤ACR<300mg/g). ACR≥300mg/g was associated with an increase in all-cause mortality (HR 2.62, 95% CI 1.55-4.45) and CVD mortality (HR 5.67, 95% CI 1.96-16.39). RCS demonstrated a nonlinear correlation between ACR and all-cause mortality in RA patients with microalbuminuria. Subgroup analysis showed that CVD mortality was higher in RA patients with microalbuminuria characterized by the following features: female, other ethnicity, eGFR≥60 ml/min/1.73 m2, hypertension or hyperlipidemia. Compared with eGFR, ACR provided better prognostic efficacy than eGFR with higher values of the area under the curve (AUC) for all-cause mortality (AUC=0.683, 95% CI 0.613-0.754) and CVD mortality (AUC=0.681, 95% CI 0.541-0.820).

Conclusion: ACR is an independent risk factor affecting the prognosis of RA patients. The all-cause mortality was increased in RA patients with albuminuria. There was an upward trend in the CVD mortality of those with macroalbuminuria when ACR increased.

KEYWORDS

urine albumin to creatinine ratio, urinary albumin excretion, rheumatoid arthritis, mortality, cardiovascular disease

1 Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by symmetrical small joint inflammation involving multiple organs throughout the body. Extra-articular manifestations occur during the progression of rheumatoid arthritis with multiple organs involved including heart, lungs, eyes, kidneys and so on, which seriously affect the prognosis of RA patients. Comorbid renal insufficiency in RA patients tends to be a persistent and sneaky condition. A cross-sectional multicenter study suggested 9% of 931 patients with RA had proteinuria and 8.8% had an eGFR <60 ml/min/1.73 m2 (1). However, when raised blood creatinine or large amounts of albuminuria are noticed, RA individuals usually have experienced kidney disease progression, which deteriorates their living conditions and brings therapeutic challenges. Renal insufficiency in patients with RA may be attributed to a variety of causes. As is known, some disease-modifying antirheumatic drugs (DMARDs) such as cyclosporine and methotrexate, are nephrotoxic. Besides, vasculitis and secondary renal amyloidosis degeneration after RA may trigger kidney damage such as concomitant nephrotic syndrome. Participants with chronic kidney disease (CKD) exhibit an alarming incidence of cardiovascular disease (CVD) events, especially adverse outcomes such as heart failure and malignant arrhythmias (2, 3). Compared with healthy controls, individuals with RA are associated with higher risk of cardiovascular events due to their highly inflammatory environments (HR 1.33, 95% CI 1.07 to 1.65, p=0.010) (4). Thus, it is essential for prediction of RA prognosis to early assess the risk of all-cause and CVD mortality associated with renal insufficiency.

The urine albumin to creatinine ratio (ACR) is a key indicator for albuminuria in CKD (5). The Kidney Disease Outcomes Quality Initiative (KDOQI) 2021 defines normal values for ACR as less than <30 mg/g, with 30-300 mg/g presenting as microalbuminuria, and those ≥300 mg/g as macroalbuminuria (6). ACR exceeding 30 mg/g and lasting for a period of greater than or equal to 3 months is considered to have CKD and a higher ACR is a significant marker of renal injury. Besides, a small increase above the normal range of ACR (30-300 mg/g) reflects the level of urinary microalbumin, which tends to indicate vascular damage and be strongly associated with cardiovascular complications in a variety of diseases (7–9). Several studies have suggested that in a normal population ACR was linearly correlated with the risk of mortality (10, 11). However, there is a lack of evidence on the relationship between ACR and mortality in RA cohorts. Besides, the relationship between adverse CVD occurrence and urinary albumin excretion in RA still requires further investigation. Other risk factors affecting RA such as demographics, lifestyle habits, and comorbidities should also be taken into account in order to demonstrate independent impact of ACR on mortality. Elucidating the association of ACR with all-cause and cardiovascular mortality among RA participants facilitates the investigation of novel, sensitive markers that predict poor prognosis and the evaluation of the effect of urine albumin excretion on RA prognosis.

2 Materials and methods

2.1 Study participants

National Health and Nutrition Examination Survey (NHANES) is a survey based on the health and nutritional status of adults and children in the USA. By demonstrating questionnaires, laboratory data, and health examinations, this platform provide a multidimensional landscape of USA population health conditions.

We combined the NHANES data from 2009-2018 for a total of 5 cycles, excluding respondents younger than 20 years of age, and excluded subjects with undocumented arthritis and ACRs from the 27,070 participants. 1,363 patients with RA were selected based on participants answered as “Rheumatoid arthritis” to the MCQ191 and MCQ195 question “What type of arthritis do you have”. 4 patients with missing mortality data and 77 patients without covariate data were excluded, and finally 1282 RA patients were enrolled in our study.

2.2 Albumin to creatinine ratio measurement

According to the NHANES website, urinary albumin and creatinine were measured by solid-phase fluorescence immunoassay and modified Jaffe kinetics. The ACR was

calculated by dividing the urinary albumin concentration by the urinary creatinine concentration in mg/g. We selected the variable URDACT in the ALB_CR dataset of the laboratory data as the value of the ACR and classified the ACR into three intervals according to KDOQI guidelines for statistical analysis: <30 mg/g, 30-300 mg/g, and ≥300 mg/g, using the RA population with ACR <30 mg/g as a reference. ACR was tested at baseline in patients with RA.

2.3 Mortality

We collected information on mortality status and follow-up time (as of 31 December, 2019) through the National Death Index Mortality Database of NHANES. The primary outcomes in our study were all-cause mortality and cardiovascular mortality, with Causes of death determined according to the International Classification of Diseases, Tenth Revision (The codes for heart disease: I00–I09, I11, I13, and I20–I51).

2.4 Covariates

Covariates such as demographics, marital status, smoking status, education, diabetes, hypertension, hyperlipidemia and estimated glomerular filtration rate (eGFR) were obtained from NHANES questionnaire and laboratory data and included in the study. The poor population was defined as poverty to income ratio (PIR) <1. The married population was defined as being married or living with partner. Smokers were classified as smoking now or having smoking history. Diabetes was defined as taking hypoglycemic medication, using insulin, having been informed by a physician of a diagnosis of diabetes mellitus, having a hemoglobin A1c (HbA1c) level of ≥ 6.5%, or having a fasting glucose of ≥ 126 mg/dl. Hypertension was defined as being on antihypertensive medication, having ever been informed by a physician of a diagnosis of hypertension, having had three consecutive systolic blood pressure measurements of ≥ 140 mmHg, or diastolic blood pressure of ≥ 90 mmHg. Hyperlipidemia was defined as having total cholesterol >200 mg/dl, triglycerides >150 mg/dl, LDL >=130 mg/dl, HDL for men <40 mg/dL, <50 mg/dL for women, or subjects who had been informed by a physician of a diagnosis of hyperlipidemia. The eGFR was determined by the CKD Epidemiology Collaboration equation (12).

2.5 Data analysis

Data were analyzed by dividing RA patients into three groups according to ACR: <30 mg/g, 30-300 mg/g and ≥ 300 mg/g. General characteristics of the population were described by a baseline table. Differences between the three groups were compared using the Kruskal-Wallis test (non-normally distributed continuous variables), the χ^2 test (categorical variables), and the Fisher's exact probability test (counting variables with theoretical numbers <10). ACR is non-normally distributed. Kaplan-Meier (K-M) curves were plotted to visualize the survival status of RA patients. Hazard ratios (HR) values and 95% confidence intervals (95% CI) for RA patients were calculated with the Cox proportional risk model, and three models were developed: model 1 was unadjusted, model 2 was adjusted for age, sex, and race, and model 3 was adjusted for age, gender, race, marital status, poverty-to-income ratio (PIR), smoking, comorbidities and eGFR. The nonlinear relationship between urinary albumin excretion rate and mortality in RA patients was investigated by the restricted cubic spline (RCS) model for RA populations with ACR less than 300 mg/g. Models fitted by RCS were similarly adjusted for covariates as model 3. The RCS model revealed no correlation between ACR <300 mg/g and cardiovascular mortality in RA patients with microalbuminuria in the adjusted model (P >0.05). Further subgroup analyses of RA patients with ACR lower than 300 mg/g were carried out to investigate the effect of ACR on mortality. The effect of ACR on mortality among RA patients of different categories was studied based on populations stratified by demographic characteristics and comorbidities. Interactivity test and sensitivity analysis were used to assess model robustness. Finally, ROC curves revealed prognostic efficacy of ACR and eGFR for all-cause mortality and CVD mortality.

All statistical analyses in this study were performed using R (version 4.3.1). A two-tailed P value less than 0.05 is considered to be statistically significant.

3 Results

3.1 Baseline characteristics

A total of 1282 adult RA patients were enrolled in this study (Figure 1). Overall, females make up 59.05% of the population, more than males do and elderly people account for a larger percentage at 58.50%. The participants were categorized into three groups according to ACR: ACR<30 mg/g, 30-300 mg/g, and ≥300 mg/g (Table 1). There were 1024 RA patients with ACR less than 30 mg/g, 212 between 30 and 300, and 46 more than 300 mg/g in study population. RA cohort had proportionally more age ≥ 60 years old patients (P <0.001) and more patients with education level below high school as ACR increased (P =0.003). Besides, there were positive correlation between prevalence of diabetes, hypertension in RA participants with ACR > 300 mg/g. As ACR rises, proportion of RA participants with eGFR <60 ml/min/1.73 m2 and all-cause mortality increase. Other covariates were not significantly different among the three ACR groups.

3.2 Association between ACR and mortality among RA patients

A total of 179 among 1282 RA patients died, with 29 fatalities attributed to cardiovascular events (Table 2). K-M curves based on

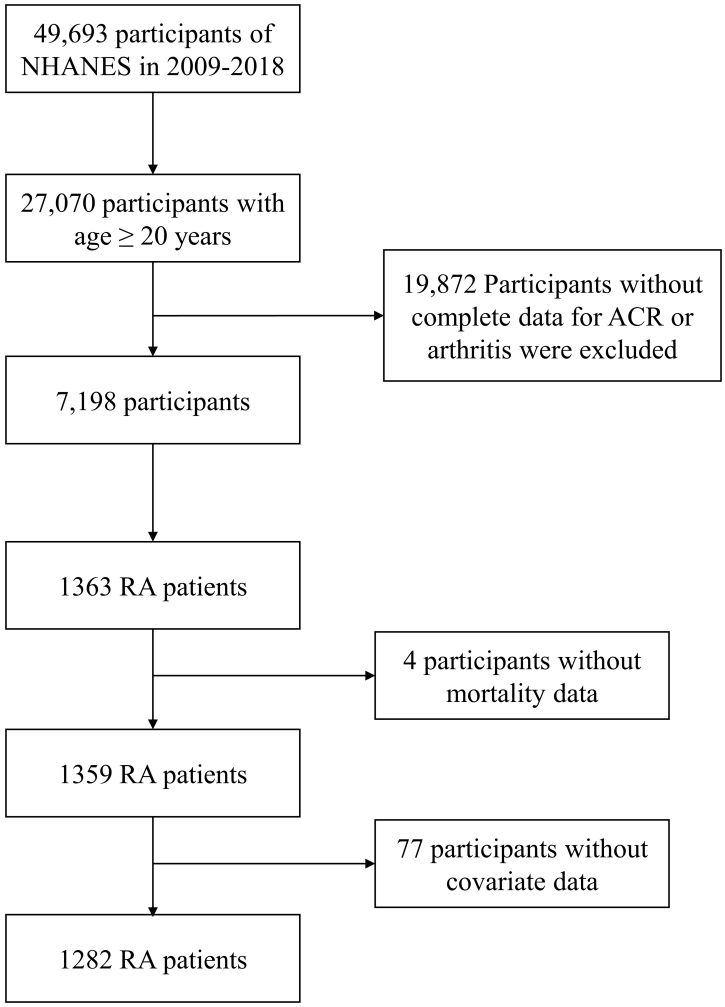

FIGURE 1
Flow chart.

the three ACR groups showed that the cumulative probability of survival was reduced in RA patients with high ACR compared to those with normal ACR in all groups (Figure 2). We observed that high ACR (30-300mg/g and ≥300mg/g groups) was associated with increased all-cause mortality compared with RA patients with normal ACR, the corresponding all-cause mortality HRs were 2.23 (95% CI 1.58,3.14) and 4.88 (95% CI 3.00,7.94) respectively (P <0.001). After adjusting demographic factors, RA participants with high ACR (30-300mg/g and ≥300mg/g groups) also tended to have higher odds of all-cause mortality in model 2. In model 3, the all-cause mortality of participants in the high ACR groups was also associated with higher all-cause mortality, and the HRs were 1.53 (95%CI 1.06,2.21) and 2.62 (95%CI 1.55,4.45), respectively after adjusted potential confounders. A similar but more significant trend was indicated by model 3 in the association of ACR above 300 mg/g with CVD mortality. We noticed that there was no statistical significance in the increase of CVD mortality in the overall population based on model 3, which might attribute to no apparent increase in CVD mortality of RA patients with microalbuminuria. And in other models, we could demonstrate a significant trend on mortality based on P for trend. These results suggested that ACR was a high-risk factor affecting the prognosis of RA patients, especially when ACR exceeds 300. As clinically significant proteinuria occurred, the risk of all-cause mortality and CVD mortality in RA patients significantly increased.

3.3 Association of ACR with mortality among RA patients with microalbuminuria

ACR reflects the 24-hour urinary albumin level directly as a measure of urinary microalbumin. ACR between 30-300 mg/g indicates elevated urinary microalbumin, however, model 3 above suggested there was no significant correlation between microalbumin excretion and CVD mortality for RA. We further investigate the non-linear relationship between mortality and ACR at this interval. RCS

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TABLE 1 Baseline variables according to the ACR group.

characteristics	total	ACR (mg/g)			
		<30	30-300	>=300	*P*-value
	1282	1024	212	46	
Gender					0.423
male	525	418 (40.82)	84 (39.62)	23 (50.00)	
female	757	606 (59.18)	128 (60.38)	23 (50.00)	
Age					<0.001
<60	532	469 (45.80)	55 (25.94)	8 (17.39)	
>=60	750	555 (54.20)	157 (74.06)	38 (82.61)	
Race					0.195
Mexican American	194	142 (13.87)	42 (19.81)	10 (21.74)	
Non-Hispanic Black	367	293 (28.61)	60 (28.30)	14 (30.43)	
Non-Hispanic White	486	399 (38.96)	70 (33.02)	17 (36.96)	
Other	235	190 (18.55)	40 (18.87)	5 (10.87)	
Marital status					0.187
No	576	447 (43.65)	106 (50.00)	23 (50.00)	
Yes	706	577 (56.35)	106 (50.00)	23 (50.00)	
Education					0.003
Below high school	412	306 (29.88)	87 (41.04)	19 (41.30)	
High School or above	870	718 (70.12)	125 (58.96)	27 (58.70)	
PIR					0.554
Not poor	948	754 (73.63)	162 (76.42)	32 (69.57)	
poor	334	237 (23.14)	50 (23.58)	14 (30.43)	
Smoke					0.522
No	993	787 (76.86)	168 (79.25)	38 (82.61)	
Yes	289	237 (23.14)	44 (20.75)	8 (17.39)	
Diabetes					<0.001
No	859	748 (73.05)	92 (56.60)	19 (41.30)	
Yes	423	276 (26.95)	120 (43.40)	27 (58.70)	
Hypertension					<0.001
No	418	385 (37.60)	29 (13.68)	4 (8.70)	
Yes	864	639 (62.40)	183 (86.32)	42 (91.30)	
Hyperlipoidemia					0.552
No	246	191 (18.65)	44 (20.75)	11 (23.91)	
Yes	1036	833 (81.35)	168 (79.25)	35 (76.09)	
eGFR (ml/min/ 1.73 m2)					<0.001
<60	192	106 (10.35)	61 (28.77)	25 (54.35)	
≥60	1090	918 (89.65)	151 (71.23)	21 (45.65)	
All causes of mortality					<0.001
Heart Diseases	29	15 (1.46)	8 (3.77)	6 (13.04)	
Diabetes	10	3 (0.29)	5 (2.36)	2 (4.35)	
Pneumonia and chronic lower respiratory diseases	14	9 (0.88)	3 (1.42)	2 (4.35)	
Cerebrovascular diseases and Alzheimer's disease	8	6 (0.59)	2 (0.94)	0 (0.00)	
Nephritis, nephrotic syndrome and nephrosis	1	0 (0.00)	0 (0.00)	1 (2.17)	
Tumor	40	31 (3.03)	6 (2.83)	3 (6.52)	
Other causes	77	50 (4.88)	22 (10.38)	5 (10.87)	
Survival	1103	910 (88.87)	166 (78.30)	27 (58.70)	

Data are shown as n% according to ACR distribution.
PIR, poverty-to-income ratio; ACR, albumin to creatinine ratio; eGFR: estimated glomerular filtration rate.

revealed a nonlinear correlation for all-cause mortality in RA patients with microalbuminuria (Figure 3A, P =0.0014, P for nonlinear=0.0329). For RA patients with microalbuminuria, there

TABLE 2 HR and 95% CI for all-cause and CVD mortality in RA patients according to ACR groups.

	ACR			*P* for trend
	<30	30-300	>=300	
All-cause mortality				
Number of deaths (%)	114(11.13%)	46(21.70%)	19(41.30%)	
Model 1: HR (95%CI),	Ref	2.23(1.58,3.14), <0.001	4.88(3.00,7.94), <0.001	<0.001
P-value				
Model 2: HR (95%CI),	Ref	1.97(1.39,2.79), <0.001	3.62(2.21,5.95), <0.001	<0.001
P-value				
Model 3: HR (95%CI),	Ref	1.53(1.06,2.21), 0.021	2.62(1.55,4.45), <0.001	<0.001
P-value				
Cardiovascular mortality				
Number of deaths (%)	15(1.46%)	8(3.77%)	6(13.04%)	
Model 1: HR (95%CI),	Ref	3.09(1.31,7.31), 0.010	11.58(4.48,29.93), <0.001	<0.001
P-value				
Model 2: HR (95%CI),	Ref	2.25(0.93,5.43), 0.072	8.92(3.34,23.81), <0.001	<0.001
P-value				
Model 3: HR (95%CI),	Ref	1.36(0.56,3.34), 0.499	5.67(1.96,16.39), 0.001	0.088
P-value				

HR, hazard ratio; 95% CI, 95% confidence intervals; CVD, cardiovascular disease.

was no correlation between ACR and their CVD mortality (Figure 3B, P =0.173, P for nonlinear=0.204). However, RCS still showed an upward trend of CVD mortality as ACR exceeded 152.44 mg/g.

3.4 Subgroup analysis of all-cause and CVD among RA patients with microalbuminuria

Further subgroup analysis of RA individuals with ACR <300 mg/g stratified by sex, age, ethnicity, diabetes mellitus, hypertension, hyperlipidemia and eGFR showed that when microalbuminuria existed, the all-cause mortality rate was higher in RA patients with the following characteristics: older, female, eGFR≥60 ml/min/1.73 m2 and those with hypertension or diabetes. Despite the existence of hyperlipidemia, all-cause mortality increased in RA patients with albuminuria, of which the HRs were 3.06(95%CI 1.50, 6.21) and 2.03 (95%CI 1.37, 3.01) compared with RA patients with normal ACR (Figure 4). Regarding the effect of ACR on CVD mortality in RA patients, subgroup analyses suggested that CVD mortality was higher in participants with the following characteristics: female, other ethnicity, eGFR≥60 ml/min/1.73 m2, those with hypertension or hyperlipidemia (Figure 5). In conclusion, female RA participants with microalbuminuria who concurrently suffer from hypertension or hyperlipidemia are at higher risk of having their prognosis significantly affected by ACR, even though their eGFR levels are over 60 ml/min/1.73 m2.

3.5 Sensitivity analysis

The propensity score of patients with ACR less than 300 mg/g was calculated and matched. After propensity score matching (PSM), all-cause mortality for RA patients with microalbuminuria was 1.72 times (95%CI 1.08,2.76) higher than that of RA patients with ACR less than 30 mg/g (Table 3), suggesting that all-cause mortality was still associated with ACR; Whereas, its elevated CVD mortality was not statistically significant, consistent with the previous results.

3.6 The prognostic efficacy of ACR and eGFR for all-cause mortality and CVD mortality

The receiver operating characteristic (ROC) curves were utilized to evaluate the prognostic value of ACR and eGFR for all-cause mortality (Figure 6A) and CVD mortality (Figure 6B) in RA patients. Compared with eGFR, ACR offered better prognostic efficacy than eGFR with higher AUC values in ten years. The AUC values of ACR for all-cause mortality and CVD mortality were 0.683 (95% CI 0.613-0.754) and 0.681 (95% CI 0.541-0.820) respectively,

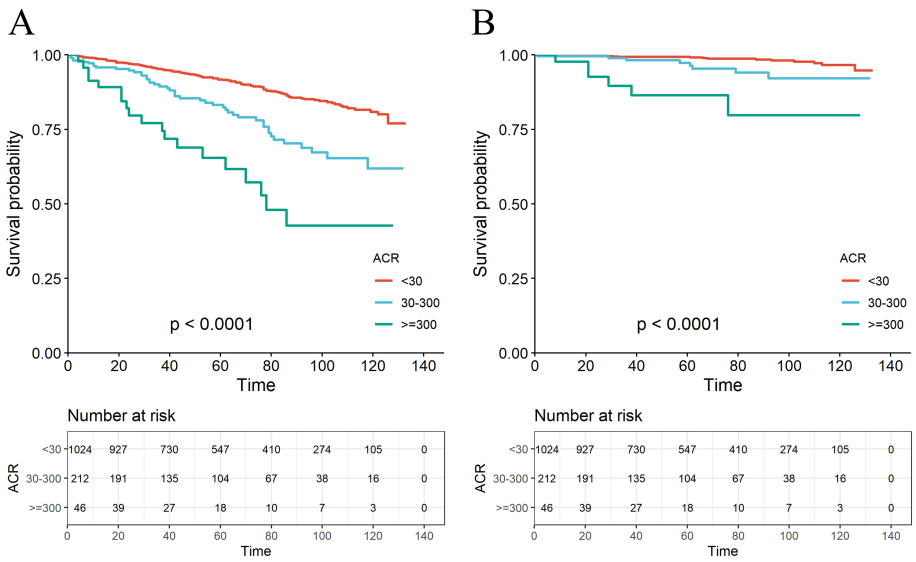

FIGURE 2
The K-M survival curve for all-cause mortality **(A)** and CVD mortality **(B)** based on the ACR group.

followed by eGFR (AUC for all-cause mortality: 0.597, 95% CI 0.549-0.646 and AUC for CVD mortality: 0.644, 95% CI 0.535-0.753).

4 Discussion

Our study showed that the urinary albumin to urinary creatinine ratio was an independent risk factor for all-cause mortality in RA patients, stratified by age, race, gender, eGFR, and other comorbidities. In RA patients with modestly elevated albuminuria (30-300 mg/g), there was a 53% increase in all-cause death compared to RA patients with normal urine albumin excretion. As is shown in RCS plot (Figure 3A), there was a steady trend toward higher mortality in the RA population with microalbuminuria. When urinary albumin excretion was markedly elevated (≥300 mg/g), all-cause mortality of RA patients was 2.62 times higher than in those with normal ACR (<30 mg/g). ACR is an essential threat contributing to cardiovascular events in normal populations (13, 14). However, in our study, when all variables were taken into account, the RA patients did not exhibit a statistically significant increase in cardiovascular mortality as urine albumin excretion modestly raised (30-300 mg/g). Based on subgroup analysis, we further discovered that a mild increase of CVD mortality was seen in RA patients who were female, of other races, eGFR above 60 ml/min/1.73 m2 and had hypertension or hyperlipidemia. Noticeably, patients with considerably higher urine protein excretion (≥300 mg/g) may have a 4.67-fold increase in cardiac cause mortality compared to those with normal ACR.

The common pathological types of rheumatoid arthritis patients combined with renal dysfunction remained controversial. It was believed that common types of RA renal biopsies included

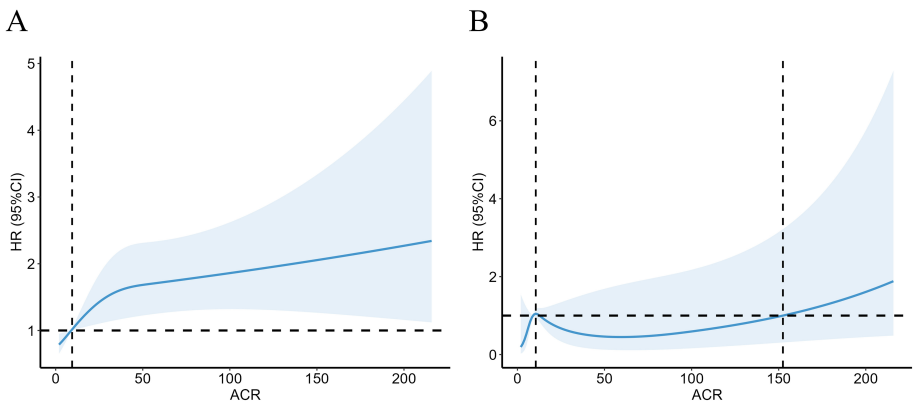

FIGURE 3
Association with all-cause **(A)** and CVD mortality **(B)** in RA at ACR <300mg/g. HR, hazard ratio; 95% CI, 95% confidence intervals; ACR, Albumin to creatinine ratio.

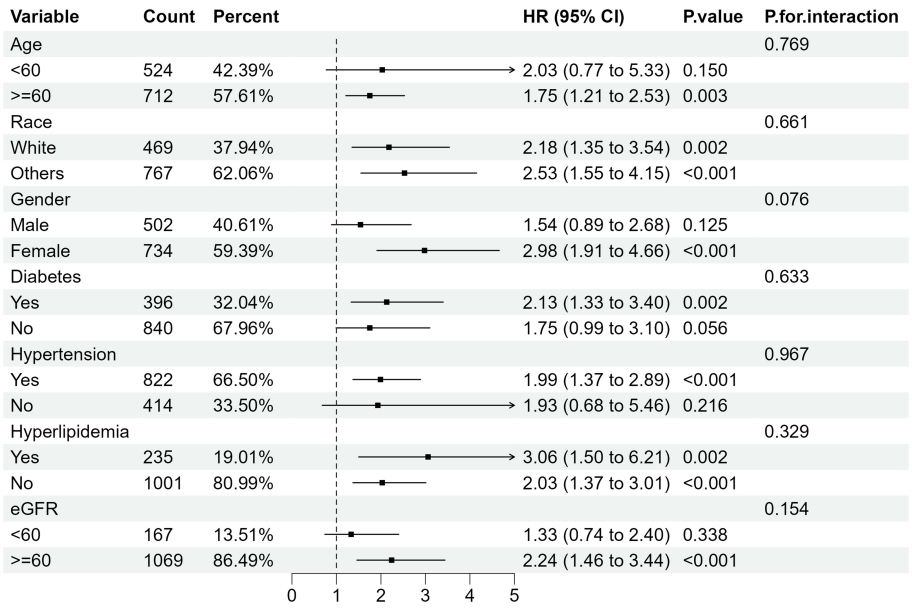

FIGURE 4
Subgroup analysis of all-cause mortality in RA patients with ACR < 300 mg/g. HR, hazard ratio; 95% CI, 95% confidence intervals; ACR, Albumin to creatinine ratio.

mesangial proliferative glomerulonephritis, IgA nephropathy and membranous glomerulonephritis (15, 16). One of important clinical manifestations of these complications is increased urinary protein excretion. During the early stage of renal involvement in rheumatoid arthritis, no clinical abnormally levels are detected on creatinine, urea nitrogen, and 24-hour urinary albumin. For the purpose of evaluating subclinical renal impairment in rheumatoid arthritis, ACR is currently essential due to its sensitivity as a renal pathological test. Therefore, in our analysis we focused primarily on the predictive significance of microalbuminuria (ACR < 300 mg/g) in individuals with RA. Clinical research on microalbuminuria in RA has demonstrated that RA disease duration is closely correlated with ACR, which is significantly greater in RA patients than in normal individuals (17). The causes of renal insufficiency in patients with RA are still up for debate. These include vasculitis, amyloidosis, or renal injury caused by pharmacological agents.

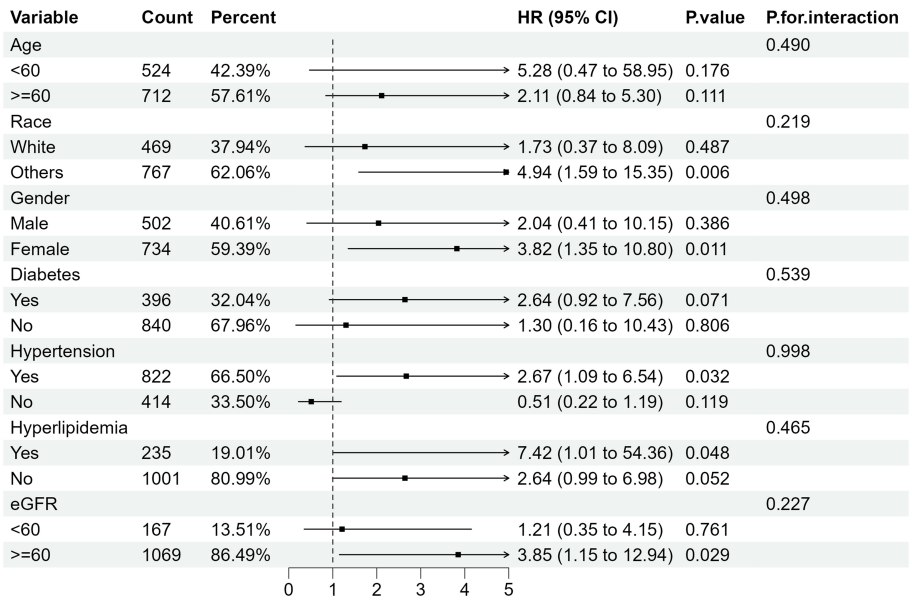

FIGURE 5
Subgroup analysis of CVD mortality in RA patients with ACR < 300 mg/g. HR, hazard ratio; 95% CI, 95% confidence intervals; ACR, Albumin to creatinine ratio.

TABLE 3 Association of all-cause mortality and CVD mortality with ACR in RA patients with ACR < 300 mg/g after PSM.

	ACR		*P*-value
	<30	30-300	
All-cause mortality			
Model 1: HR (95%CI)	Ref	1.70(1.08,2.70)	0.023
Model 2: HR (95%CI)	Ref	1.64(1.03,2.60)	0.035
Model 3: HR (95%CI)	Ref	1.72(1.08,2.76)	0.022
Cardiovascular mortality			
Model 1: HR (95%CI)	Ref	2.25(0.68,7.46)	0.187
Model 2: HR (95%CI)	Ref	2.25(0.67,7.50)	0.187
Model 3: HR (95%CI)	Ref	2.76(0.81,9.37)	0.105

HR, hazard ratio; 95% CI, 95% confidence intervals; ACR, Albumin to creatinine ratio.

Increased vascular permeability in the inflammatory environment of patients with RA may lead to alter glomerular vasculature penetration to plasma albumin, which consequently raises urinary albumin excretion. Renal damage caused by amyloidosis typically has a long latency period and is asymptomatic in the early stages before producing significant quantities of proteinuria (18). Additionally, pharmacological factors are the most common reported causes of renal insufficiency in RA A prospective study showed that NSAIDs hastened the deterioration of renal function in RA patients with advanced kidney damage as some DMARDs did (19). Concomitant use of methotrexate and NSAIDs increased risk of acute renal failure significantly. And methotrexate monotherapy may exacerbate renal insufficiency in RA patients with renal dysfunction (20, 21). Our study demonstrated that elevated ACR significantly increased the risk of mortality in RA patients regardless of micro- or macro-proteinuria; Therefore, early identification of renal injury in RA patients by ACR facilitates physicians to clarify development of diseases and promptly adjust potentially nephrotoxic drugs to improve the prognosis of RA patients.

In addition to being an important indicator for assessing renal insufficiency, ACR can predict the occurrence of cardiovascular events in people with RA to some extent. It has been found that elevated urinary albumin excretion increases the prevalence of cardiovascular complications such as atherosclerosis in patients with RA (22–24). Due to the chronically elevated inflammatory burden in RA patients, they have a higher CVD risk than the normal group. Urinary albumin excretion can be regarded as an important indicator for assessing CVD mortality of RA populations, for reasons that may include either: 1) It reflects endothelial dysfunction or 2) It may indicate the acute phase inflammatory response. Urinary albumin excretion mirrors serum albumin levels which serve an important role in maintaining endothelial integrity. Serum albumin lessens endothelial dysfunction by directly inhibiting oxidative stress and inflammatory pathways (25). It also carries substances that scavenge free radicals, like sphingosine-1-phosphate, which shields the endothelium (26). Besides, an association has been found between urinary protein excretion and vascular Willebrand factor (vWF), a hemostatic factor released in response to endothelial cell damage. Both ACR and vWF could embody endothelial damage and increased permeability, contributing to atherosclerotic plaque formation and atherosclerosis (27). Urinary albumin excretion varies with inflammatory cytokine secretion which further promotes plaque rupture during the acute inflammatory phase. An early myocardial infarction is characterized by a brief and transient rise in urine albumin, especially microalbuminuria, without functional or structural renal damage. A cox proportional risk model has revealed that urinary albumin excretion rate was a better predictor of in-hospital mortality than Killip class or left ventricular ejection fraction (28).

We found that although an increase in cardiovascular mortality was observed by restricted cubic spline plots when ACR exceeded

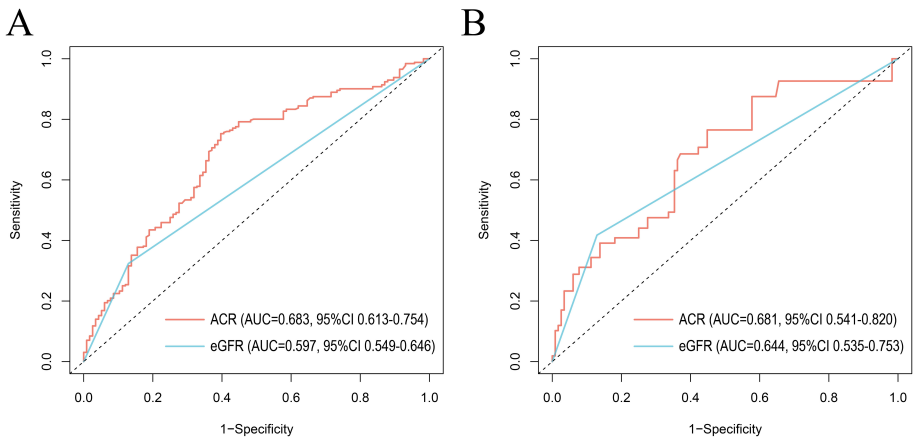

FIGURE 6
ROC curves of ACR and eGFR for all-cause mortality **(A)** and CVD mortality **(B)** at 10 years. ROC, The receiver operating characteristic; ACR, albumin to creatinine ratio; eGFR, estimated glomerular filtration rate. AUC, area under the curve; 95% CI, 95% confidence intervals.

152.44 mg/g, there was no statistically significant increase in cardiac cause-specific mortality in the presence of microalbuminuria in RA patients compared with those with normal urinary albumin excretion. This suggests that in contrast to the general population, microalbuminuria in RA patients has little effect on CVD mortality within a certain range. We speculate that this may be due to the fact that renal disease was the primary cause of microalbumin excretion in RA patients, with a relatively weak correlation to cardiovascular events. However, the impact of ACR on CVD mortality increased dramatically over 300 mg/g, indicating that ACR may be an effective predictor of an adverse prognosis for cardiovascular events in people with RA to some extent. To access its prognostic efficacy, ROC curves were plotted and suggested that ACR hold a higher prognostic value for both all-cause mortality and CVD mortality in RA compared to eGFR, another indicator usually used for CKD assessment. Meanwhile, ACR testing is an affordable and non-invasive tool in clinical practice.

Microalbuminuria measurement has not been popularized in the clinic for patients with rheumatic diseases, despite the fact that ACR has been extensively utilized in the assessment and diagnosis of CKD (29, 30). The above advantages may allow us to choose ACR as one of the routine tests for RA patients. It helps early recognition of adverse prognosis especially for targeted populations. Our subgroup analysis suggested that RA patients characterized by the following features: female, other ethnicity, eGFR≥60 ml/min/1.73 m2, hypertension or hyperlipidemia share a higher CVD risk and seem to be targeted testing population. Other researchers found that patients with RA disease of more than 10 years, positive RF, positive ACPA and presence of extra articular manifestations are at a higher risk for CVD (31). ACR testing may be more necessary under those conditions. Based on the NHANES, this study covered over 1,000 RA patients and assessed the independent impact of urinary albumin excretion on the prognosis of adult RA patients in the United States. Our study not only revealed that the association between ACR and mortality in RA participants, also proposed that ACR can be considered as a regular marker for renal assessment and outcome prediction in RA. However, the current analysis still has some limitations. Firstly, RA data collected from NHANES belongs to questionnaire data, with a definition based on "What type of arthritis does it belong to". It may result in recall bias. Secondly, NHANES is still lacking for more refined statistics about RA specific antibodies such as anti-citrullinated protein antibody as a public database. Besides, a small amount of data on CVD mortality in the cohort may affect statistical analysis of association of ACR with adverse outcomes. Therefore, large prospective cohort studies based on more detailed clinical characteristics are still essential for further validating the correlation between ACR and the prognosis of RA patients.

5 Conclusion

After adjustment for relevant covariates including demographic, lifestyle and comorbidity factors, ACR was an important independent risk factor affecting the prognosis of adult RA patients. There was an increase in all-cause mortality in the groups with microalbuminuria or macroalbuminuria. In our investigation, ACR did not significantly correlate with cardiovascular death in RA patients with microalbuminuria. However, ACR did significantly correlate with cardiovascular death in cases of macroalbuminuria. Overall, ACR was closely related to the prognosis of RA patients and could be considered as a sensitive and independent indicator for physicians to predict the mortality especially CVD mortality in the process of diagnosis and treatment.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: The data underlying this article are available in NHANES (https://www.cdc.gov/nchs/nhanes/index.htm).

Ethics statement

The studies involving humans were approved by Institutional Review Board of the National Centre for Health Statistics. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

ZB: Investigation, Writing – original draft, Visualization. RS: Investigation, Supervision, Writing – review & editing. RW: Methodology, Writing – review & editing. YF: Writing – review & editing. XZ: Software, Validation, Writing – review & editing. CG: Supervision, Writing – review & editing. XL: Project administration, Writing – review & editing. CW: Funding acquisition, Methodology, Supervision, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by the National Natural Science Foundation of China (No. 81971543), the Four "Batches" Innovation Project of Invigorating Medical through Science and Technology of Shanxi Province (No. 2022XM05), and the Central Guidance Special Funds for Local Science and Technology Development (YDZJSX20231A061).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers | Frontiers in Immunology

TYPE Original Research
PUBLISHED 17 December 2024
DOI 10.3389/fimmu.2024.1493182

OPEN ACCESS

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RECEIVED 08 September 2024
ACCEPTED 26 November 2024
PUBLISHED 17 December 2024

CITATION
Wang X, Li B, Wei R, Hu B, Feng Y, Yang B, Rong S and Li B (2024) Development and validation of a nomogram for predicting the risk of obstructive coronary artery disease in rheumatoid arthritis patients based on LDL-C, Th17 cells, and IL-17.
Front. Immunol. 15:1493182.
doi: 10.3389/fimmu.2024.1493182

Development and validation of a nomogram for predicting the risk of obstructive coronary artery disease in rheumatoid arthritis patients based on LDL-C, Th17 cells, and IL-17

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Objective: This study aims to develop and validate a nomogram model for predicting the risk of obstructive coronary artery disease (CAD) in patients with rheumatoid arthritis (RA), incorporating low-density lipoprotein cholesterol (LDL-C), Th17 cells, and interleukin (IL)-17 levels. The proposed model seeks to enable personalized cardiovascular risk assessment for RA patients, thereby optimizing clinical management strategies.

Methods: A total of 120 patients with rheumatoid arthritis (RA) who were treated at the Second Hospital of Shanxi Medical University between January 2019 and September 2023 were enrolled in this study. Based on coronary angiography results, patients were categorized into the RA-obstructive CAD group and the RA-non-obstructive CAD group. Additionally, 53 healthy controls (HC group) were included. Clinical characteristics, laboratory parameters, peripheral blood lymphocyte subsets, and cytokine levels were collected for analysis. Univariate logistic regression was used to identify risk factors associated with RA-obstructive CAD. These variables were further refined using a random forest model for optimal selection. Finally, multivariate logistic regression analysis was performed with the selected variables to develop a nomogram model, which was subsequently validated to assess its performance.

Results: Compared with the RA-non-obstructive CAD group, the RA-obstructive CAD group demonstrated significantly elevated levels of immune cell subsets, such as Th17 cells, and cytokines, including IL-17, IL-2, and IL-4, along with a reduction in Treg cells. (2) In the training cohort, univariate and multivariate logistic regression analyses identified LDL-C (OR = 0.04, P < 0.001), Th17 cells (OR = 0.76, P = 0.005), and IL-17 (OR = 0.75, P = 0.001) as independent risk factors for obstructive CAD in RA patients. Subsequently, a predictive nomogram model for RA-obstructive CAD risk was developed based on these indicators, incorporating LDL-C, Th17 cells, and IL-17.

Conclusion: This study developed a predictive nomogram for RA-obstructive CAD by combining traditional risk factors, such as LDL-C, with immune

biomarkers Th17 and IL-17. The model demonstrated robust predictive accuracy, enabling more precise risk assessment of CAD in RA patients. It offers clinicians a valuable tool for advancing cardiovascular risk management in RA, underscoring its significant potential for clinical application.

KEYWORDS

rheumatoid arthritis, obstructive coronary artery disease, nomogram, LDL-C, Th17 cells, IL-17

1 Introduction

Rheumatoid arthritis (RA) is a prototypical immune-mediated autoimmune disease, primarily characterized by chronic synovitis and vasculitis, which can ultimately lead to joint dysfunction. Beyond local joint damage, RA induces systemic chronic inflammation, significantly increasing the risk of atherosclerosis and obstructive coronary artery disease (CAD) (1, 2). Compared to the general population, RA patients experience a 48% higher incidence and a 50% higher mortality rate from cardiovascular disease (CVD) (3, 4). Even after controlling for traditional cardiovascular risk factors such as smoking, hypertension, and hyperlipidemia, approximately 50% of RA patients still develop atherosclerosis (5–7). Therefore, the specific predictors of obstructive CAD risk in RA remain insufficiently defined.

Recent studies have elucidated the pivotal role of immune dysregulation and persistent inflammation in the pathogenesis of both RA and obstructive CAD (8, 9). In RA, an imbalance in peripheral Th17/Treg cell populations, characterized by an increase in pro-inflammatory Th17 cells and a reduction in Treg cell function, plays a critical role in the development of atherosclerosis (10). Th17 cells primarily modulate immune responses through the secretion of cytokines such as IL-17, IL-21, and IL-22, with IL-17 playing a central role in the inflammatory processes associated with RA and obstructive CAD (11–14). IL-17 not only activates synovial cells to secrete inflammatory mediators, exacerbating joint inflammation (15, 16), but also induces the production of pro-inflammatory factors by fibroblasts and endothelial cells, stimulates smooth muscle cell proliferation, and promotes arterial wall inflammation, thereby driving the progression of atherosclerosis (15). Treg cells, which are critical in maintaining immune tolerance and suppressing excessive inflammation, are often dysfunctional in RA patients, leading to immune imbalance and promoting the overactivation of Th17 cells, further exacerbating inflammatory responses (17). The reduction of Treg cells not only intensifies joint inflammation but also diminishes their protective role in endothelial cells, thereby increasing vascular inflammation (18). The interplay between excessive Th17 activation and impaired Treg function represents a key driver of vascular pathology in both RA and obstructive CAD, forming a complex immunological network that underpins their pathogenesis.

Despite the established association between immune dysregulation, inflammation, and increased cardiovascular risk in RA, these factors have not been adequately incorporated into most existing cardiovascular risk assessment tools. Current models, such as the Framingham Risk Score (FRS) and SCORE, fail to sufficiently account for the impact of inflammation and immune imbalance on atherosclerosis, often underestimating the CAD risk in RA patients (19, 20). Although the ERS-RA risk score proposed by Solomon et al. (21) combines traditional cardiovascular risk factors with RA-related markers (e.g., inflammation, disease duration, and corticosteroid use), its predictive performance does not surpass that of the FRS. Therefore, there is a pressing need for a dedicated obstructive CAD risk prediction model specifically tailored for RA patients.

This study aims to analyze the clinical characteristics and immunological differences in RA patients with obstructive CAD, integrating serum lipid profiles, immune cell populations, and cytokine levels to develop and validate a personalized cardiovascular risk prediction nomogram. This model is designed to enable clinicians to provide more precise cardiovascular risk assessments and tailored therapeutic strategies for RA patients. By facilitating early identification of high-risk individuals and implementing effective preventive measures, the model has the potential to reduce cardiovascular events, enhance treatment outcomes, and ultimately improve patient quality of life and survival. These findings hold significant clinical value for optimizing patient care.

2 Materials and methods

2.1 Clinical characteristics

This study included 120 patients diagnosed with RA who attended the Rheumatology Department of the Second Hospital of Shanxi Medical University between January 2019 and September 2023. Based on prior coronary angiography results, patients were divided into two groups: 60 RA patients with obstructive coronary

artery disease (RA-obstructive CAD) and 60 RA patients without obstructive CAD (RA-non-obstructive CAD). No significant differences were observed between the two groups in terms of age, sex, or disease duration. Additionally, 53 healthy individuals undergoing routine health examinations at our hospital's physical examination center were included as the healthy control group (HC group). All RA patients met the 2010 classification criteria for RA established by the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) (22).

Inclusion criteria for the RA-obstructive CAD group were as follows: patients who underwent coronary angiography due to chest discomfort, chest pain, or abnormal electrocardiogram findings, with a diagnosis of CAD based on the 2016 American Heart Association guidelines (23). Exclusion criteria included the presence of other autoimmune diseases, coronary branch lesions (e.g., lesions in the diagonal branch of the left anterior descending artery, obtuse marginal branch of the left circumflex artery, or posterior descending branch of the right coronary artery), left main coronary artery disease, a history of non-ST-elevation myocardial infarction (NSTEMI) or ST-elevation myocardial infarction (STEMI), other cardiovascular diseases (e.g., heart failure, congenital heart disease, or valvular heart disease), malignancies, infections, or severe dysfunction of other organs.

Inclusion criteria for the RA-non-obstructive CAD group were as follows: patients presenting with chest discomfort, chest pain, or abnormal electrocardiogram findings, with coronary angiography confirming the absence of significant stenosis or mild stenosis (<50%) consistent with the expert consensus of the European Association of Percutaneous Cardiovascular Interventions (24). Exclusion criteria mirrored those of the RA-obstructive CAD group, including other autoimmune diseases, coronary branch lesions (e.g., lesions in the diagonal branch of the left anterior descending artery, obtuse marginal branch of the left circumflex artery, or posterior descending branch of the right coronary artery), left main coronary artery disease, malignancies, infections, severe cardiovascular diseases, and significant dysfunction of other organs.

Exclusion criteria for the HC group included: autoimmune diseases; cardiovascular diseases (e.g., coronary artery disease, heart failure, hypertension, congenital heart disease); metabolic diseases; cancers; infections or patients undergoing antimicrobial therapy; and individuals with abnormal liver or kidney function.

This study was approved by the Medical Ethics Committee of the Second Hospital of Shanxi Medical University (approval number [2024]YX-292). Clinical and laboratory data were retrospectively collected from the clinical database. Clinical characteristics included age, sex, body mass index (BMI), traditional cardiovascular risk factors, clinical cardiology diagnoses, and medication usage. Laboratory tests included the Disease Activity Score 28 (DAS28), rheumatoid factor (RF), anti-citrullinated protein antibody (Anti-CCP), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), routine blood count, liver and kidney function tests, lipid profile, immunoglobulins, absolute counts and frequencies of peripheral blood lymphocyte subsets, and cytokine levels.

2.2 Detection of the absolute and relative counts of peripheral blood lymphocyte subsets by using flow cytometry

Whole blood was collected from all patients using heparinized tubes, and peripheral blood mononuclear cells (PBMCs) were isolated by density gradient centrifugation with Ficoll-Hypaque. Centrifugation conditions were set at room temperature for 20–30 minutes at 800–1,000 × g, and the resulting PBMCs were resuspended to an appropriate concentration. Lymphocyte subsets in peripheral blood were then sequentially stained with fluorescence-labeled monoclonal antibodies. Specifically, anti-CD3-FITC, anti-CD8-PE, anti-CD45-PercP, and anti-CD4-APC were used to stain T lymphocytes; anti-CD3-FITC, anti-CD16 +CD56-PE, anti-CD45-PercP, and anti-CD19-APC were used for B lymphocytes and NK cells; anti-CD4-FITC and anti-IFN-γ-APC for Th1 cells; anti-CD4-FITC and anti-IL-4-PE for Th2 cells; anti-CD4-FITC and anti-IL-17A-PE for Th17 cells; and anti-CD4-FITC, anti-CD25-APC, and anti-FOXP3-PE for Treg cells. All fluorescence-labeled monoclonal antibodies used in this study were purchased from BD Biosciences (Franklin Lakes, NJ, USA) and the experiments were conducted according to the manufacturer's instructions. Absolute and relative counts of peripheral blood lymphocyte subsets were determined using a FACSCalibur flow cytometer and BD Multitest software (BD Biosciences, Franklin Lakes, NJ, USA).

2.3 Cytokine levels assessed by bead-based multiplex immunoassay

Blood samples from all patients were centrifuged within 1 hour of collection to obtain serum, which was stored at -20°C until analysis, with a maximum storage time of 96 hours. Serum were separated under the following centrifugation conditions: room temperature, 15-20 minutes, 1,500-2,000 × g. Serum levels of seven cytokines—interleukin (IL)-2, IL-4, IL-6, IL-10, IL-17, tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ)—were measured using a bead-based multiplex immunoassay. The Th1/Th2/Th17 cytokine detection kits were purchased from Cellgene Biotechnology Co., Ltd. (Jiangxi, China) and assays were conducted following the manufacturer's protocol. Cytokine concentrations (pg/mL) were determined using the BioPlex 200 system, and data analysis was performed with BioPlex Manager software.

2.4 Statistical analysis

In this study, the normality and homogeneity of variance of the data were first assessed using the Kolmogorov-Smirnov test and Levene's test. For data with a normal distribution, means ± standard deviations (SD) were used, and between-group comparisons were performed using independent sample t-tests. For data that were not normally distributed, medians (interquartile range, IQR) were used

for description, and Kruskal-Wallis H tests were applied for between-group comparisons. Categorical data were expressed as frequencies, and between-group comparisons were performed using chi-square tests. To adjust for the effects of covariates, analysis of covariance (ANCOVA) was used to test the differences between groups. All statistical analyses were conducted using SRA 27.0 software (SRA Inc., Chicago, IL, USA).

The study population of 120 RA patients was randomly divided into a training group (96 patients) and a validation group (24 patients) in an 8:2 ratio using a random number table. First, univariate logistic regression was performed to identify risk factors associated with RA complicated by obstructive CAD, and statistically significant variables were incorporated into a random forest model. Variables were ranked according to their mean decrease in Gini (MDG) values from the random forest model, and variables were progressively selected for multivariate logistic regression analysis based on the lowest out-of-bag error estimate (OBB). A nomogram prediction model was constructed based on the identified risk factors. The discriminative ability of the model was evaluated using the area under the receiver operating characteristic curve (AUC). Calibration was verified using a calibration curve and the Hosmer-Lemeshow test, while clinical utility was assessed via decision curve analysis (DCA). All data analyses and visualizations were performed using R software (version 3.6.3, R Foundation for Statistical Computing, Vienna, Austria).

3 Results

3.1 Comparison of baseline characteristics, clinical features, and laboratory data among RA-obstructive CAD, RA-non-obstructive CAD, and HC groups

This study included a total of 120 patients (42 males, 78 females; mean age 66.37 ± 10.24 years) and 53 healthy controls (17 males, 36 females; mean age 48.19 ± 11.87 years). The baseline demographic information, clinical features, and laboratory data for all participants are summarized in Table 1. Among the RA-obstructive CAD and RA-non-obstructive CAD groups, some patients received medication, including nonsteroidal anti-inflammatory drugs (NSAIDs), conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), biologic agents (bDMARDs), and corticosteroids (GC), with no significant differences between the two groups. Additionally, some RA-obstructive CAD patients were treated with statins, antiplatelet agents, β-blockers, renin-angiotensin-aldosterone system inhibitors, angiotensin-converting enzyme inhibitors, and other vasodilators.

Compared to the HC group, both the RA-obstructive CAD and RA-non-obstructive CAD groups exhibited significantly elevated ESR and CRP levels, with the RA-obstructive CAD group showing notably higher CRP levels than the RA-non-obstructive CAD group. Regarding serum lipoproteins, triglyceride (TG) levels were lower and high-density lipoprotein cholesterol (HDL-C) levels were higher in the HC group. The RA-obstructive CAD group displayed higher levels of low-density lipoprotein cholesterol (LDL-C) and HDL-C compared to the RA-non-obstructive CAD group. Furthermore, serum immunoglobulin A (IgA) and immunoglobulin G (IgG) levels were lower in the HC group, while the RA-obstructive CAD group exhibited elevated IgA and IgG levels relative to the RA-non-obstructive CAD group. No significant differences were observed in other parameters (Supplementary Table 1).

3.2 Differences in peripheral blood lymphocyte subsets and CD4+ T cell levels between the RA-obstructive CAD and RA-non-obstructive CAD groups

We compared the quantities and percentages of peripheral blood lymphocyte subsets and CD4+ T cell subsets between the two RA groups and the HC group. Compared with the HC group, the total T cell count ($P<0.001$) and percentage ($P<0.001$), total B cell count ($P<0.001$) and percentage ($P<0.001$), CD4+ T cell count ($P<0.001$) and percentage ($P<0.001$), CD8+ T cell count ($P<0.001$) and percentage ($P=0.032$), Th1 cell count ($P<0.001$), Th2 cell count ($P=0.003$), Th17 cell count ($P<0.001$) and percentage ($P<0.001$), Th1/Th2 ratio ($P=0.006$), and Th17/Treg ratio ($P<0.001$) were all significantly elevated. The NK cell percentage ($P<0.001$) and Treg cell count ($P<0.001$) and percentage ($P<0.001$) in the HC group were significantly higher than those in both RA groups (Tables 2A, B; Figures 1A, B).

Additionally, we compared the peripheral blood lymphocyte subsets and CD4+ T cell subsets between the RA-obstructive CAD and RA-non-obstructive CAD groups. We found that the total T cell count ($P<0.001$), CD4+ T cell count ($P<0.001$), CD8+ T cell count ($P<0.001$), Th17 cell count ($P<0.001$) and percentage ($P=0.019$), Th1/Th2 ratio ($P=0.032$), and Th17/Treg ratio ($P<0.001$) were significantly higher in the RA-obstructive CAD group, while the Treg cell count ($P=0.011$) and percentage ($P<0.001$) were lower compared to the RA-non-obstructive CAD group (Tables 2A, B; Figures 1A, B; Supplementary Table 2).

3.3 Differences in cytokine levels between the RA-obstructive CAD and RA-non-obstructive CAD groups

We compared cytokine levels between the RA groups and the HC group. Compared to the HC group, RA patients exhibited significantly elevated levels of IL-2 ($P<0.001$), IL-4 ($P<0.001$), IL-6 ($P<0.001$), IL-10 ($P<0.001$), IL-17 ($P<0.001$), IFN-γ ($P<0.001$), and TNF-α ($P<0.001$) (Table 3; Figure 2; Supplementary Table 2).

Additionally, we compared cytokine levels between the RA-obstructive CAD and RA-non-obstructive CAD groups. The RA-obstructive CAD group exhibited significantly higher levels of cytokines, including IL-2 ($P<0.001$), IL-4 ($P<0.001$), IL-6 ($P=0.037$), IL-10 ($P=0.001$), IL-17 ($P<0.001$), IFN-γ ($P<0.001$), and TNF-α ($P<0.001$) (Table 3; Figure 2; Supplementary Table 2).

10.3389/fimmu.2024.1493182

TABLE 1 Clinical Characteristics of the RA-Obstructive CAD, RA-Non-Obstructive CAD, and HC Groups.

	RA-Obstructive CAD (n=60)	RA-Non-Obstructive CAD (n=60)	HC (n=53)	*P*
Demographics				
Age (Years)[a]	66.92 ± 9.09	65.82 ± 11.33	48.19 ± 11.87	<0.001***
Male/n (%)[b]	22 (36.7%)	20 (33.3%)	17 (32.1%)	0.196
Female n (%)[b]	38 (63.3%)	40 (66.7%)	36 (67.9%)	
BMI[a]	23.53 ± 4.66	23.33 ± 3.79	22.66 ± 3.96	0.353
Course of disease (month)[c]	66.00 (50.25-78.75)	63.00 (48.25-77.00)	–	0.466
Traditional risk factors				
Smoking n (%)[b]	34 (56.7%)	30 (50.0%)	29 (54.7)	0.323
Drinking n (%)[b]	15 (25.0%)	10 (16.7%)	6 (11.3%)	<0.001***
Hypertension n (%)[b]	14 (23.3%)	13 (21.7%)	–	0.827
Diabetes n (%)[b]	11 (18.3%)	6 (10.0%)	–	0.191
Clinical cardiologic diagnosis				
Stable angina n (%)[b]	32 (53.3%)	–	–	–
Unstable angina n (%)[b]	28 (46.7%)	–	–	–
Current use of medication				
NSAIDs n (%)[b]	43 (71.7%)	46 (76.7%)	–	0.532
csDMARDs n (%)[b]	45 (75.0%)	47 (78.3%)	–	0.666
bDMARDs n (%)[b]	1 (1.7%)	2 (3.3%)	–	0.559
GC n (%)[b]	40 (66.7%)	40 (68.3%)	–	0.845
Statins n (%)[b]	58 (96.7%)	–	–	–
Anti-platelet drug n (%)[b]	57 (95.0%)	–	–	–
Beta-blockers n (%)[b]	18 (30.0%)	–	–	–
ACEI/ARBs n (%)[b]	5 (8.3%)	–	–	–
Coronary-expansion drugs n (%)[b]	17 (28.3%)	–	–	–
Laboratory Characteristics				
DAS 28[c]	6.58 (6.10-7.04)	6.52 (6.17-6.86)	–	0.442
RF (U/mL)[c]	70.70 (48.93-106.50)	59.62 (40.00-98.70)	–	0.436
Anti-CCP (U/mL)[c]	641.17 (323.34-841.00)	525.60 (278.95-780.35)	–	0.228
ESR (mm/h)[c]	38.00 (18.00-69.00)	25.50 (12.75-81.25)	9.00 (7.00-14.00)	<0.001***
CRP (mg/L)[c]	12.56 (3.28-42.90)	3.26 (1.52-9.51)	1.32 (0.85-2.32)	<0.001***
Complete blood count				
WBC ($*10^9$/L)[c]	6.97 (5.54-8.23)	7.19 (5.28-8.57)	6.74 (4.78-7.60)	0.072
RBC ($*10^{12}$/L)[c]	4.14 (3.78-4.57)	4.21 (3.76-4.60)	4.23 (3.98-4.50)	0.959
Hb (g/L)[c]	121.50 (111.50-136.75)	123.50 (107.25-138.00)	123.00 (116.50-129.00)	0.897
PLT ($*10^9$/L)[c]	266.00 (203.25-322.50)	252.50 (204.25-295.25)	245.00 (158.50-287.00)	0.093
LY ($*10^9$/L)[c]	1.51 (1.06-1.90)	1.44 (1.18-1.75)	1.26 (1.15-1.70)	0.521
MONO ($*10^9$/L)[c]	0.51 (0.35-0.66)	0.45 (0.36-0.57)	0.43 (0.37-0.48)	0.079
NEUT ($*10^9$/L)[c]	5.26 (3.99-6.47)	4.70 (3.66-6.28)	4.91 (3.48-5.43)	0.050

(Continued)

TABLE 1 Continued

	RA-Obstructive CAD (n=60)	RA-Non-Obstructive CAD (n=60)	HC (n=53)	*P*
Liver Function Test				
ALT (U/L)[c]	15.85 (10.23-19.18)	13.60 (9.53-18.70)	13.80 (9.40-17.25)	0.218
AST (U/L)[c]	18.20 (13.85-22.65)	18.65 (15.85-20.90)	20.08 (16.30-22.65)	0.991
TBIL (μmol/L)[c]	10.30 (8.58-13.45)	9.80 (8.03-13.55)	9.70 (8.10-11.95)	0.336
DBIL (μmol/L)[c]	2.10 (1.70-3.25)	2.10 (1.50-2.60)	2.10 (1.50-2.95)	0.481
IBIL (μmol/L)[c]	8.15 (6.83-11.08)	7.75 (6.57-10.95)	7.70 (6.10-9.25)	0.284
CHOL (mmol/L)[c]	3.91 (3.24-4.75)	3.92 (3.21-4.43)	3.85 (3.42-4.41)	0.896
TG (mmol/L)[c]	1.13 (0.87-1.66)	1.17 (0.90-1.51)	1.02 (0.82-1.31)	0.044*
HDL-C (mmol/L)[c]	1.24 (1.06-1.51)	1.08 (0.90-1.36)	1.28 (1.15-1.44)	<0.001***
LDL-C (mmol/L)[c]	3.11 (2.08-4.44)	1.53 (1.18-2.11)	1.63 (1.23-2.13)	<0.001***
Kidney Function Test				
BUN (mmol/L)[c]	5.35 (4.33-6.40)	5.80 (4.70-6.90)	5.30 (4.35-6.30)	0.357
Cr (μmol/L)[c]	56.00 (47.25-62.00)	58.00 (51.75-65.00)	54.00 (47.50-60.50)	0.081
UA (μmol/L)[c]	252.50 (188.75-308.00)	259.00 (215.00-313.25)	250.00 (221.00-276.00)	0.197
Immunoglobulin				
IgA (g/L)[c]	2.89 (2.58-4.07)	2.08 (1.64-2.84)	1.92 (1.22-2.37)	<0.001***
IgG (g/L)[c]	12.57 (11.37-14.80)	11.38 (10.28-13.07)	11.29 (9.23-14.38)	0.008**
IgM (g/L)[c]	1.01 (0.69-1.54)	1.09 (0.61-1.55)	0.99 (0.62-1.26)	0.366

a Date with mean ± standard deviation.
b Data with number (n)/percentage (%).
c Date with median and 25th and 75th percentiles.
BMI, Body mass index; NSAIDs, Nonsteroidal antiinflammatory drugs; csDMARDs, Conventional synthetic disease-modifying antirheumatic drugs; bDMARD, Biological disease-modifying antirheumatic drug; GC, Glucocorticoid; ACEI, Angiotensin-converting enzyme inhibitors; ARB, Angiotensin receptor blockers; DAS28, Disease activity score 28; RF, Rheumatoid factor; Anti-CCP, Anti-cycliccitrullinated peptide; ESR, Erythrocyte sedimentation rate; CRP, C-reactive protein; WBC, White blood cell; RBC, Red blood cell; Hb, Hemoglobin; PLT, Platelet; LY, Lymphocyte; MONO, Monocyte; NEUT, Neutrophils; ALT, Alanine transaminase; AST, Aspartic transaminase; TBIL, Total bilirubin; DBIL, Direct bilirubin; IBIL, Indirect bilirubin; CHOL, Cholesterol; TG, Triglycerides; HDL-C, High density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; BUN, Blood urea nitrogen; Cr, Creatinine; UA, Uric acid; IgA, Immunoglobulin A; IgG, Immunoglobulin G; IgM, Immunoglobulin M.*P<0.05, **P<0.01, ***P<0.001.

3.4 Development of a personalized prediction model for RA patients with obstructive CAD

In this study, 120 RA patients were randomly assigned to a training group (96 patients) and a validation group (24 patients). No significant differences were observed between the two groups in terms of clinical data, laboratory results, and peripheral blood lymphocyte subsets (P>0.05). To identify distinguishing factors between the RA-obstructive CAD and RA-non-obstructive CAD groups, univariate logistic regression analysis was performed on clinical characteristics, laboratory markers, peripheral blood lymphocyte subsets, CD4+ T cell subsets, and cytokine levels in the training group. The analysis revealed significant differences in CRP, uric acid (UA), HDL-C, LDL-C, IgA, CD4+ T cells, CD8+ T cells, Th17, Treg, Treg ratio, IL-2, IL-4, IL-17, IFN-γ, and TNF-α between the two groups (P<0.05)(Figure 3). These statistically significant variables were then input into a random forest model, and the importance of each variable was ranked based on the MDG (Figure 4A). Based on the ranking, random forest regression analysis was conducted, revealing that selecting 8 variables minimized the OBB (Figure 4B). Subsequently, the top 8 variables (LDL-C, IL-17, IgA, IL-4, Th17, CRP, IL-2, and IFN-γ) were entered into a stepwise multivariate logistic regression analysis. The results identified LDL-C, IL-17, and Th17 as significantly differing factors (Table 4). These variables were then incorporated into a risk prediction model for RA-obstructive CAD, resulting in the construction of nomogram prediction model 1 (Figure 4C). Considering that Th17 and IL-17 are not traditional CAD risk factors, they were excluded from the model, and prediction model 2 was subsequently developed. The predictive performance of both models was then compared.

3.5 Validation of the nomogram

After comparing the two prediction models, we found that model 1 had an AUC of 0.97, while model 2 had an AUC of 0.88, with a significant difference between them (p=0.003), indicating that model 1 outperformed model 2 in terms of discriminative

TABLE 2 Absolute counts and proportions of peripheral blood lymphocytes in the RA-Obstructive CAD, RA-Non-Obstructive CAD, and HC Groups.

(A)	RA-Obstructive CAD (n=60)	RA-Non-Obstructive CAD (n=60)	HC (n=53)	*p*
totalT (cells/μL)	1225.71 (970.23-1538.75)	939.48 (730.65-1216.34)	778.66 (548.75-1018.14)	<0.001***
totalB (cells/μL)	169.29 (96.90-304.63)	122.35 (85.17-216.37)	86.36 (58.00-121.82)	<0.001***
CD4+ T (cells/μL)	694.29 (595.83-962.43)	555.07 (362.68-771.16)	349.27 (180.89-530.56)	<0.001***
CD8+ T (cells/μL)	473.67 (368.32-568.12)	348.34 (238.52-467.11)	244.50 (145.35-349.55)	<0.001***
NK (cells/μL)	191.68 (142.79-275.42)	175.55 (90.61-284.70)	194.49 (138.39-295.09)	0.37
Th1 (cells/μL)	103.05 (65.18-154.31)	86.09 (50.35-135.44)	49.24 (21.37-92.39)	<0.001***
Th2 (cells/μL)	7.08 (5.00-12.02)	8.33 (5.70-13.17)	5.19 (3.35-8.79)	0.003**
Th17 (cells/μL)	11.53 (6.08-18.38)	7.33 (4.51-9.99)	4.43 (2.72-6.47)	<0.001***
Treg (cells/μL)	23.15 (11.85-32.90)	31.61 (17.15-42.36)	34.93 (25.53-48.16)	<0.001***
(B)	**RA-Obstructive CAD (n=60)**	**RA-Non-Obstructive CAD (n=60)**	**HC (n=53)**	***p***
T%	73.90 (65.68-80.55)	73.87 (65.81-78.14)	66.75 (61.62-73.59)	<0.001***
B%	10.69 (6.49-14.69)	10.78 (6.23-15.34)	7.78 (5.11-10.00)	<0.001***
CD4+ T%	42.93 (37.19-49.27)	41.78 (32.64-48.73)	33.23 (25.56-40.68)	<0.001***
CD8+ T%	26.97 (20.21-36.54)	25.15 (19.68-32.89)	22.56 (18.55-29.83)	0.032*
CD4+ T/CD8+ T	1.67 (1.11-2.25)	1.61 (1.11-2.18)	1.37 (1.09-1.90)	0.338
NK%	11.28 (8.52-17.39)	13.38 (7.75-20.49)	18.88 (14.60-26.01)	<0.001***
Th1%	15.95 (10.85-24.82)	15.31 (10.55-22.54)	14.21 (8.40-17.87)	0.081
Th2%	1.30 (0.86-1.67)	1.41 (1.12-1.75)	1.25 (0.81-1.64)	0.155
Th17%	1.55 (1.10-2.61)	1.25 (0.80-1.90)	1.07 (0.67-1.55)	<0.001***
Treg%	3.78 (2.88-4.75)	4.47 (3.79-5.86)	6.43 (5.19-9.62)	<0.001***
Th1/Th2	13.03 (8.10-20.80)	10.32 (6.23-16.88)	9.24 (5.87-13.35)	0.006**
Th17/Treg	0.40 (0.30-1.03)	0.25 (0.17-0.40)	0.20 (0.11-0.31)	<0.001***

Date with median and 25th and 75th percentiles.
T, T lymphocyte; B, B lymphocyte; NK, Natural killer cell; Th1, T-helper 1 cells; Th2, T-helper 2 cells; Th17, T-helper17 cells; Treg, Regulatory T cells. *P<0.05, **P<0.01, ***P<0.001.

ability (Figure 4D). To further evaluate the model's discriminatory power, we plotted the ROC curves for both groups. The results showed an AUC of 0.974 for the training group (Figure 4G) and an AUC of 0.896 for the validation group (Figure 4H). In both groups, the AUC exceeded 0.75, demonstrating the model's strong discriminative ability.

Additionally, we assessed the model's calibration by plotting calibration curves, which showed a high degree of alignment between the predicted and observed curves, suggesting robust calibration performance. Further, the Hosmer-Lemeshow test yielded a p-value of 0.827 (P>0.05) (Figure 4E), providing additional support for the model's excellent fit.

3.6 Clinical use

We then generated the DCA, which showed that the cut-off value (59.6%) obtained from the ROC analysis (Figure 4G) lies within the threshold probability range of the DCA curve. Further analysis indicated that, when the threshold probability for diagnosing obstructive CAD in RA patients was set at 59.6%, approximately 40 out of 100 RA patients at risk for obstructive CAD diagnosed using this model would benefit, without causing unnecessary harm to other patients (Figure 4F).

4 Discuss

In this study, a nomogram model developed from electronic medical record (EMR) data integrates traditional LDL-C with emerging immune biomarkers, Th17 and IL-17, to provide a novel approach for assessing obstructive CAD risk in patients with RA. The findings reveal significant differences in multiple clinical and laboratory parameters, immune cell composition, and cytokine levels between the RA-obstructive CAD and RA-non-obstructive CAD groups, particularly in the elevated inflammatory markers CRP, Th17 cells, and IL-17. These results align with existing literature, further emphasizing the close link between

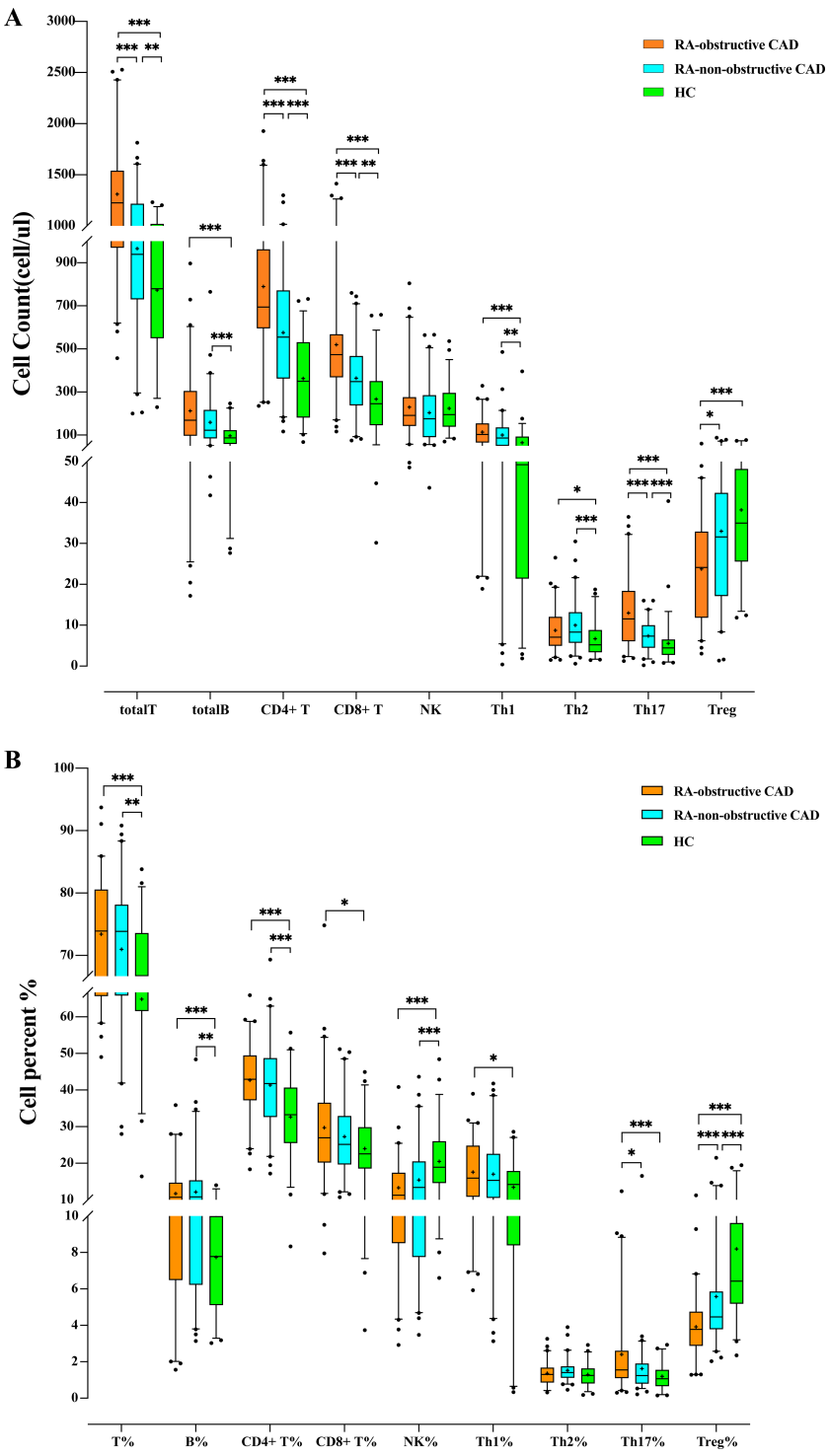

FIGURE 1
(A) Comparison of peripheral blood lymphocyte subsets and CD4+T cell counts among each study group. **(B)** Comparison of the proportion of peripheral blood lymphocyte subsets and CD4+ T cells among each study group. (*p < 0.05, **p < 0.01, ***p < 0.001).

immune dysregulation in RA patients and heightened cardiovascular risk (25, 26).

Compared to traditional cardiovascular risk assessment models, our proposed model, based on immune biomarkers, places greater emphasis on the evaluation of immune-related risk factors. Although classical tools, such as the Framingham Risk Score, are widely used for cardiovascular disease risk prediction (27), these models primarily rely on conventional factors such as lipid levels and blood pressure, and fail to adequately account for the unique immune-inflammatory state in RA patients. RA patients often exist in a state of chronic low-grade inflammation, which not only exacerbates joint damage but also significantly elevates the risk of

TABLE 3 Cytokine Levels in Peripheral Blood of the RA-obstructive CAD, RA-non-obstructive CAD, and HC Groups.

	RA-obstructive CAD (n=60)	RA-non-obstructive CAD (n=60)	HC (n=53)	*p*
IL-2	2.83 (2.18-4.56)	2.07 (1.08-2.72)	1.28 (1.05-1.54)	<0.001***
IL-4	4.01 (2.53-5.93)	1.93 (1.37-3.30)	1.57 (1.23-2.41)	<0.001***
IL-6	12.21 (6.99-29.91)	7.47 (5.11-19.68)	3.38 (2.39-4.87)	<0.001***
IL-10	5.41 (3.86-7.72)	4.34 (2.74-5.40)	2.71 (1.98-3.42)	<0.001***
IL-17	11.67 (5.28-26.56)	3.26 (0.36-5.88)	1.78 (0.28-3.52)	<0.001***
IFN-γ	4.35 (3.03-6.72)	2.69 (2.02-3.81)	2.64 (1.74-3.27)	<0.001***
TNF-α	3.72 (2.64-6.31)	2.51 (1.76-4.67)	1.73 (1.35-2.69)	<0.001***

Date with median and 25th and 75th percentiles.
IL-2, Interleukin-2; IL-4, Interleukin-4; IL-6, Interleukin-6; IL-10, Interleukin-10; IL-17, Interleukin-17; INF-γ, Interferon-γ; TNF-α, Tumor necrosis factor-α.***P<0.001.

cardiovascular disease. In this context of immune dysregulation, the predictive capability of traditional models may be limited.This study demonstrates that elevated levels of LDL-C, IL-17, and Th17 cells are closely associated with the occurrence of obstructive CAD in RA patients, highlighting the potential value of these immune biomarkers in assessing the risk of RA-obstructive CAD. Although a direct comparison with traditional risk assessment models was not conducted in this study, the identification of the unique role of immune biomarkers may help address the limitations of conventional models. Incorporating immune biomarkers into cardiovascular risk assessment could provide a more comprehensive tool for clinical use, particularly in the RA patient population, thereby enhancing prediction accuracy.

In this study, immune cell analysis revealed that in the RA-obstructive CAD group, T cells, CD4+ T cells, CD8+ T cells, Th17 cells, and the Th1/Th2 and Th17/Treg ratios were significantly elevated, while the number of Treg cells was reduced. These findings suggest that immune imbalance may play a promoting role in the progression of RA-obstructive CAD. Additionally, we observed increased levels of various pro-inflammatory cytokines (such as IL-2, IL-4, IL-6, IL-10, IL-17, IFN-γ, and TNF-α) in the RA-obstructive CAD group, which are closely associated with sustained inflammatory responses and exacerbated cardiovascular damage. Compared to healthy controls, both the RA-non-obstructive CAD and RA-obstructive CAD groups exhibited significantly elevated ESR and CRP levels, with particularly higher CRP levels in the RA-obstructive CAD group. These findings

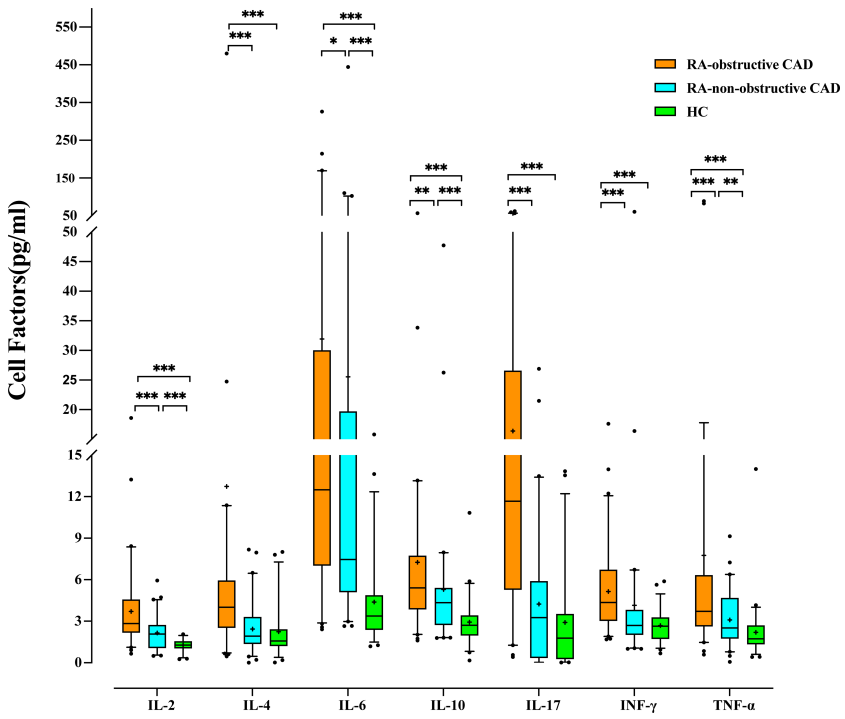

FIGURE 2
Comparison of Cytokine levels among each study group. (*p < 0.05, **p < 0.01, ***p < 0.001).

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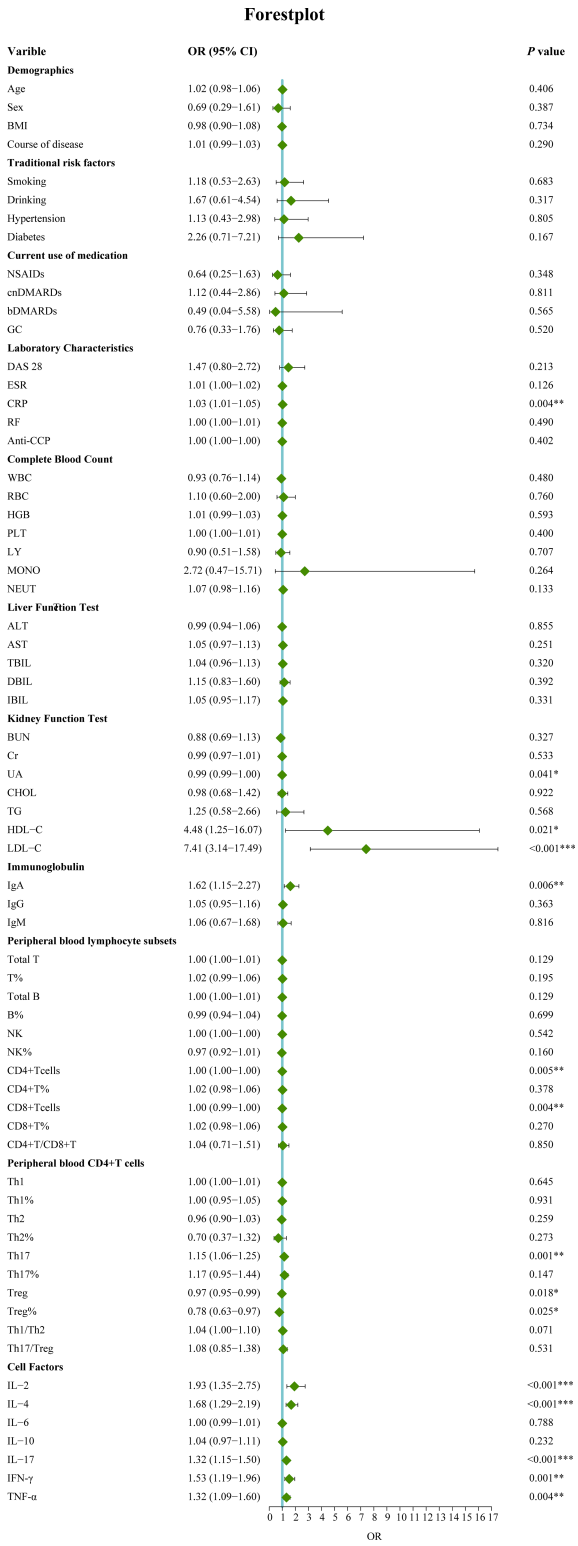

FIGURE 3
Univariate logistic regression analysis of factors associated with obstructive CAD in RA patients. (*p < 0.05, **p < 0.01, ***p < 0.001). OR, Odds ratio; 95%CI, 95% confidence interval; BMI, Body mass index; NSAIDs, Nonsteroidal antiinflammatory drugs; csDMARDs, Conventional synthetic disease-modifying antirheumatic drugs; bDMARD, Biological disease-modifying antirheumatic drug; GC, Glucocorticoid; DAS28, Disease activity score 28; ESR, Erythrocyte sedimentation rate; CRP, C-reactive protein; RF, Rheumatoid factor; Anti-CCP, Anti-cyclicitrullinated peptide; WBC, White blood cell; RBC, Red blood cell; Hb, Hemoglobin; PLT, Platelet; LY, Lymphocyte; MONO, Monocyte; NEUT, Neutrophils; ALT, Alanine transaminase; AST, Aspartic transaminase; TBIL, Total bilirubin; DBIL, Direct bilirubin; IBIL, Indirect bilirubin; CHOL, Cholesterol; TG, Triglycerides; HDL-C, High density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; BUN, blood urea nitrogen; Cr, Creatinine; UA, Uric acid; IgA, Immunoglobulin A; IgG, Immunoglobulin G; IgM, Immunoglobulin M. T, T lymphocyte; B, B lymphocyte; NK, Natural killer cell; Th1, T-helper 1 cells; Th2, T-helper 2 cells; Th17, T-helper17 cells; Treg, Regulatory T cells.IL-2, Interleukin-2; IL-4, Interleukin-4; IL-6, Interleukin-6; IL-10, Interleukin-10; IL-17, Interleukin-17; INF-γ, Interferon-γ; TNF-α, Tumor necrosis factor-α.

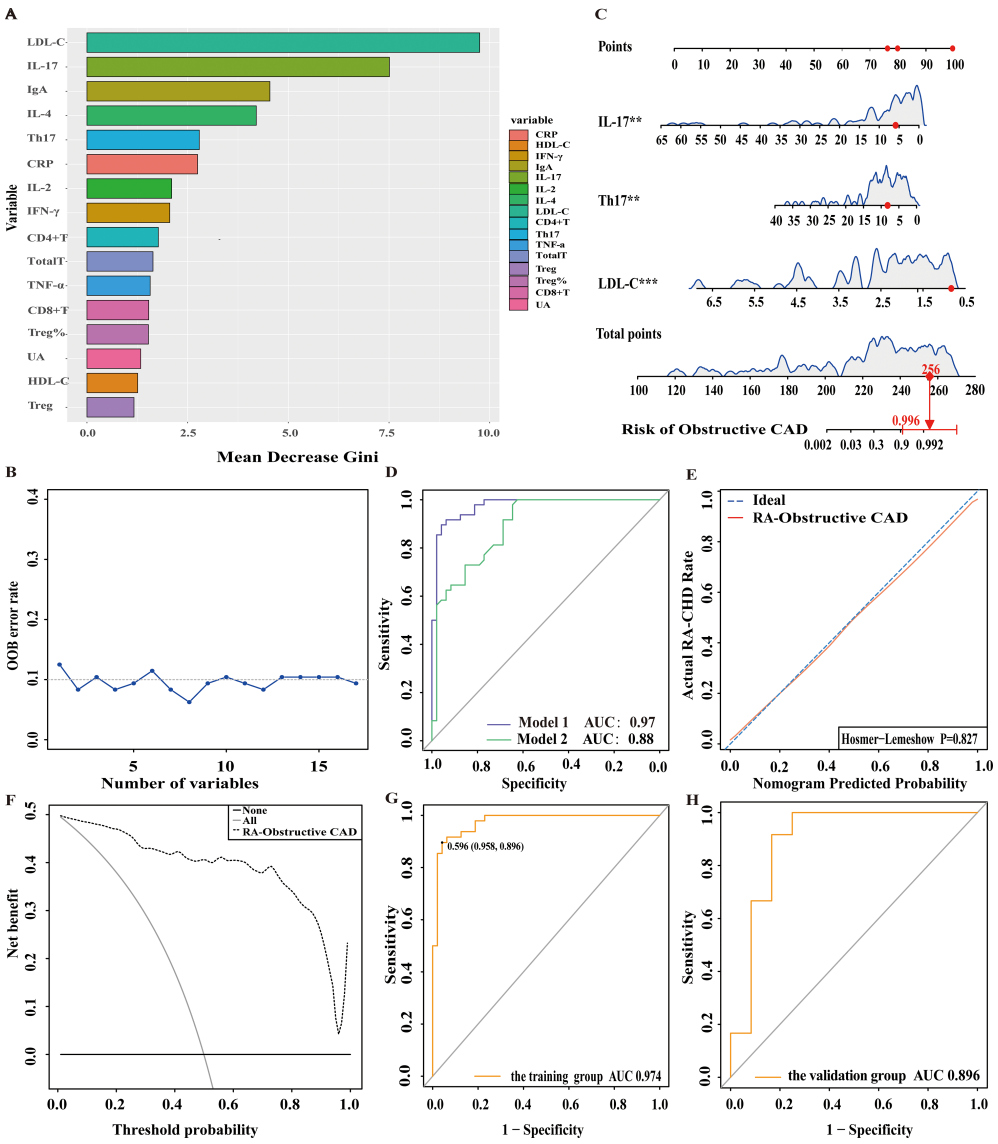

FIGURE 4
Nomogram for predicting and assessing the risk of obstructive CAD in RA patients. **(A)** Ranking of risk factors for obstructive CAD development in RA patients by importance. **(B)** The relationship between the number of predictive indicators for obstructive CAD and the out-of-bag (OOB) error rate. **(C)** Nomogram for predicting the risk of obstructive CAD in RA patients. **(D)** Receiver operating characteristic (ROC) curves for predicting obstructive CAD risk in RA patients. Model 1: Nomogram incorporating LDL-C, Th17, and IL-17; Model 2: Nomogram incorporating LDL-C as the sole predictor. **(E)** Calibration curve for obstructive CAD risk prediction in RA patients. **(F)** DCA for predicting obstructive CAD risk in RA patients. **(G)** ROC curve of the nomogram for predicting obstructive CAD risk in the training cohort. **(H)** ROC curve of the nomogram for validating obstructive CAD risk in the external validation cohort.

TABLE 4 Multivariate logistic regression analysis of factors associated with obstructive CAD in RA patients.

	Model 1		Model 2		*p*
	OR (95% CI)	*p*	OR (95% CI)	*p*	
LDL-C	11.28 (3.59-75.97)	0.003**	7.41 (3.14-17.49)	<0.001***	0.003**
Th17	1.28 (1.09-1.60)	0.003**	–	–	
IL-17	1.28 (1.07-1.63)	0.006**	–	–	
AUC	0.97 (0.94-1.00)		0.88 (0.81-0.94)		

OR, Odds ratio; 95%CI, 95% Confidence interval; LDL-C, Low-density lipoprotein cholesterol; Th17, T-helper17 cells; IL-17, Interleukin-17; AUC, Area under the ROC curve. **p<0.01, ***P<0.001.

further confirm the elevated systemic inflammation in RA-obstructive CAD patients, which may contribute to the increased incidence of cardiovascular disease.

Th17 cells and their secreted cytokine IL-17 play a crucial role in the inflammatory response and the development of atherosclerosis. Previous studies have shown that IL-17 is closely associated with atherosclerosis (28), particularly in immune-mediated cardiovascular diseases. Th17 cells secrete cytokines such as IL-17, which, by releasing chemokines like CXCL1, CXCL2, and CXCL8, recruits neutrophils and monocytes to sites of atherosclerotic lesions. IL-17 also stimulates macrophages to produce pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1β (29–31). Furthermore, IL-17 can promote the production of matrix metalloproteinases (MMPs) in fibroblasts, endothelial cells, and epithelial cells (31, 32). Through these mechanisms, IL-17 enhances endothelial inflammation, increases arterial wall permeability, and stimulates smooth muscle cell proliferation, which may play a key role in the pathogenesis of atherosclerosis. In contrast, regulatory Treg cells are essential for maintaining immune tolerance and suppressing excessive immune responses. However, in RA-obstructive CAD patients, impaired Treg function may lead to dysregulated inflammatory responses. The reduction of Treg cells is closely linked to the increase in Th17 cells, driving the progression of RA and related cardiovascular diseases (25). Our data support this notion, demonstrating elevated Th17 cells and IL-17 in RA-obstructive CAD patients, which may exacerbate the progression of atherosclerosis and serve as potential targets for immunotherapy.

To further explore the role of these immune biomarkers in RA-obstructive CAD, we conducted univariate logistic regression analysis to compare clinical characteristics, immune features, and cytokine levels between RA-non-obstructive CAD and RA-obstructive CAD patients, followed by random forest analysis to identify key variables. Multivariate logistic regression analysis revealed that LDL-C, IL-17, and Th17 are independent risk factors for RA-obstructive CAD. Based on these findings, two nomogram models were constructed. Model 1 (including LDL-C, IL-17, and Th17) outperformed Model 2 in predicting RA-obstructive CAD risk (AUC = 0.97 vs. AUC = 0.88), validating the importance of immune biomarkers in RA-obstructive CAD risk assessment. Notably, Th17 cells and IL-17 not only serve as immunological markers for RA but also play a significant role in the immune mechanisms underlying cardiovascular diseases.

Further validation through ROC curve and decision curve analysis (DCA) confirmed the practical applicability of the prediction model in clinical settings. The model demonstrated an AUC greater than 0.75 in both the training and validation cohorts, indicating strong discriminatory power for clinical risk prediction of RA-obstructive CAD. The optimal cutoff value was determined using the Youden index (Youden index = sensitivity + specificity - 1), with the maximum index corresponding to a cutoff of 59.6%. When this threshold was applied in DCA, the model showed a high clinical net benefit, suggesting that intervention should be considered when the predicted risk exceeds 59.6%. This model effectively identifies the risk of obstructive CAD in RA patients and supports targeted interventions in high-risk individuals, optimizing treatment strategies while avoiding unnecessary diagnostic and therapeutic risks.

Although this study provides a valuable tool for personalized risk prediction in RA-obstructive CAD, several limitations remain. First, the sample size is relatively small, and the study is based on a single-center design. Future research should involve large-scale multicenter clinical studies to further validate the model's accuracy and generalizability. Second, while this study highlights the potential value of immune markers in assessing RA-obstructive CAD risk, it did not incorporate other traditional cardiovascular risk factors. Future studies should design larger, more diverse randomized clinical trials or cohort studies that integrate immune markers with traditional cardiovascular risk factors to optimize cardiovascular disease risk assessment and intervention strategies in RA patients. Additionally, further investigation into the biological pathways through which these markers influence CAD is needed. Third, this study did not compare the proposed model with existing cardiovascular risk assessment tools. Future research should involve randomized clinical trials or cohort studies to directly compare this model with traditional risk models to assess its clinical applicability and potential for broader use. Fourth, as the nomogram was developed based on a cohort of hospitalized RA patients with high disease activity and predominantly coronary atherosclerosis, future studies should aim to validate the model in asymptomatic RA patients with better clinical control through large-scale multicenter cohort studies. Finally, although IL-17 plays a crucial role in the immune mechanisms of RA-obstructive CAD, its sensitivity and specificity remain relatively low, potentially influenced by other immune factors or external environmental factors. Therefore, future research should focus on improving the accuracy and reliability of IL-17 detection and actively explore more specific immune biomarkers.

In conclusion, the immune biomarker-based risk prediction model proposed in this study offers a novel approach for assessing and managing the risk of RA-obstructive CAD, with significant potential for clinical application. With further validation and optimization, this model is expected to play a key role in personalized treatment and cardiovascular risk management for RA patients.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by the Ethics Committee of the Second Hospital of Shanxi Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for

participation was not required from the participants or the participants' legal guardians/next of kin because this study was approved by the Ethics Committee of the Second Hospital of Shanxi Medical University (Approval No. (2024) YX 292). As a retrospective study, the requirement for obtaining informed consent from all enrolled patients was waived.

Author contributions

XW: Data curation, Software, Writing – original draft, Writing – review & editing. BCL: Data curation, Software, Writing – original draft. RW: Data curation, Investigation, Writing – original draft. BH: Data curation, Investigation, Writing – original draft. YF: Data curation, Investigation, Writing – original draft. BY: Writing – review & editing, Supervision. SR: Conceptualization, Writing – review & editing. BL: Conceptualization, Supervision, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by the Research Project of Shanxi Provincial Health and Family Planning Commission (Nos. 2020068) and the key Medical Research Projects of Shanxi Province (Nos. 2023XM029 and 2021XM09).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2024.1493182/full#supplementary-material

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frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 17 December 2024
DOI 10.3389/fmed.2024.1442858

OPEN ACCESS

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RECEIVED 03 June 2024
ACCEPTED 18 November 2024
PUBLISHED 17 December 2024

CITATION
Xu C, Khin LW, Tam HZ, Goh LL, Koh ET, Dalan R and Leong KP (2024) Haptoglobin 2-2 genotype is associated with increased risk of cardiovascular disease in patients with rheumatoid arthritis: a matched case-control study.
Front. Med. 11:1442858.
doi: 10.3389/fmed.2024.1442858

Haptoglobin 2-2 genotype is associated with increased risk of cardiovascular disease in patients with rheumatoid arthritis: a matched case-control study

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Introduction: Traditional risk factors do not fully explain the increased risk of cardiovascular disease (CVD) in patients with rheumatoid arthritis (RA). The *Haptoglobin (Hp)* 2-2 genotype confers a lower anti-oxidant and higher inflammatory effect on the vasculature compared to the non-*Hp* 2-2 genotype. This study investigates the association of the *Hp* genotype with CVD in patients with RA.

Methods: Data from 69 RA patients with CVD and 207 sex- and ethnicity-matched RA patients without CVD, collected from 1 January 2000 to 31 December 2020, were retrieved from the Tan Tock Seng Hospital RA Registry. CVD was examined against demographics, clinical and laboratory variables in univariate models. Associations between the *Hp* genotypes and CVD were analyzed using conditional logistic regression.

Results: We studied 276 patients (65.2% female, 82.6% Chinese, median age 60.9 years). Most participants were in low disease activity or remission (79.3%). The *Hp* 2-2 genotype was present in 49.6% (137/276). In the group with CVD, the prevalence of the *Hp* 2-2 genotype was 50.9% (29/57) in the Chinese, 100% (5/5) in the Indians, and 28.6% (2/7) in the Malays. In the non-CVD group, the respective prevalence was 46.8% (80/171), 66.7% (10/15), and 52.4% (11/21). In univariate analysis, the matched odds ratio (OR) of the *Hp* 2-2 genotype for CVD in RA was 1.34 [95% confidence interval (CI): 1.22–1.47; $p < 0.001$]. The *Hp* 2-2 genotype was significantly associated with CVD (adjusted matched OR: 1.13; 95% CI: 1.01–1.27; $p = 0.033$) in the multivariate logistic regression model after adjusting the confounding factors, including age, smoking, diabetes, hypertension, hyperlipidemia, anti-CCP autoantibodies, and disease activity.

Conclusion: The *Hp* 2-2 genotype is associated with an increased risk of CVD in patients with RA in this multi-ethnic cohort.

KEYWORDS

rheumatoid arthritis, cardiovascular disease, *Haptoglobin* genotypes, inflammation, personalized medicine

Introduction

Rheumatoid arthritis (RA) is an archetype of multi-systemic chronic inflammatory disease (1). Cardiovascular disease (CVD) is one of the major causes of mortality and morbidity of RA (1). The risk of CVD in RA is comparable to that conferred by diabetes mellitus (DM), after adjusting for the traditional risk factors (2). CVD disproportionately affects the young RA population (3). The European Alliance of Association for Rheumatology (EULAR) recommends raising the risk derived from standard algorithms by 1.5 for RA patients (4). However, it has been argued that this method does not reclassify into more appropriate risk categories since it does not address RA-specific risks.

Haptoglobin (Hp) is an acute phase reactant that prevents oxidative damage by binding oxygenated free hemoglobin (5). There are two alleles of the *Hp* gene, namely *Hp*1 and *Hp*2, and three genotypes, *Hp* 1-1, *Hp* 1-2 and *Hp* 2-2. The anti-oxidant effect of *Hp* 2-2 is inferior to the other two (5). *Hp* 2-2 is associated with an increased risk of CVD in patients with DM (6–9). *Hp* 2-2 is overexpressed in patients with a family history of RA (10) and systemic lupus erythematosus (SLE) (11, 12). High serum level of Hp is associated with inadequate response to methotrexate in RA (13). However, the role of *Hp* genotypes in reclassifying CVD risk in RA has not been investigated. This study aims to study the association of *Hp* genotypes with CVD in RA in a multi-ethnic Asian cohort.

Materials and methods

Patient's clinical data and sample

The Tan Tock Seng Hospital (TTSH) RA Registry is a longitudinal multi-ethnic disease registry in Singapore inaugurated in 2001 (14, 15). RA patients fulfilled the 1987 American Rheumatism Association criteria or the 2010 American College of Rheumatology (ACR)/EULAR criteria (16, 17). The presence of CVD was reported by the attending physicians. We identified 69 patients with CVD in our Registry. We also selected sex- and ethnicity-matched RA patients without CVD in a ratio of one case to three controls. Biobanked DNA samples, serum samples, and matching clinical data were retrieved. The study was approved by the institutional review board (NHG DSRB reference number 2006/00011).

Haptoglobin genotype and protein measurement

The *Hp* genotyping was performed using TaqMan-based real-time polymerase chain reaction (PCR) as previously described (18). Plasma haptoglobin was measured using the immunoturbidimetric method on the Beckman Coulter AU system.

Statistics

The distribution of demographic and clinical characteristics was summarized using descriptive statistical methods. The normality of the data was assessed for continuous variables; mean (standard deviation, SD) or median (interquartile range, IQR) were used to summarise normally distributed or skewed data, respectively. Frequency and percentage were used to summarise the categorical variables.

Univariate and multivariate conditional logistic regression were performed to estimate the effect size of the covariate of interest, *Hp* 2-2 genotype, in the prediction of pre-specified clinical outcome (i.e., presence or absence of CVD event), because the study design was a gender and ethnicity matched case-control study (19, 20).

The pre-specified clinical outcome was the presence or absence of a CVD event (binary outcome), and the main covariate of interest was the *Hp* 2-2 genotype.

In our study, variables were initially selected for inclusion in the model if they were either theoretically relevant based on prior literature or demonstrated a bivariate association with the outcome at a significance level of $p \leq 0.10$.

In the univariate variable selection stage, variables with a p-value ≤ 0.1 with odds ratios that exclude 1 were selected as preliminary predictors for inclusion in the multivariate model in order not to miss any potentially important clinical predictors. For the final multivariate conditional logistic regression model, statistical significance was defined by the conventional $p \leq 0.05$, with odds ratios excluding 1.

In the multivariate conditional logistic regression model, a stepwise backward regression approach with robust variance estimation and frequency weighted analysis options were applied to account for the 1:3 matching (1 case:3 controls) in the study design.

During the backward stepwise process, covariates identified as potential confounders were included based on known associations with both the exposure and outcome variables with pre-determined p-value cutoff ≤ 0.10, as well as including variables exhibiting p-value ≤ 0.10 in the univariate variable selection stage. This approach was adopted to ensure that potentially significant clinical predictors were retained in the multivariate model.

Variables were then removed sequentially if they did not meet the final significance threshold of $p < 0.05$ with odds ratios excluding 1 after adjusting for other variables in the model.

To assess the model fit, the Hosmer–Lemeshow goodness-of-fit test was performed. The final model selection was based on the model with the lower deviance, defined by the −2×log-likelihood (−2LL) value, which is the better model. The final fitted model was chosen based on the −2×log-likelihood (−2LL) value with the number of significant clinically important variables in the model.

Effect sizes were presented as adjusted matched odds ratios (matched OR) with 95% CI.

Statistical significance was set at two-sided 5% level and all analyses were conducted using STATA 16.1.

Results

Clinical characteristics of patients with RA

This study included 276 patients, mostly female (65.2%) and of Chinese ethnicity (82.6%). There were 69 RA patients with CVD and 207 sex- and ethnicity-matched RA patients without CVD. The median age was 60.9 years [interquartile range (IQR): 53.8–68.0], and a quarter of the patients had a history of smoking (Table 1). The prevalences of diabetes, hypertension, and hyperlipidemia were 14.5, 46.4, and 57.2%, respectively (Table 1). The median RA duration was 119.2 (IQR:

TABLE 1 Baseline characteristics and univariate analyses of the association between baseline characteristics and events of CVD in patients with RA.

	All	No CVD	CVD	Univariate		
	n = 276	*n* = 207	*n* = 69	Matched OR	95% CI	*p*
Demographic						
Age (years), median (IQR)	60.9 (53.8–68.0)	59.8 (52.4–66.5)	66.6 (59.3–74.0)	1.08	1.08–1.09	**<0.001**
Female, *n* (%)	180 (65.2)	135 (65.2)	45 (65.2)			
Ethnicity						
Chinese, *n* (%)	228 (82.6)	171 (82.6)	57 (82.6)			
Malay, *n* (%)	28 (10.1)	21 (10.1)	7 (10.1)			
Indian, *n* (%)	20 (7.3)	15 (7.3)	5 (7.3)			
Smoking status						
Ever, *n* (%)	69 (25.0)	52 (25.2)	17 (24.6)	1.00	0.88–1.13	0.961
Clinical risk factors						
Disease duration (months)	119.2 (32.8–215.2)	114.9 (31.3–207.0)	121.1 (39.3–251.8)	1.10	1.07–1.14	**<0.001**
Diabetes, *n* (%)	40 (14.5)	23 (11.2)	17 (25.0)	2.54	2.25–2.87	**<0.001**
Hypertension, *n* (%)	128 (46.4)	77 (37.4)	51 (75.0)	5.76	5.14–6.46	**<0.001**
Hyperlipidemia, *n* (%)	158 (57.2)	105 (51.0)	53 (77.9)	4.07	3.62–4.59	**<0.001**
Positive RF, *n* (%)	234 (84.8)	173 (84.8)	61 (89.7)	1.19	1.04–1.37	**0.014**
Positive anti-CCP, *n* (%)	221 (80.1)	161 (77.8)	60 (87.0)	2.39	2.07–2.77	**<0.001**
DAS-28						
Remission/low disease activity, *n* (%)	219 (79.3)	165 (80.1)	54 (78.3)	ref	ref	**<0.001**
Moderate/severe disease activity, *n* (%)	56 (20.3)	41 (19.9)	15 (21.7)	1.33	1.17–1.50	
Cumulative prednisolone (g), median (IQR)	4.1 (1.1–1.2)	3.6 (0.9–1.1)	4.9 (2.0–14.9)	1.0007	1.0003–1.0011	**<0.001**
Genotype						
Hp 2-2 Genotype, n (%)	137 (49.6)	101 (48.8)	36 (52.2)	1.34	1.22–1.47	**<0.001**

CVD, cardiovascular disease; RA, rheumatoid arthritis; *n*, number; OR, odds ratio; 95% CI, 95% confidence interval; RF, rheumatoid factor; CCP, cyclic-citrullinated peptide; DAS-28, disease activity score 28; ref, reference; IQR, interquartile range. Median (IQR) for continuous variables and *n* (%) for categorical variables were shown. Bold values indicates statistically significant.

32.8–215.2) months, with high positivity for rheumatoid factor (84.8%) and anti-cyclic citrullinated peptides (anti-CCP) autoantibodies (80.1%), and most were in remission or low disease activity (79.3%) (Table 1).

Hp 2-2 genotype in different populations

The overall prevalence of the *Hp* 2-2 genotype was 49.6% (137/276). We found that 47.8% (109/228) of Chinese, 46.4% (13/28) of Malay, and 75% (15/20) of Indian patients carry the *Hp* 2-2 genotype (Table 2). Among patients with CVD classified into the three ethnicities, 50.9% (29/57) of the Chinese, 28.6% (2/7) of the Malays, and 100% (5/5) of the Indians carry *Hp* 2-2 genotype (Table 2). Among the patients without CVD, there were 46.8% (80/171) Chinese, 52.4% (11/21) Malay, and 66.7% (10/15) Indian patients carrying the *Hp* 2-2 genotype (Table 2). The haptoglobin protein level was significantly lower in patients with the *Hp* 2-2 genotype (mean ± SD: 130.0 ± 66.3 mg/dL) than those with the non *Hp* 2-2 genotype (mean ± SD: 161.2 ± 82.8 mg/dL) ($p < 0.001$) (Table 2).

Univariate analysis of risk factors for CVD

In univariate analysis, traditional clinical risk factors significantly associated with CVD events were age (66.6 vs. 59.8 years in CVD and control group respectively, $p < 0.001$), diabetes (25.0% vs. 11.2%, OR 2.54, 95% CI 2.25–2.87, $p < 0.001$), hypertension (75% vs. 37.4%, OR 5.76, 95% CI 5.14–6.46, $p < 0.001$), and hyperlipidemia (77.9% vs. 51.0%, OR 4.07, 95% CI 3.62–4.59, $p < 0.001$) (Table 1). RA-specific factors associated with CVD events include disease duration (median 118.6 vs. 100.3 months in CVD and control group respectively, $p < 0.001$), rheumatoid factor and anti-CCP autoantibodies positivity (OR 1.19, $p = 0.0135$ and OR 2.39, $p < 0.001$, respectively), moderate and severe disease activity (OR = 1.33, 95% CI 1.17–1.50, $p < 0.001$), and higher cumulative dose of prednisolone (4.9 g vs. 3.6 g in CVD and control groups respectively, $p < 0.001$) (Table 1).

TABLE 2 Overall characteristics of patients based on *Hp* 2-2 genotype status.

	Non-Hp 2-2 (*n* = 139)		*p*	Hp 2-2 (*n* = 137)		*p*
	Control (*n* = 106)	Case (*n* = 33)		Control (*n* = 101)	Case (*n* = 36)	
Age (years) median (IQR)	59.9 (53.0–66.9)	66.7 (59.3–73.9)	**<0.001**	59.7 (52.3–66.1)	66.0 (59.1–75.0)	**<0.001**
Female, *n* (%)	70 (66.0)	19 (57.6)	—	65 (64.4)	26 (72.2)	—
Ethnicity						
Chinese, *n* (%)	91 (85.9)	28 (84.9)	—	80 (79.2)	29 (80.6)	—
Malay, *n* (%)	10 (9.4)	5 (15.2)	—	11 (10.9)	2 (5.6)	—
Indian, *n* (%)	5 (4.7)	0 (0)	—	10 (9.9)	5 (13.9)	—
Smoking						
Ever, *n* (%)	27 (25.5)	10 (30.3)	**0.011**	25 (25.0)	7 (19.4)	**0.011**
Diabetes, *n* (%)	11 (10.4)	8 (24.2)	**<0.001**	12 (12.0)	9 (25.7)	**<0.001**
Hypertension, *n* (%)	36 (34.0)	26 (78.8)	**<0.001**	41 (41.0)	25 (71.4)	**<0.001**
Hyperlipidemia, *n* (%)	54 (50.9)	26 (78.8)	**<0.001**	51 (51.0)	27 (77.1)	**<0.001**
Haptoglobin (mg/dL), mean (SD)	161.2 (82.8)		—	130.0 (66.3)		**<0.001**
Haptoglobin (mg/dL), mean (SD)	161.0 (85.0)	162.0 (76.4)	0.316	126.3 (64.1)	140.2 (72.2)	**<0.001**
DAS-28						
Remission/low disease activity, *n* (%)	83 (78.3)	27 (81.8)	**0.001**	82 (82.0)	27 (75.0)	**<0.001**
Moderate/severe disease activity, *n* (%)	23 (21.7)	6 (18.2)		18 (18.0)	9 (25.0)	
Positive RF, *n* (%)	90 (85.7)	29 (87.9)	**0.034**	83 (83.8)	32 (91.4)	**<0.001**
Positive anti-CCP, *n* (%)	85 (80.2)	30 (90.9)	**0.001**	76 (75.3)	30 (83.3)	**0.037**
Disease duration (months), median (IQR)	88.9 (20.4–165.0)	106.4 (63.2–165.1)	**0.001**	106.4 (31.2-224.6)	156.8 (33.3–244.7)	**0.014**
Cumulative prednisolone (g), median (IQR)	3.4 (0.9–8.6)	5.4 (3.2–18.4)	**0.001**	3.8 (0.9–13.2)	4.5 (1.7–13.6)	**<0.001**

n, number; RF, rheumatoid factor; CCP, cyclic-citrullinated peptide; DAS-28, disease activity score 28. Mean (SD, standard deviation) or median (IQR, interquartile range) for continuous variables and *n* (%) for categorical variables were shown. Bold values indicates statistically significant.

The prevalence of the *Hp* 2-2 genotype was higher in the CVD group compared to controls (52.2% vs. 48.8%), with a matched odds ratio of 1.34 (95% CI 1.22–1.47, $p < 0.001$) (Table 1).

Multivariate analysis of risk factors for CVD

In multivariate analysis, after adjusting for age, smoking, diabetes, hypertension, hyperlipidemia, anti-CCP autoantibodies, and disease activity, the *Hp* 2-2 genotype remained independently associated with CVD (adjusted matched OR 1.13, 95% CI 1.01–1.27, $p = 0.033$) (Table 3). Other statistically significant associations with CVD events include age (adjusted matched OR 1.06, $p < 0.001$), smoking (adjusted matched OR 1.43, $p < 0.001$), diabetes (adjusted matched OR 1.21, $p = 0.013$), hypertension (adjusted matched OR 2.78, $p < 0.001$), hyperlipidemia (adjusted matched OR 2.77, $p < 0.001$), the presence of anti-CCP autoantibodies (adjusted matched OR 3.27, $p < 0.001$), and moderate/severe disease activity (adjusted matched OR 2.21, $p < 0.001$) (Table 3).

Discussion

Our study shows that the *Hp* 2-2 genotype is significantly associated with the risk of CVD in RA patients in a Singaporean multi-ethnic cohort, independent of traditional CVD risk factors. This suggests that the *Hp* 2-2 genotype could be a potential biomarker for more accurate CVD risk predication in RA patients.

We found that the prevalence of the *Hp* 2-2 genotype varies among different ethnic groups. In decreasing order of frequency, they are Indians (75.0%), Chinese (47.8%), and Malays (46.4%), which aligns with previous studies on diabetes in Singapore (18) and other countries (21). The prevalence of RA also varies among different ethnicities, with a higher prevalence in India compared to other Asian countries (22). This could be due to genetic and environmental factors (22, 23). Previous studies reported that the prevalence of the *Hp* 2-2 genotype was higher in patients with a family history of RA (10) and SLE (11, 12). The over-representation of Indian ethnicity (12.1%) in our multi-ethnic RA cohort (14), compared to 7.5% in the population (24), and the increased risk of CVD in the Indian population (25),

TABLE 3 Multivariate analyses of the association between *Hp* genotype and events of CVD in patients with RA.

	Adjusted matched OR	95% CI	*p*
Hp 2-2 genotype	1.13	1.01–1.27	**0.033**
Age	1.06	1.05–1.07	**<0.001**
Smoking	1.43	1.22–1.68	**<0.001**
Diabetes	1.21	1.04–1.42	**0.013**
Hypertension	2.78	2.42–3.19	**<0.001**
Hyperlipidemia	2.77	2.43–3.14	**<0.001**
Positive anti-CCP	3.27	2.80–3.82	**<0.001**
DAS-28			
Remission/low disease activity	reference	—	**<0.001**
Moderate/severe disease activity	2.21	1.86–2.61	

Hp, haptoglobin; RA, rheumatoid arthritis; OR, odds ratio; 95% CI, 95% confidence interval; CCP, cyclic-citrullinated peptide; DAS-28, disease activity score 28; CVD, cardiovascular disease. Bold values indicates statistically significant.

suggest that the *Hp* 2-2 genotype could play a role in these differences. Strikingly, all Indian patients with CVD were *Hp* 2-2 genotype carriers in our study, although the number was low.

In our study, the protein level of Hp was not different between non-CVD and CVD patients within the non *Hp* 2-2 subgroup, but higher in CVD patients than non-CVD patients within the *Hp* 2-2 subgroup. The antioxidant function might be impaired despite higher protein levels in patients with *Hp* 2-2. Serum haptoglobin α2 (expressed by *Hp* 2–1 or *Hp* 2-2 genotype), with lower antioxidant capacity than haptoglobin α1 (expressed by *Hp* 1–1 genotype), was found in higher concentration in patients with SLE (11). The high baseline haptoglobin protein level predicted poor response to MTX, independent of the DAS 28 score, and inflammatory markers (13). Our findings suggest the *Hp* 2-2 genotype may result in impaired antioxidant functions, potentially leading to enhanced inflammation and a diminished response to methotrexate, thereby increasing CVD risk.

The association of the *Hp* 2-2 genotype with DM and CVD complications in DM is well documented (6–9). Our study shows that the *Hp* 2-2 genotype is an independent risk factor for CVD in RA patients, even after adjusting traditional risk factors, including DM. The link between the *Hp* 2-2 genotype and increased CVD risk in our RA cohort is consistent with findings in DM populations. This parallel suggests a common pathogenic mechanism in these chronic inflammatory conditions (26). Inflammation is a stronger predictor for CVD than LDL in this era of statin therapy (27). The impaired antioxidant function of Hp 2-2 might lead to chronic inflammation. Furthermore, the *Hp* 2-2 genotype is associated with the disease severity (28), and survival (29) in CVD. Therefore, antioxidant therapies could be investigated as a potential intervention to mitigate CVD complications in the RA population, as demonstrated in DM (9).

The burden of CVD in RA is comparable to that in DM (2). The traditional risk prediction model is not accurate in RA, even with the 1.5-time multiplier recommended by EULAR (4). *Hp* polymorphism has been extensively studied in patients with DM, and the *Hp* 2-2 genotype has shown the potential for refining the cardiovascular risk assessment (30, 31). Moreover, the predictive value of traditional risk factors, i.e., elevated glycosylated hemoglobin (HbA1c), is more pronounced among patients with the *Hp* 2-2 genotype (7, 32). Elevated homocysteine levels (33) and increased Carotid Intima-Media Thickness (CIMT) (34) are associated with increased CVD risk. Incorporating risks such as *Hp* 2-2, homocysteine levels, and CIMT into risk algorithms could enhance their predictive accuracy and enable precise risk stratification in RA, leading to timely implementation of optimal therapy and ultimately improving outcomes.

This study has a few strengths. First, a multi-ethnic Asian cohort allows for examining genetic risk factors across diverse populations. This is particularly relevant given the variability in the prevalence of the *Hp* 2-2 genotype among different ethnicities. Second, the study has 20-year follow-up, providing a broad dataset for analysis. Third, by matching controls to cases on important variables such as sex and ethnicity, the study design controlled for confounding factors. Limitations include the relatively small sample size, the retrospective CVD diagnosis potentially introducing selection bias, and the high proportion of likely post-menopausal women, which may elevate baseline CVD risk and affect generalizability. Additionally, it is known the medications use may affect the risk of CVD in RA (35). Therefore, the potential for bias due to unmatched medication use between the two groups warrants cautious interpretation.

Our study provides evidence for the *Hp* 2-2 genotype as an independent risk factor for CVD in patients with RA. Future research should focus on prospective validation of these findings in larger cohorts and explore the mechanistic pathways linking the *Hp* 2-2 genotype to CVD in RA. Furthermore, clinical trials assessing the efficacy of antioxidant therapies in reducing CVD risk in RA patients with the *Hp* 2-2 genotype would be a logical extension of this work.

The TTSH Rheumatoid Arthritis Study Group

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Data availability statement

The datasets used and/or analyzed for this study are available from the corresponding author upon reasonable request. Requests to access these datasets should be directed to Chuanhui Xu. E-mail: xuchuanhui2008@gmail.com.

Ethics statement

The studies involving humans were approved by NHG DSRB reference number 2006/00011. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

CX: Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Validation, Writing – original draft. LK: Formal analysis, Investigation, Methodology, Software, Writing – review & editing. HT: Formal analysis, Investigation, Methodology, Software, Writing – review & editing. LG: Investigation, Methodology, Writing – review & editing. EK: Data curation, Investigation, Resources, Writing – review & editing. RD: Conceptualization, Formal analysis, Funding acquisition, Methodology, Supervision, Writing – review & editing. KL: Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Supervision, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This work is supported by Tan Tock Seng Hospital FY2021 Pitch-for-Fund Program Grant (Grant ID: PFFP 21-08), NHG-LKC Medicine Clinician-Scientist Career Scheme (CSCS-22-02-01), and Ng Teng Fong Healthcare Innovation Program (NTF_SRP_P1).

Acknowledgments

The authors thank Ms. Amelia Lim Qiu Ru, Ms. Choong Ying Qi, and Mr. Shih-Huan Chou for their assistance with data collection.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers | Frontiers in Immunology

TYPE Review
PUBLISHED 24 February 2025
DOI 10.3389/fimmu.2025.1470488

OPEN ACCESS

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RECEIVED 25 July 2024
ACCEPTED 31 January 2025
PUBLISHED 24 February 2025

CITATION
Parisi S, Ditto MC, Ghellere F, Panaro S, Piccione F, Borrelli R and Fusaro E (2025) Update on tocilizumab in rheumatoid arthritis: a narrative review.
Front. Immunol. 16:1470488.
doi: 10.3389/fimmu.2025.1470488

Update on tocilizumab in rheumatoid arthritis: a narrative review

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Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by joint pain, swelling, and stiffness, affecting approximately 1% of the adult population. Tocilizumab (TCZ), a monoclonal antibody targeting the IL-6 receptor, has emerged as an effective treatment for RA. This narrative review provides an update on TCZ's efficacy and safety based on data from randomized controlled trials (RCTs) and real-world evidence (RWE). TCZ, available in subcutaneous (SC) and intravenous (IV) formulations, has shown significant benefits in RA management. Key clinical trials, including SAMURAI, OPTION, RADIATE, and TOWARD, have demonstrated TCZ's efficacy as monotherapy and in combination with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), particularly in patients with inadequate responses to methotrexate or TNF inhibitors. Long-term studies, such as STREAM, have highlighted TCZ's sustained efficacy and favorable safety profile over 5 years. The impact of TCZ on cardiovascular health, lipid profiles, and the risk of infections has been a focal point, with findings suggesting no significant increase in cardiovascular disease risk compared to other RA therapies. RWE further highlights the effectiveness of TCZ, identifying predictors of response, such as age, and emphasizes its suitability for biologic-naïve and overweight patients. Special considerations include TCZ use in RA-associated interstitial lung disease and amyloidosis. Overall, TCZ remains a pivotal option in RA treatment, with a well-established safety and efficacy profile supported by extensive clinical and real-world data.

KEYWORDS

rheumatoid arthritis (RA), tocilizumab (TCZ), efficacy and safety, randomized controlled trials (RCTs), real-world evidence (RWE), IL-6 receptor inhibitor

1 Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by pain and swelling in the joints, along with stiffness and fatigue. This leads to enduring synovitis and gradual joint deterioration, resulting in reduced functionality and an elevated risk of illness and mortality. RA affects 1% of the adult population and stands as a significant contributor to disability (1). The global prevalence in Italy is estimated at around 0.5% (2). The pathogenesis of RA remains not fully understood. Individuals genetically predisposed to this condition develop it through interactions with various environmental factors, such as smoking habits (3). Moreover, the presence of the "shared epitope" is another significant genetic factor in RA predisposition, particularly for ACPA-positive RA (4).

Interleukin-6 (IL-6) plays a pivotal role in RA pathogenesis. It is a versatile cytokine with diverse roles in immunity, exhibiting both pro-inflammatory and anti-inflammatory effects. IL-6 is produced mainly by myeloid cells, and its dysregulation is linked to autoimmune diseases like RA. High levels of this cytokine are associated with RA disease activity, highlighting its significance in rheumatic conditions and inflammation. Depending on different types of stimuli, other cytokines, such as TNF-alpha and IL-1, stimulate the production of IL-6, triggering a series of reactions in both innate and adaptive immunity (3, 5–7). In terms of innate immunity, IL-6 plays a role in the maturation of inflammatory infiltrate by promoting neutrophil migration and mononuclear cell infiltration. Additionally, it acts as a chemoattractant for monocytes at the site of inflammation. Regarding acquired immunity, IL-6 exerts its effects on both T cells and B cells. Indeed, through T cells, it promotes the differentiation of B cells into active plasma cells leading to increased levels of serum gamma-globulins.

IL-6 exerts its effects through three different pathways: IL-6 signaling, IL-6 trans-signaling and IL-6 trans-presentation. In the first one, myeloid cells produce IL-6 in response to immune stimuli, which binds to IL-6R on target cells. This forms a complex with gp130, activating signaling pathways that induce acute phase protein production like C-reactive protein (CRP) in the hepatocytes (3, 8). In the second one, IL-6 binds to the soluble IL-6 receptor (sIL-6R) in the bloodstream, forming a complex that interacts with gp130 on various cell types, including those lacking membrane-bound IL-6 receptors. This enables broader cellular effects, signaling emergent events, such as an infection throughout the body (8, 9). The third signaling pathway is characterized by a unique mechanism where T cells respond to IL-6 despite lacking IL-6Rα expression. Dendritic cells present IL-6/IL-6Rα complex to T cells via gp130 molecules, distinct from traditional IL-6 pathways. Unlike other IL-6 signaling modes, IL-6 antibodies fail to inhibit trans-presentation, but anti-IL-6Rα antibodies can neutralize it (10).

Persistent dysregulation of IL-6 is linked not only with autoimmune diseases but also in some cancers since elevated IL-6 levels are involved in inflammation-driven tumors. In the elderly, a common pro-inflammatory pathway involving cytokines, such as IL-6 connects age-related conditions and promotes tumorigenesis (6, 11, 12).

Understanding IL-6 biology is crucial for IL-6-targeted therapies. In the context of RA, two classes of IL-6-targeted inhibitors are particularly relevant: anti-IL-6 receptor monoclonal antibodies, such as tocilizumab (TCZ; approved for RA in 2010), sarilumab (2017) and olokizumab (currently under investigation for RA), and anti-IL-6 monoclonal antibodies, such as siltuximab (2014) (7). However, it should be noted that siltuximab is approved for non-RA indications, such as Castleman disease, and is not intended for RA treatment. Targeting the IL-6 receptor, as seen with TCZ and sarilumab, offers advantages by potentially blocking other cytokines in the IL-6 family (3). The R4RA trial by Humby et al. demonstrated that stratification of patients based on synovial RNA sequencing improves the predictability of response to anti-IL-6 therapies (13). For instance, in B-cell-poor patients, tocilizumab showed superior efficacy compared to rituximab, highlighting the importance of tissue-specific molecular profiling in guiding treatment choices and advancing precision medicine (13, 14).

Anti-IL-6 therapies differ in their targets and applications. IL-6 receptor inhibitors like tocilizumab and sarilumab block both classic and trans-signaling, making them effective in RA. In contrast, ligand inhibitors such as ziltivekimab, under investigation for cardiovascular and renal diseases, focus on suppressing IL-6-driven inflammation in conditions like atherosclerosis. Ridker et al. highlight that ligand inhibitors might offer advantages in diseases where trans-signaling plays a key role (15). These differences are critical for tailoring treatments, with receptor inhibitors broadly impacting IL-6 activity while ligand inhibitors target specific inflammatory pathways (15).

TCZ, an approved therapy for RA, blocks both classic and trans-signaling pathways (Figure 1). Its success in RA treatment underscores IL-6's significance, motivating the exploration of novel therapeutic avenues (9, 10). TCZ is a genetically engineered humanized monoclonal antibody created by grafting the complementarity-determining region of a mouse anti-human IL-6 receptor onto human IgG. It can dissociate the complex composed of IL-6 and soluble IL-6 receptor (sIL-6R), inhibiting both the classic pathway and the trans-signaling pathway, the latter constituting the pro-inflammatory activity of IL-6 (16). TCZ is administered either as an IV infusion or subcutaneous injection. TCZ was first approved in Japan for moderate to severe RA (2005), then in 2009 in Europe and in 2010 in the USA (Table 1). Currently, it is also being investigated for other conditions, including cytokine release syndrome and severe COVID-19, thanks to its significant anti-inflammatory properties. Thus, guidelines for the treatment of COVID-19 have included it for both severe forms and for children under emergency use (16, 17). As of 2022, the FDA approved TCZ for the treatment of COVID-19 in hospitalized adult patients receiving systemic corticosteroids and requiring oxygen support, as recommended in COVID-19 guidelines (18). Then, it was approved for emergency use in the treatment of COVID-19 pediatric patients aged 2 years to <18 years (19, 20).

When using TCZ, its impact on lipid profiles and its immunosuppressive effects must be taken into account, as they increase the risk of infections. Indeed, the 5-year extension STREAM study demonstrates that the drug maintains sustained long-term efficacy with a favorable safety profile, even if the rate of serious infections reported in 17.5% of patients enrolled in this

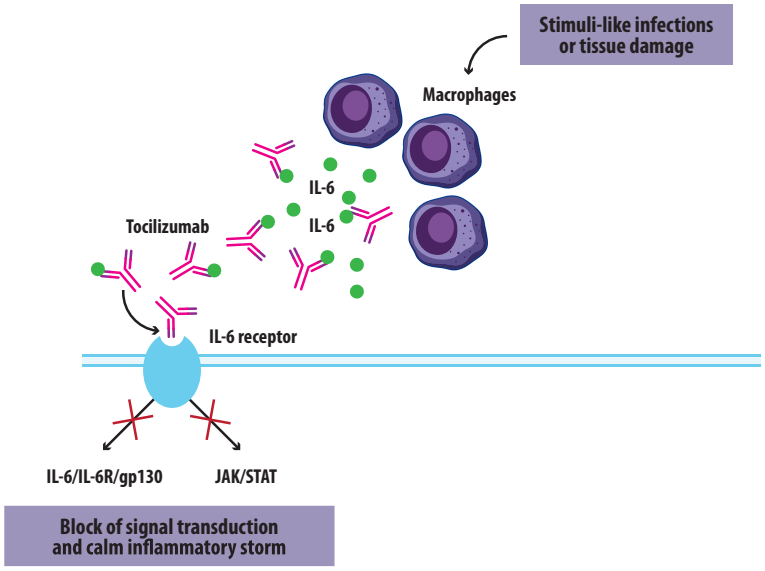

FIGURE 1
Tocilizumab mechanism of action.

study was 5.7 events per 100 patient-years (16). Moreover, regarding the trend toward a worsening lipid profile during TCZ treatment, another study demonstrated no statistically significant changes in it observed over the long term (21).

For autoimmune conditions, such as RA, beyond TCZ, sarilumab is also available. They are both IL-6 receptor inhibitors and have shown efficacy in RA monotherapy, demonstrating more efficacy than adalimumab (3). Differences between them include their structure, administration, dosage, and indications. TCZ is a humanized monoclonal antibody administered intravenously or subcutaneously, while sarilumab is fully human and given subcutaneously. Dosage frequency varies: subcutaneous (SC) TCZ is a 162 mg weekly injection, while intravenous (IV) formulation is given at the dosage of 8 mg/kg every 4 weeks; sarilumab SB is a 200 mg every 2 weeks injection. TCZ IV formulation may allow for dosage adjustment up to 4 mg/kg; sarilumab may allow for dosage reduction to 150 mg every 2 weeks. TCZ is approved for RA, juvenile idiopathic arthritis (JIA), systemic JIA, giant cell arteritis (GCA) and COVID-19, while sarilumab is indicated for moderate to severe RA. Biosimilar development reflects their established efficacy and safety (3, 10, 22–25). Biosimilar TCZ has demonstrated an efficacy and safety profile equivalent to that of the originator (26).

This narrative review aims to provide an update on TCZ in RA based on published data, randomized control trials, and real-world evidence.

2 Methods

To explore the literature about the use of TCZ in the management of RA, a PubMed search for full-text articles was conducted using the following search string: (((tocilizumab [Title/Abstract]) OR tocilizumab [Title/Abstract]) AND rheumatoid arthritis [Title/Abstract]). Inclusion criteria encompassed publications in the English language, for which abstracts were available. PubMed and EMBASE databases were searched for studies published between 1 January 2005 and 31 December 2023. The keywords for the search were: “tocilizumab”, “IL-6”, “IL-6 receptor”, “IL-6 inhibitor”, and “rheumatoid arthritis”. According to their related Emtree and Mesh terms, each database was searched with a specific string developed on these keywords.

TABLE 1 Summary of Tocilizumab market launch and label indications.

Year of market introduction	Brand name	Available formulations	Warnings and safety precautions	Year and approved indications for EU use
Japan 2005 EU 2009 USA 2010	Tosymra (Japan) RoActemra (EU) Actemra (USA)	Subcutaneous and intravenous	Risk of infections, infusion reactions, allergic reactions, gastrointestinal reactions, liver impairment, and reactions to concomitant medications. Recommend hematological monitoring	2009 Rheumatoid Arthritis 2011 Systemic Juvenile Idiopathic Arthritis 2017 Giant Cell Arteritis

3 Results

3.1 TCZ efficacy and safety profile emerging from randomized controlled trials

Given the assumption that comparing results across clinical trials due to disparate patient populations with varying prior treatments and disease histories is challenging, below, we provide an overview of all clinical trials involving TCZ in the treatment of RA over the past 18 years (Figure 2, Table 2).

Several phase III trials have demonstrated the clear efficacy of TCZ in various scenarios related to RA. In 2007, SAMURAI (in Japan) (27) and 2008 OPTION (28) evaluated the efficacy and safety of TCZ monotherapy compared to methotrexate monotherapy in patients with RA who were intolerant to methotrexate or had an inadequate response to it. RADIATE and TOWARD demonstrated the efficacy and safety of TCZ in patients with RA who had an inadequate response or intolerance to one or more TNF inhibitors (29) and also to conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) (30). In 2009, STREAM was the first study to demonstrate the excellent long-term safety and efficacy of TCZ monotherapy over 5 years in patients with active RA. Not only were hemoglobin levels enhanced and the frequency of neutropenia reduced but also patients' quality of life was strongly improved. Because an increase in total cholesterol levels is often associated with an elevated risk of cardiovascular disease, further investigation was needed to assess whether TCZ might contribute to an increased risk of developing ischemic heart disease (12). In the same year, the SATORI study demonstrated the efficacy and safety of TCZ in Japanese patients with RA who had an inadequate response to methotrexate (such as in other previous studies). In 2010, the AMBITION study established TCZ as an initial biological agent (monotherapy), demonstrating statistically superior clinical efficacy compared to a standard methotrexate (MTX) dose regimen (20 mg/week). While ACR20 was used as a regulatory endpoint, TCZ also achieved higher ACR50 and ACR70 response rates, which are more clinically relevant measures of meaningful improvement in RA. In this 6-month study, TCZ monotherapy exhibited greater efficacy in patients with relatively early active RA (according to the 2010 ACR/EULAR classification), for whom MTX had not previously failed, compared to MTX monotherapy. Besides, this study sustained that TCZ monotherapy causes lipid elevations and reversible neutropenia linked to IL-6R inhibition. The long-term significance of these effects is yet to be determined (31). In 2013, the ADACTA study compared the efficacy of TCZ monotherapy with adalimumab monotherapy in patients with RA who were intolerant to MTX or for whom continued treatment with MTX was considered inappropriate (32). In 2014, the MUSASHI study provided a sustained favorable safety and efficacy profile of TCZ as monotherapy in a Japanese cohort of RA patients. The study compared the subcutaneous formulation to the intravenous one, demonstrating its noninferiority. The availability of a subcutaneous formulation of TCZ offers a significant enhancement to the quality of life for RA patients due to shorter administration time and home administration. From week 24 to 108, there was a gradual increase in the proportion of patients who achieved a positive response and an improvement in the clinical response. Overall, after 108 weeks of exposure, there was no attenuation of the therapeutic response (33). In the same year, the SUMMACTA study compared the efficacy and safety of SC versus IV formulations of TCZ (TCZ SC 162 mg weekly versus TCZ IV 8 mg/kg every 4 weeks) in patients with RA with an inadequate response to biologic DMARD (bDMARDs). TCZ SC demonstrated higher efficacy in terms of ACR20 response, while the DAS28 remission was similar between the TCZ SC and the TCZ IV. Clinical safety profiles were comparable, except for a higher incidence of Injection Site Reactions more commonly seen with TCZ SC (34).

In 2014, the BREVACTA study aimed to assess the efficacy and safety of TCZ SC compared to subcutaneous placebo (PBO-SC) in patients with moderate to severe RA who had an inadequate response to bDMARDs. Notably, joint damages were reduced, and the incidence of infections and serious infections was similar between the treatment groups (35).

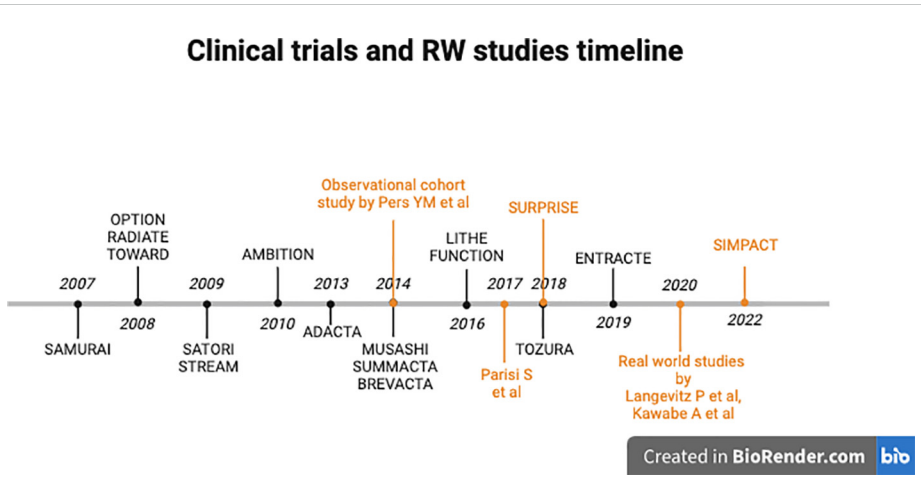

FIGURE 2
Timeline of clinical trials (black) and real-world studies (orange) involving Tocilizumab in RA.

10.3389/fimmu.2025.1470488

TABLE 2 Summary of registration studies.

Trial	Phase	Patients (n)	Design	Comparison group	Duration	Endpoint	Ref
SAMURAI	III	306	Open	csDMARDs	12 months	Inhibition of structural joint damage progression (TCZ monotherapy)	(27)
OPTION	III	623	Double-blind	MTX	6 months	ACR20 response at week 24	(28)
RADIATE	III	499	Randomized, double-blind, placebo-controlled	MTX	6 months	ACR20 response at week 24	(29)
TOWARD	III	1220	Double-blind	csDMARDs	6 months	ACR20 response at week 24; improvement of ACR50/70 at week 24	(30)
SATORI	III	127	Double-blind	MTX	6 months	ACR20 response at week 24	(12)
STREAM	III	143	Open-label	–	5 years	ACR improvement criteria, DAS28, and EULAR response	(12)
AMBITION	III	286	Randomized controlled	–	5 years	Long-term efficacy and safety up to 264 weeks	(31)
ADACTA	IV	452	Randomized, double-blind, parallel group	Adalimumab	6 months	Change in disease activity score using 28 joints (DAS28) from baseline to week 24	(32)
MUSASHI	III	348	Double-blind, parallel group, double-dummy, comparative	TCZ SB vs TCZ IV	6 months	Comparison of TCZ SC vs TCZ IV; ACR20 at week 24	(33)
SUMMACTA	III	1262	Randomized, double-blind, parallel group	TCZ SB vs TCZ IV?	2 years	ACR20/50/70 response at week 24 in TCZ SC vs TCZ IV group. Remission as DAS28 <2.6 and a decrease from baseline of ≥0.3 HAQ-DI at week 24	(34)
BREVACTA	III	656	Randomized, double-blind, placebo-controlled, parallel group	MTX	6 months	ACR20 week 24; radiographic progression and safety	(35)
LITHE	III	1196	Double-blind	MTX	1 year	Mean change from baseline in GmTSS and adjusted mean AUC for change from baseline in the HAQ-DI at week 104	(11)
FUNCTION	III	1157	Double-blind randomized controlled	MTX	6 months	Achieving remission (DAS28-ESR <2.6) at week 24 and radiographic efficacy by mTSS	(5)
TOZURA	IV	1804	Multinational, open-label, single-arm, common-framework	csDMARDs	6 months	DAS28-ESR at week 24. ACR response 20/50/70/90	(36)
ENTRACTE	IV	3080	Randomized, open-label, parallel group	Etanercept	5 years	ACR20 response week 24. Onset of MACE and related complications; all-cause mortality	(37)

csDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; MTX, methotrexate; SB, subcutaneous biologic; IV, intravenous.

In 2016, LITHE investigated the efficacy, also radiologically, of TCZ in RA refractory to MTX patients. Radiological disease progression (according to the sharp total score) was reduced after two years of treatment (11).

In the same year, the FUNCTION study investigated the impact of inhibiting IL-6 signaling with TCZ as a first-line therapeutic option for RA in a population exclusively comprising MTX-naive patients with early progressive RA (5). Throughout the 52-week study, the group receiving 8 mg/kg TCZ in combination with MTX consistently demonstrated superior outcomes across all efficacy measures. This included improvements in clinical outcomes and enhanced functional ability (measured by HAQ-DI score). Additionally, the combination therapy inhibited joint damage progression, as evidenced by radiographic measures such as the van der Heijde-modified Sharp score, and achieved better disease control, as reflected by DAS28-ESR scores. While 8 mg/kg TCZ with MTX emerged as the most effective treatment, both 4 mg/kg TCZ with MTX and 8 mg/kg TCZ monotherapy proved to be good alternative treatments. These alternatives are particularly valuable for subsets of patients, such as those unable to tolerate MTX or the higher 8 mg/kg dose due to contraindications or adverse reactions (5).

In 2018, the TOZURA study evaluated the efficacy and safety of TCZ-SC as monotherapy or in combination with csDMARDs in patients with moderate to severe RA who had an inadequate response to csDMARD or anti-TNF agent therapy or who were

MTX naïve. Results have demonstrated that TCZ-SC was efficacious in patients with RA, with combination therapy and monotherapy being comparably effective and with the observed safety profile being consistent with the known TCZ profile (36).

In 2019, the ENTRACTE trial compared the risk of major adverse cardiovascular events (MACE) in patients with RA treated with TCZ or the TNF inhibitor etanercept. Similar to findings from the STREAM study, given that RA is associated with a higher burden of atherosclerosis and increased mortality from atherosclerotic events and cardiovascular disease (CVD) compared to individuals without RA, the elevation of lipids with atherogenic potential raised concerns regarding the CVD risk-to-benefit ratio of TCZ in RA. However, the findings from this trial suggest that the risk of CVD following treatment with TCZ does not appear to be significantly higher than with etanercept, at least within the initial years of therapy (37).

The results of the ENTRACTE trial, summarized in Table 3, provide a detailed comparison of the cardiovascular safety outcomes between TCZ and etanercept. Notably, while the overall risk of MACE was comparable, specific differences were observed in adverse event profiles, including rates of serious infections and gastrointestinal perforations, highlighting the need for vigilant monitoring during TCZ therapy.

About the intricate relationship between lipid metabolism and CV risk in RA, the research showed that RA patients often exhibit lower levels of traditional blood lipids, such as total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), and high-density lipoprotein cholesterol (HDL-c), particularly under hyperinflammatory conditions. This phenomenon is termed the 'lipid paradox' because, despite these lower lipid levels, RA patients have a significantly increased risk of CVD. The systemic inflammation characteristic of RA leads to alterations in lipid metabolism, resulting in dysfunctional HDL that promotes LDL oxidation and plaque formation. These changes in lipid subcomponents and their functions contribute to the increased cardiovascular risk observed in RA patients (38).

3.1.1 TCZ's broader implications or cardiovascular benefits

Emerging evidence suggests that TCZ may exert significant cardiovascular benefits beyond its established role in managing RA. By targeting IL-6, TCZ not only reduces systemic inflammation but also influences key mediators of cardiovascular risk, such as endothelial dysfunction, monocyte activity, neutrophil extracellular trap (NET) formation (NETosis), and oxidative stress – principal drivers of atherosclerosis and CVD. Ruiz-Limón et al. demonstrated that TCZ improved endothelial function, as assessed by postocclusive hyperemia using Laser Doppler, and decreased oxidative stress in monocytes and neutrophils from RA patients (39). TCZ also reduced the percentage of low-density granulocytes and inhibited NETosis generation, a known contributor to vascular damage and thrombosis. Furthermore, Ruiz-Limón et al. showed that TCZ reversed the pro-inflammatory and prothrombotic status of RA monocytes by modulating specific intracellular pathways (39).

These findings suggest that TCZ's cardiovascular benefits extend beyond its anti-inflammatory properties to include direct vascular and cellular effects. Additionally, earlier studies by Kume et al. highlighted that TCZ attenuates arterial stiffness, as measured by the cardio-ankle vascular index (CAVI) and aortic augmentation index, further supporting its role in improving vascular health. The modulation of lipid profiles by TCZ, particularly its impact on increasing HDL cholesterol, adds another layer of potential cardiovascular benefit. By targeting IL-6, a cytokine implicated in atherogenesis and plaque destabilization, TCZ may positively influence atherosclerotic plaque progression and stability (40).

Taken together, these findings highlight TCZ's potential to reduce the pro-atherothrombotic profile in RA patients through the restoration of endothelial function, inhibition of oxidative stress and modulation of monocyte and neutrophil activity (39). Its ability to attenuate arterial stiffness and improve lipid profiles further

TABLE 3 Summary of ENTRACTE trial results.

Parameter	Tocilizumab group (number of events)	Etanercept group (number of events)	Hazard ratio (95% CI)	Comments
Major adverse cardiovascular events	83	78	1.05 (0.77–1.43)	No significant difference in MACE risk between groups
Cardiovascular-related death	36	35	1.03 (0.64–1.63)	Similar risk between groups.
Nonfatal myocardial infarction	28	31	0.89 (0.54–1.49)	Lower but nonsignificant trend of MI in tocilizumab group.
Nonfatal stroke (all types)	24	15	1.53 (0.80–2.92)	Higher incidence in tocilizumab group but nonsignificant.
Hospitalized heart failure	12	8	1.50 (0.61–3.67)	Small number of events with nonsignificant differences.
Adverse events related to infections	159 serious infections	111 serious infections	1.39 (1.08–1.79)	Infection-related AEs were more frequent in the tocilizumab group.
Gastrointestinal perforations	8	1	8.43 (1.06–67.26)	Significantly higher risk of gastrointestinal perforations in tocilizumab group.

supports its promise. These properties position TCZ as a promising candidate for broader exploration in populations at high cardiovascular risk, such as those with subclinical atherosclerosis or metabolic syndrome (40).

3.2 TCZ efficacy and safety profile emerging from real-world studies

Results of several real-world studies that have evaluated the efficacy of TCZ and the safety of treatments in routine clinical practice have been analyzed (Figure 2, Table 4). Patients involved in these studies may significantly differ from those included in clinical trials. The RWE insights are valuable as they demonstrate the true impact of treatments in real-life settings.

A retrospective observational real-life study conducted across five academic centers in France assessed the efficacy of TCZ in combination with csDMARDs or biologic-naive patients based on the European League Against Rheumatism (EULAR) response criteria. The study specifically included patients with a history of arterial hypertension, ischemic heart disease, stroke or arteritis. However, three predictors of a better response to TCZ were identified: young age, high baseline CRP level, and no history of CVD. The findings suggest that offering TCZ to young patients without previous CVD and with a CRP level >10 mg/l leads to greater effectiveness and lower rates of primary failure. These identified predictors of response are valuable as they enable personalized treatment, allowing the selection of the most suitable biologic agent based on the individual patient's profile. This approach not only improves medical cost-effectiveness but also reduces the number of non-responding patients (41). Moreover, these findings suggest that patients with comorbidities, specifically those with CVD, are more likely to discontinue treatment for their cardiovascular condition. This leads to reduced efficacy in managing RA due to poor adherence to the therapy rather than being an issue related to TCZ.

An RWE study also demonstrated TCZ effectiveness in treating inflammation in RA patients, both with clinical evaluation and with ultrasonography with rapid reduction of the power Doppler signal (42).

In 2018, the SURPRISE study demonstrated that TCZ led to remission in more than 90% of patients and that, after TCZ discontinuation, continued MTX therapy maintained low disease activity (43).

Another real-life setting phase IV study program recruited patients who were administered TCZ-SC on a weekly basis for a minimum of 24 weeks, either as monotherapy or in combination with a csDMARD. The results align with findings from other real-life studies and other randomized controlled studies confirming the safety, tolerability, and efficacy profile of the treatment (44).

The FIRST registry is a prospective observational cohort study designed to assess the long-term safety and effectiveness of biologic therapies, including TCZ, in patients with RA. It aims to gather real-world data on the use of these treatments in routine clinical practice and to monitor their outcomes over time, encompassing a follow-up period of up to 5 years. This RW study highlighted the growing proportion of elderly individuals, so the importance of tailoring therapeutic approaches for elderly RA patients, considering the increased prevalence of comorbidities, arises. Notably, the FIRST study prioritizes the examination of pre-existing lung diseases among the various comorbidities. Elderly RA patients frequently exhibit heightened disease activity and more substantial functional

TABLE 4 Summary of real-world studies.

Trial	Patients	Design	Comparison group	Duration	Endpoint
Pers et al. (41)	204	RW	–	6 months	Identify predictors of response and remission to TCZ in RA patients seen in daily routine clinical practice
Parisi et al. (42)	29	RW	–	6 months	Evaluate the response of TCZ in RA patients who are not responders to previous biologic therapy
Kaneko et al. (43) SURPRISE	105	RW	–	2 years	TCZ-free remission and low disease-activity rates, functional outcome, and radiological outcomes were assessed with the modified total Sharp score (mTSS) and safety. The efficacy of reinstituted TCZ/MTX was also evaluated
Langevitz et al. (44)	100	Multi-center, open-label, single-arm	–	6 months	Proportion of patients achieving remission and LDA based on the CDAI after 24 weeks of treatment with SC TCZ. Change in SDAI up to 24 weeks; proportion of patients achieving SDAI remission and LDA after 24 weeks; change in Disease Activity Score with DAS28-ESR up to 24 weeks
Kawabe et al. (45)	1362	RW	Abatacept	3 years	Effectiveness and safety of bDMARDs
Nagy et al. (46) SIMPACT	337	Open-label, non-controlled, non-randomized, non-interventional study	–	6 months	Change in DAS28 and CDAI scores, the proportion of patients achieving remission in the whole population and in subgroups defined based on prior RA treatment history, and age, weight or biological sex *post hoc*

RW, real world; TCZ, tocilizumab; RA, rheumatoid arthritis; MTX, methotrexate; bDMARDs, biologic disease-modifying anti-rheumatic drugs; CDAI, Clinical Disease Activity Index; SC, subcutaneous; SDAI, Simplified Disease Activity Index; LDA, low disease activity; DAS28-ESR, Disease Activity Score with 28 Joint Count using Erythrocyte Sedimentation Rate.

limitations compared to their younger counterparts. Within the FIRST registry, findings indicate that the optimal effectiveness and safety of TCZ are observed in patients aged below 75 years. For patients aged 75 years or older, TCZ and abatacept (ABA) therapies may be considered suitable options. Additionally, in patients under the age of 65 years, TNF inhibitors demonstrated greater efficacy in improving disease activity, and they were associated with increased frequency of discontinuation due to remission. Thus, tailoring therapeutic strategies based on age groups emerges as a potential avenue to enhance the outcomes of bDMARD therapy for RA, addressing the unique considerations associated with age and comorbidities in this patient population (45).

The SIMPACT study aimed to assess the efficacy and safety of MTX-free TCZ-SC therapy in RA patients in a real-world setting. The study observed patients for a 24-week treatment period in Hungarian centers, where treating physicians prescribed TCZ-SC. The results indicated a significant reduction in disease activity measured by both DAS28 and CDAI, with a more pronounced clinical response observed in biologic-naïve patients and a lower response noted in patients over 75 years of age. While real-world clinical data on TCZ therapy in elderly patients is limited, recent findings align with those of the REACTION study, suggesting that younger age is associated with a better clinical response and remission rate 6 months after TCZ initiation (46). Additionally, the study reported a significant decrease in the frequency of co-administered medications, including oral corticosteroids (CSs) and DMARDs. To enhance the efficacy of bDMARDs, both EULAR recommendations and American College of Rheumatology (ACR) guidelines suggest supplementing bDMARDs with csDMARDs, such as MTX (46).

3.3 Tocilizumab efficacy and safety on specific populations

3.3.1 Interstitial lung disease

Interstitial lung disease (ILD) encompasses a spectrum of disorders affecting the lung interstitium, including Usual Interstitial Pneumonia (UIP) and Non-Specific Interstitial Pneumonia (NSIP) patterns. UIP is characterized by fibrosis with honeycombing and traction bronchiectasis, often associated with a poor prognosis and commonly seen in idiopathic pulmonary fibrosis (IPF). In contrast, NSIP presents with more uniform interstitial inflammation and fibrosis, exhibiting a better response to treatment and associated with various connective tissue diseases. Distinguishing between these patterns is crucial for appropriate management and prognostication in ILD patients (47).

ILD stands as a significant extra-articular manifestation of RA, impacting its morbidity and mortality rates. Pulmonary manifestations of RA typically manifest within the initial five years of the disease, with instances where they precede joint symptoms. Interstitial lung disease (ILD) is fortunately not a frequent complication (3.2–5.9%) but may also be currently underestimated (48–51).

ILD can be attributed to the chronic inflammatory processes inherent to RA itself, as well as to the immunomodulatory effects of DMARDs used in its treatment. Some csDMARDs and bDMARDs have been linked to the onset or exacerbation of ILD, presenting difficulties in determining an appropriate and safe treatment strategy (48–50).

TCZ exhibits a favorable safety profile in patients with RA-associated interstitial lung disease (RA-ILD), potentially stabilizing lung involvement. Thus, while MTX has a limited role in ILD development and progression, TCZ monotherapy maintains efficacy, making it suitable for cases with both ILD and high articular disease activity, where MTX use is less recommended. Early ILD diagnosis in RA patients is crucial for understanding its natural history, identifying predictive factors, and evaluating the true impact of certain DMARDs, such as MTX, on this severe extra-articular complication (52, 53).

3.3.2 Secondary amyloidosis

In secondary amyloidosis, hepatocytes produce the serum amyloid protein (AA), which forms insoluble extracellular deposits. Kidneys are the most commonly affected organs (>90%) (54), but amyloid deposition can also occur in other organs, such as the spleen, liver, heart, adrenal glands, thyroid glands, lungs and gastrointestinal tract. Systemic AA amyloidosis may arise from poorly controlled RA or in patients with a long history of RA, where pro-inflammatory cytokines, such as IL-6, play a key role in driving systemic inflammation. RA accounts for over 60% of cases of AA amyloidosis, whereas only 7–26% of RA patients develop amyloidosis (55). Since the first reports of TCZ for systemic AA amyloidosis emerged in 2006, when Okuda et al. reported improvements in serum AA amyloid levels, reductions in proteinuria, and histological improvement in a 26-year-old woman with juvenile idiopathic arthritis, there have been several reports confirming its efficacy (56, 57). TCZ decreased proteinuria and stabilized kidney function, thereby improving clinical disease activity. Furthermore, TCZ has shown benefits in treating AA amyloidosis associated with other various underlying conditions, including familial Mediterranean fever, multicentric Castleman disease, viral hepatitis (58) and amyloid heart disease (59). Additionally, the literature suggests that TCZ may preserve renal function even in cases of end-stage kidney disease, potentially delaying the progression of renal dysfunction in RA patients with AA amyloidosis (59). Interestingly, in two retrospective studies, it has been demonstrated that TCZ was more clinically beneficial (according to the DAS28 score) than anti-TNF therapy in patients with AA amyloidosis complicating rheumatic diseases (60, 61).

The mechanism underlying the efficacy of TCZ in AA amyloidosis has yet to be understood and may vary depending on the inflammatory status of the patient at treatment onset. It is hypothesized that TCZ is able to block the transcription of AA amyloid protein but also allows for regression of deposits already present, which may account for the improved GFR in some cases (62).

3.3.3 Overweight/obesity

Obesity is considered a mild chronic inflammatory disease and has been identified as a risk factor for developing RA. White adipose tissue produces cytokines, such as TNF and IL-6, which have pro-inflammatory activity and are implicated in RA pathogenesis (63).

Obesity has been reported to negatively impact the efficacy of cytokine-targeted therapies but not cell-targeted therapies, and this effect is more pronounced in women than in men (63).

Even though the impact of obesity on the effectiveness of TCZ in RA remains controversial (63), the response to this drug is not significantly affected by weight or BMI, contrary to other biologic therapies, such as TNF inhibitors, making it a viable treatment option for overweight or obese RA patients (64, 65).

In normal weight individuals, adipose tissue is composed of adipocytes that cooperate with immune system cells, which secrete molecules contributing to the maintenance of an anti-inflammatory phenotype. As body weight increases, adipocytes enlarge and produce chemotactic molecules that recruit immune cells, primarily monocytes, from the circulation. These monocytes infiltrate the adipose tissue, differentiating into a pro-inflammatory state. Once differentiated, macrophages secrete pro-inflammatory cytokines, such as IL-6 and TNF, which act in both autocrine and paracrine manners with adipocytes, perpetuating the inflammatory state within the tissue. These cytokines are then also released into the circulation, promoting the systemic inflammation characteristic of obese individuals (66). This is documented by the direct correlation between increased BMI and circulating levels of the two cytokines. It is interesting to note that in obese patients, adipose tissue contributes to approximately 30% of the circulating levels of IL-6 (67). Furthermore, by improving RA control and enabling greater physical activity, biologics like TCZ may indirectly aid in weight management and the associated inflammatory burden.

3.3.4 Pregnancy and breastfeeding

Initial recommendations from the European Medicines Agency (EMA) sustained that TCZ should not be used during pregnancy unless absolutely necessary. Women of childbearing age should use effective contraception during treatment with TCZ and for up to 3 months after discontinuation. Currently, TCZ has been approved and advised for women who are pregnant or may become pregnant only when the potential benefits of treatment outweigh the potential risks. Even though there are many documented cases in which TCZ was successfully used throughout pregnancy with no abnormalities recorded in the newborns, effective contraception is strongly recommended due to limited data on its safety (68, 69). It is important to note that better control of RA during pregnancy, even with the use of biologics, such as TCZ, is generally more beneficial for both the mother and the baby than the risks associated with uncontrolled disease.

About breastfeeding, the passage of TCZ into breast milk is currently unknown. Saito et al. showed that TCZ might be safe for both pregnancy and breastfeeding because of its low degree of transplacental transmission. However, since information is still limited, the indications for TCZ should be carefully considered, and its use should be approached with caution in pregnant women and during breastfeeding (70).

3.3.5 Elderly patients

Data emerging from a large observational study (ICHIBAN), which involved elderly patients (>65 years old), show that long-term TCZ treatment is effective and has an acceptable safety profile compared to younger patients (71). In real-world conditions in Germany, patients with RA treated with TCZ for up to 2 years generally did not discontinue therapy due to adverse events, except for cases involving elderly patients who experienced infections (71).

Patients with age-associated comorbidities (such as diabetes, coronary heart disease, anemia, renal impairment, lung disease, infections and malignant tumors) treated with TCZ experienced reductions in RA disease activity compared to those without such comorbidities (72). When administering a biologic drug concomitantly with MTX to treat this kind of population, achieving an adequate MTX dose may be challenging, leading to decreased efficacy. Prolonged steroid therapy should be used cautiously because it can induce progressive osteoporosis and increase the risk of fractures in elderly patients (73). As demonstrated by Bauer in 2020 (74), immunosenescence in elderly patients with RA is characterized by reduced thymic output and expansion of senescent T cells, leading to a compromised immune system. Senescent T cells, particularly the CD28- subset, exhibit a pro-inflammatory phenotype known as the senescence-associated secretory phenotype (SASP), which contributes to chronic inflammation and disease progression. This cascade of events exacerbates RA by promoting the release of pro-inflammatory cytokines, such as IL-6 (74), thereby further supporting the usage of TCZ in these patients.

3.4 Tocilizumab adverse effects and general considerations

The most frequent adverse effects reported in the literature after TCZ treatment are infections, neutropenia, malignancies and diverticulitis.

3.4.1 Infections

Infections, particularly those involving the respiratory and urinary tract, could arise as the result of the inhibition of the IL-6 pathway, which compromises the host's defense against various microorganisms. The TOWARD study presents data on serious infections, complications of diverticulitis, hypersensitivity reactions and tuberculosis reactivation. Other infections include invasive pulmonary infections such as candidiasis, aspergillosis, coccidioidomycosis, pneumocystis jirovecii pneumonia, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis, and bacterial arthritis (30). The RADIATE study showed the efficacy of TCZ plus MTX in patients with an inadequate response to TNF antagonist treatment, reported a case of staphylococcal polyarthritis infection after TCZ (in the 8 mg/kg group) and a case of necrotizing pneumonia (in the 4 mg/kg group), both of which resolved without sequelae. No cases of tuberculosis or opportunistic infections were observed (30). The STREAM study noted pneumonia, herpes zoster, and acute bronchitis as the most frequently reported infections. At least two patients with a history of tuberculosis received TCZ without experiencing recurrence or exacerbation of tuberculosis despite the lack of prophylactic use

of antituberculosis drugs (12). However, the risk of TB can be effectively mitigated through adequate screening and management, which has made TB a minor concern in well-trained rheumatology practices. Compared to corticosteroids, commonly used in RA, TCZ offers a more targeted mechanism, avoiding the broad immunosuppressive effects of corticosteroids. Corticosteroids are linked to a higher risk of serious infections, including tuberculosis and fungal infections. While TCZ increases infection risk, it is comparable to or potentially lower than prolonged corticosteroid therapy, which also carries risks like impaired wound healing and metabolic complications.

A retrospective real-world study investigated the risk of HBV reactivation in patients undergoing long-term TCZ therapy for RA. The study highlighted the growing recognition of the risk of hepatitis B virus (HBV) reactivation during immunosuppressive therapy, including in rheumatology. Biological agents like TCZ, which decrease IL-6 levels therapeutically, may pose a risk of HBV reactivation since IL-6 inhibits HBV replication. Current treatment guidelines recommend initiating antiviral prophylaxis before immunosuppressive or cytotoxic therapy in HBsAg+ patients at high risk of HBV reactivation. Interestingly, none of the HBsAg+ patients who received antiviral prophylaxis experienced HBV reactivation in this study. Notably, HBV reactivation in HBsAg+ patients often occurred within the first year of TCZ treatment and could lead to fulminant hepatitis despite early preemptive treatment. Even HBsAg-/HBcAb+ patients, who have a very low risk, still require monitoring of HBV DNA and HBV markers to mitigate any potential reactivation risks (75). Adequate vaccination screening and updates are essential before initiating immunosuppressive therapies, such as TCZ. This includes assessing and addressing hepatitis B immunity to reduce the risk of HBV reactivation during treatment.

3.4.2 Neutropenia

Neutropenia is another frequent adverse effect in patients receiving TCZ. Some possible mechanisms by which TCZ may result in lower neutrophil counts include blocking IL-6-induced neutrophil survival, downregulation of other inflammatory cytokines, and margination of neutrophils from the circulation into tissues. In the TOWARD study, during the double-blind controlled period and with long-term exposure, the pattern and incidence of decreases in neutrophil counts remained consistent with what was seen in the 6-month controlled clinical trials. Grade 3 neutropenia occurred in 3.7% of patients receiving TCZ and none of the patients in the control group, and no grade 4 neutropenia was reported. The transient nature of grade 3 neutropenia, the lack of association with infection in this 24-week study, and the lack of need to adjust concomitant treatment suggest that this effect is not a significant issue. However, evaluation of the impact of lower neutrophil counts during long-term treatment will require long-term follow-up (30). A reduction in mean neutrophil counts occurred also in the RADIATE study, albeit transiently (29). Prolonged neutropenia may increase the risk of serious infections in patients treated with TCZ. Nonetheless, the superior efficacy of TCZ provides initial evidence of a benefit–risk profile that supports its use in patients with active moderate to severe RA (31). Grade 2 neutropenia was observed in 17 patients and grade 3 in nine patients of the STREAM study; however, all events were transient, and no patients experienced neutropenia with fever or withdrew due to neutropenia (12).

3.4.3 Malignancies

The LITHE study showed that malignancy rates were higher in the 4 mg/kg tocilizumab-MTX group (1.92/100 PY; total 521.90 PY) compared to the placebo-MTX (0.70/100 PY; total 284.81 PY) and 8 mg/kg tocilizumab-MTX (0.98/100 PY; total 1320.41 PY) groups. Twenty-three malignancies were reported in tocilizumab-treated patients up to week 104, with 17 of these reported within the first 52 weeks of the study. The most commonly reported malignancies were basal cell carcinoma (4 patients) and prostate cancer (two patients). All other malignancies were reported once (including cervix carcinoma, lung squamous cell carcinoma, endometrial cancer, gastroesophageal cancer, renal cell carcinoma, thyroid cancer, and others). Overall, malignancy rates were low among the tocilizumab- and placebo-treated groups and within the range observed in other populations of patients with RA. However, as observed during year 1 of LITHE, malignancy rates during year 2 remained higher in the 4 mg/kg tocilizumab-MTX group compared to the placebo-MTX and 8 mg/kg tocilizumab-MTX groups. The reason for the higher malignancy rate in the 4 mg/kg tocilizumab-MTX group during year 1 is unclear; however, the rate was unlikely to change significantly during Year 2. Data from large registries, including ARTIS, provide long-term evidence suggesting no increased malignancy risk in RA patients treated with biologics. For example, the study by Wadström et al. demonstrated that the risk of malignancies in biologic-treated patients was comparable to that of the general RA population, further supporting the overall safety profile of these therapies over extended periods (76). During year 2, the number of patient-years (PY) increased by 13% in the placebo-MTX group, 60% in the 4 mg/kg tocilizumab-MTX group, and 321% in the 8 mg/kg tocilizumab-MTX group, mainly because most patients switched from placebo-MTX or 4 mg/kg tocilizumab-MTX to 8 mg/kg tocilizumab-MTX in year 2. Increased malignancy rates were not observed in the 4 mg/kg tocilizumab groups of other phase III studies (77).

It should be emphasized that RA is associated with an increased risk of developing various types of cancers, as supported by multiple studies. This elevated cancer risk is partly due to the chronic inflammation and immune dysregulation inherent to RA. The study by Huss et al. reveals that patients with RA have a higher incidence of malignancies compared to the general population, with hazard ratios (HR) of 1.2, indicating a 20% increased risk overall (78). Hence, RA treatments, particularly with bDMARDs and targeted synthetic DMARDs (tsDMARDs), do not consistently increase the overall cancer risk, although certain drugs, such as abatacept, show a potential signal for increased cancer risk after prolonged treatment periods (78). Thus, ongoing surveillance and individualized risk assessment in RA patients undergoing such

therapies, especially considering the complex interplay between the disease, its treatments, and cancer risk, is an unmet need (78).

3.4.4 Intestinal injuries

Intestinal mucosal injury induced by TCZ is rare and typically occurs under specific circumstances. In patients receiving TCZ treatment, symptomatic diverticulitis was found to be more frequently associated with perforation compared to other treatments. Studies suggest that the risk of diverticular perforation may be slightly higher in patients treated with TCZ compared to csDMARDs or anti-TNF agents but lower than that associated with corticosteroids (79, 80). This type of mucosal injury often occurs in the presence of diverticulosis. The mechanism behind intestinal perforation involves TCZ, potentially masking abdominal pain and suppressing the elevation of CRP, thus impeding the healing process of intestinal injuries caused by diverticulitis. However, the exact pathological mechanism underlying TCZ-induced intestinal ulcers remains unclear. Cases of intestinal perforation as a complication of TCZ treatment have been linked to concomitant diverticulosis. There have also been reports of COVID-19 patients treated with TCZ developing ulcerative lesions that spread from the ileum to the ascending colon (81). Gastrointestinal perforation (GIP) represents another rare yet severe complication occasionally observed in RA patients. The risk of both GIP and diverticulitis appears to rise with TCZ therapy for RA. In susceptible RA patients, the neutralization of IL-6 may contribute to diverticulitis, potentially altering colonic contractions and leading to an unusual inflammatory presentation. Consequently, the gastrointestinal epithelium may fail to repair the initial lesion, potentially culminating in GIP (63).

4 Conclusions

Overall, results from completed clinical trials demonstrated that:

- TCZ efficacy and safety profile compared to other drugs, TNF inhibitors and other bDMARD (11, 29, 30, 36);
- TCZ has a safety and efficacy profile as monotherapy in patients with RA, available in two equivalent formulations (SC and IV) (33, 34);
- The risk of CVD following treatment with TCZ is not significantly higher when compared to the risk associated with other drugs, such as TNF inhibitors (12, 37);

Results from real-world findings add to the established body of knowledge and important evidence and strengthen previous findings from clinical trials and other real-world data. In particular, they demonstrated that:

- Smoking is not associated with a poorer response to TCZ (41);
- TCZ treatment shows an age-related decrease in efficacy and is more effective in biologic-naïve patients (46).

About TCZ efficacy and safety on specific populations, it has been demonstrated that:

- TCZ exhibits a favorable safety profile in RA-associated ILD, potentially stabilizing lung involvement (48);
- TCZ reduces AA amyloid deposition in various organs (56, 57);
- TCZ a suitable option for overweight or obese RA patients (65);
- Limited data on TCZ in pregnant and breastfeeding women TCZ safety warrants careful consideration of its use (68, 69);
- TCZ treatment in elderly patients with age-related comorbidities resulted in reduced RA disease activity (72).

The most frequent adverse effects of TCZ include serious infections, neutropenia and diverticulitis attributed to its mechanism of action. Understanding and monitoring these adverse effects are crucial for optimizing the safety and efficacy of TCZ therapy in RA patients (12, 29–31, 75, 79, 80).

Author contributions

SiP: Writing – review & editing. MD: Writing – review & editing. FG: Writing – review & editing. SaP: Writing – review & editing. FP: Writing – review & editing. RB: Writing – review & editing. EF: Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Acknowledgments

Editorial assistance was provided by Raffaella Gatta, PhD, and Aashni Shah (Polistudium SRL, Milan, Italy). This assistance was supported by Fresenius Kabi. Editorial assistance was supported by Fresenius Kabi.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers | Frontiers in Immunology

TYPE Systematic Review
PUBLISHED 15 April 2025
DOI 10.3389/fimmu.2025.1543157

OPEN ACCESS

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RECEIVED 10 December 2024
ACCEPTED 25 March 2025
PUBLISHED 15 April 2025

CITATION
Sturm B, Zang A-L, Stingl J, Hasseli-Fräbel R, Fanouriakis A, Schwarting A, Geber C, Weinmann-Menke J, Alhaddad M and Triantafyllias K (2025) Ocular markers of microangiopathy and their possible association with cardiovascular risk in patients with systemic inflammatory rheumatic diseases: a systematic review.
Front. Immunol. 16:1543157.
doi: 10.3389/fimmu.2025.1543157

Ocular markers of microangiopathy and their possible association with cardiovascular risk in patients with systemic inflammatory rheumatic diseases: a systematic review

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Individuals with autoimmune rheumatic diseases (ARDs) are at a higher cardiovascular (CV) risk due to systemic inflammation, which contributes to endothelial dysfunction, atherosclerosis, and structural changes in the vessel walls. Along with traditional CV risk factors like dyslipidaemia, arterial hypertension, obesity, and impaired glucose metabolism, these patients have a severe prognosis with higher CV morbidity and mortality rates. To date, there is limited data on the optimal CV screening methods for individuals with ARDs, as conventional risk algorithms may underestimate the influence of chronic inflammation. In comparison to macrovascular assessment methods, such as carotid-femoral pulse wave velocity and carotid sonography, microvascular changes, which may precede macrovascular disease, have been less investigated. The ocular microvasculature reflects systemic vascular health and can reveal early signs of CV disease. Changes in retinal vessels have been linked to an increased long-term risk of CV mortality and ischemic stroke in longitudinal studies of the general population, such as the large Atherosclerosis Risk in Communities (ARIC) study. Additionally, various cross-sectional and follow-up studies in patients with

ARDs have demonstrated associations between ocular vessel changes, traditional CV risk scores, and disease-related characteristics, suggesting a potential role for ocular assessments in CV risk screening. In this review work, research from 26 studies retrieved from the PubMed and Web of Science databases has been highlighted. Herein, we evaluate the techniques of retinal vessel analysis (RVA), optical coherence tomography angiography (OCT-A), spectral domain-OCT (SD-OCT), and retrobulbar color Doppler. Specifically, we examine the available data on their associations with key CV risk factors, systemic inflammation, surrogate CV markers, and traditional CV risk scores. Furthermore, we discuss their potential diagnostic value in both ARDs and the general population. Despite current limitations, such as small sample sizes and methodological heterogeneity, initial findings suggest that these techniques may provide valuable insights into microangiopathy and CV risk. Future research should focus on larger, well-designed longitudinal studies to establish their prognostic value and potential integration into clinical practice.

KEYWORDS

retinal vessel analysis (RVA), optical coherence tomography angiography (OCT-A), spectral domain optical coherence tomography (SD-OCT), retrobulbar color Doppler, microangiopathy, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), systemic sclerosis (SSc)

1 Introduction

Rheumatic diseases originate from autoimmune mechanisms, whereby the immune system mistakenly attacks the body's own tissues (1). These diseases are characterized by chronic inflammation affecting various organs, occurring as a result of a genetic predisposition and environmental triggers (1). Systemic inflammatory diseases, such as arthritides and connective tissue disorders, are associated with an increased risk of comorbidities including CV events (e.g. stroke, coronary artery occlusion myocardial infarction) (2–7). Additionally, these diseases are linked to increased morbidity and mortality rates (8–13). Patients with systemic lupus erythematosus (SLE) face a twofold increased risk of CV mortality, while those with rheumatoid arthritis (RA) have a 1.5-fold higher risk of CV events (14). Chronic systemic inflammation underlies endothelial dysfunction and accelerated atherosclerosis (15, 16).

Additional factors contributing to the higher CV risk in rheumatic diseases include anti-inflammatory therapies like glucocorticoids, which may cause dyslipidemia, hypertension, and a diabetic metabolic state (17). Research in SLE and other ARDs suggests that ongoing systemic inflammatory may accelerate atherosclerosis and increase CV risk, even during disease remission. Evidence indicates that CV events occur up to two years prior to the formal SLE diagnosis (15). These findings highlight the need for surrogate markers to identify patients at risk, enabling early intervention and improved outcomes.

1.1 Traditional risk scores

Many traditional CV risk assessment scores, such as Systematic Coronary Risk Evaluation (SCORE/SCORE2), the Prospective Cardiovascular Münster Study (PROCAM) score, and the Framingham Risk Score (FRS) (18–20) were developed for the general population. They depend on major modifiable CV-risk factors (18, 21, 22). SCORE/SCORE2 estimates 10-year CV risk in Europeans aged 40 to 69 without a history of CVD or diabetes, with SCORE2-OP involving those aged 70 and above. It considers blood lipid values, systolic blood pressure, age, sex, and smoking (23, 24). The European Alliance of Associations for Rheumatology (EULAR) recommends SCORE2 for assessing CV risk in patients with RA, axial spondylarthritis (AS), and psoriatic arthritis (PsA), using a 1.5 multiplication factor to adjust for RA (25, 26).

The PROCAM score, which is used in Germany, focuses on coronary heart disease (CHD) risk and includes lipid values, systolic blood pressure, smoking, family history, and diabetes (27). The FRS estimates 10-year CHD risk based on variables like blood pressure and cholesterol (28, 29). To improve screening for connective tissue diseases, additional factors like mental illness, SLE, RA, chronic kidney disease, atrial fibrillation and family history of CVD were included in the modified FRS and SCORE and new scores such as QRISK2 and QRISK3 were introduced (30, 31). However, evidence is limited on whether scores developed for the general population could apply accurately to rheumatic patients, and the efficacy of these adjusted scores in predicting CV risk remains inconclusive

(25, 26, 32, 33). This highlights the need for further surrogate markers for a more precise CV risk assessment (34).

1.2 Surrogate CV markers

Most studies on surrogate CV markers focus on large vessels, including arterial stiffness, carotid sonography, Ankle-Brachial-Index (ABI)-Doppler and other macroangiopathy indicators (35–41). Our research group and others have examined carotid-femoral pulse-wave velocity (cfPWV) and carotid sonography in ARDs, such as RA (42), PsA (43), mixed connective tissue disease (44), SLE (45), antisynthetase syndrome (33), idiopathic inflammatory myopathies (46) and fibromyalgia (47).

Conversely, data concerning arterial alterations of the microvasculature are scarce. Nevertheless, the link between microvascular and macrovascular changes has been established, with endothelial dysfunction as a critical initiating factor in a deleterious cycle (48–51) (Figure 1). In a recent review by Hysa et al. (52), the authors discuss how ARDs lead to ocular microvascular damage through immune complex formation, complement activation, and antibody-mediated endothelial injury. This endothelial dysfunction in ocular vessels reflects broader vascular involvement, suggesting that retinal microvascular changes could serve as early indicators of systemic vascular damage.

Importantly, arterial stiffness in the microvasculature of target organs can lead to CV complications, such as isolated systolic hypertension and increased pulse pressure (53, 54). Retinal vessels

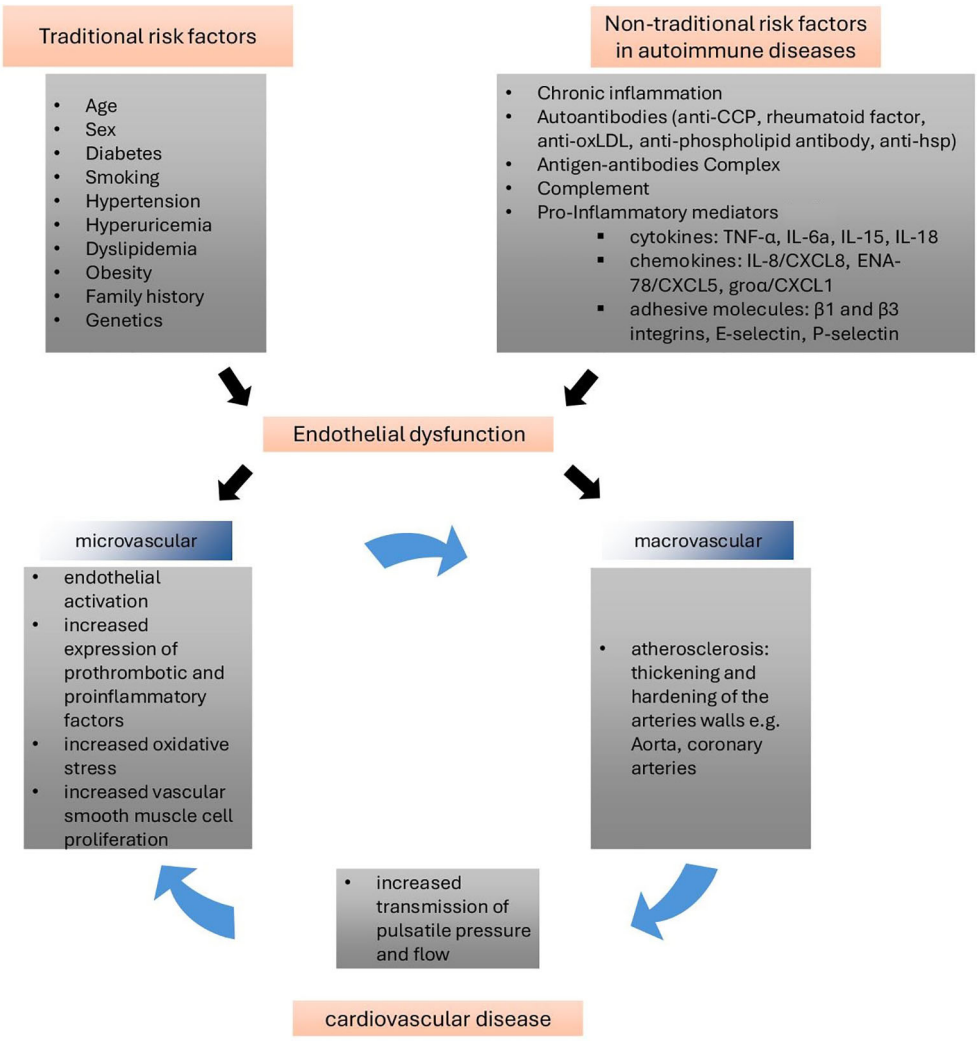

FIGURE 1
Vicious circle of endothelial dysfunction in ARDs (48, 49). Endothelial dysfunction, driven by traditional and non-traditional risk factors, plays a pivotal role in macro- and microvascular changes, contributing to significant cardiovascular morbidity and mortality. From a pathophysiological standpoint, microvascular dysfunction may serve as a precursor to large artery remodeling, as chronic inflammation could accelerate the atherosclerotic process. Conversely, the stiffening of large vessels amplifies pulsatile pressure transmission to the microvasculature, causing damage to microvascular beds and end organs, thus creating a vicious cycle between small and large vessels. Anti-CCP: anti-cyclic citrullinated peptide; anti-oxLDL: anti-oxidized low-density lipoprotein; TNF-α: tumor necrosis factor-alpha; IL: interleukin; ENA-78: epithelial neutrophil-activating protein-78; groα: growth-regulated oncogene-alpha. (adapted from 48).

are particularly suitable for assessing microvascular health, and the retinal vascular phenotype has been shown to be predictive of CV risk (55). Methods like static and dynamic retinal vessel analysis (SRVA, DRVA) have been extensively studied in the general population (55). Additionally, advanced ocular examinations, such as optical coherence tomography with angiography or analysis with a spectrometer (56–58) and doppler ultrasound of ocular vessels have been employed to determine retinal blood flow and vascular resistance in cross-sectional studies (59–61).

Interestingly, data on ocular markers of angiopathy and CV risk in rheumatic diseases are limited and have not yet been collectively presented. This review provides an overview of the existing studies on retinal vessel examination methods and their potential value in assessing CV risk in ARDs.

2 Pathophysiology

The microvasculature encompasses the smallest components of the circulatory system, consisting of blood vessels with diameters less than 300 µm (62). It comprises arterioles, capillaries, and venules, which facilitate the delivery of oxygen and nutrients to tissues while enabling the removal of metabolic waste products. These vessels allow essential exchange between the bloodstream and surrounding cells, crucial for maintaining tissue and organ functions. Moreover, they are involved in the regulation of immune responses within the body (63). Endothelial cells, in conjunction with the smooth muscle cells that coat the vessels, are responsible for maintaining vessel tone and regulating blood flow. Their function is highly dependent on oxygen (62–64). Should vessel alterations occur, in terms of vascular density or morphology, the viability of the surrounding tissue and organs can be jeopardized (65, 66). Endothelial dysfunction, characterized by the production of reactive oxygen species (ROS) and reduced availability of nitric oxide (NO), is a pivotal mediator influenced by intrinsic factors within endothelial cells (63, 67). It is postulated that these ROS, which are triggered by CV risk factors such as smoking, hypertension, and hyperglycemia, initiate a cascade of angiopathy-associated events (67). Initially, these processes contribute to endothelial dysfunction, which subsequently leads to arteriolosclerosis and atherosclerosis (67). The impairment of the small vessels due to structural changes, functional dilatation, and platelet activation or thrombotic microangiopathies leads to an increase in vascular resistance, and thus to reduced perfusion of end-organs, such as the eyes, kidneys, lungs, brain and heart (67–70) (Figure 2).

Embryologically, the retina originates from diencephalon, as does the optic nerve. Consequently, there are similarities between the central nervous system and the cerebrovascular bed (55). Similar to the blood-brain barrier (BBB), there is also a blood-retina barrier, which is intended to protect the vulnerable retinal tissue from potential insults (e.g. immune cells, larger molecules). However, the permeability of the blood-retina barrier is greater than that of the BBB, which is why the retina is more exposed to oxidative stress (55, 71). This explains why the retina is susceptible to systemic CV risks, as ROS play a crucial role in the pathogenesis of atherosclerosis and manifestation of CVD (72, 73). One of the earliest signs of arterial hypertension are microvascular changes, such as an impaired vasomotor function, which can lead to enhanced vasoconstriction or reduced vasodilation. Additionally, there may be anatomic alterations, such as tortuosity, and a rarefaction of arterioles or capillaries. The narrowing of retinal arterioles is indicative of an elevated systemic vascular tone (74). A substantial body of evidence has demonstrated a robust and independent correlation between blood pressure and arteriolar narrowing of retinal vessels (75–77). Therefore, the retinal vessels represent an intriguing interface, wherein the association of alterations in retinal microvascular endothelial dysfunction with systemic CV risk factors can be estimated (78, 79).

3 Methods

We employed a search strategy to identify relevant literature (Figure 3). Given the limited data available on ARDs, we included various study designs, such as cross-sectional and longitudinal studies, as well as case-cohort and registry-based analyses. Additionally, relevant long-term follow-up studies and meta-analyses from the general population were considered. We focused on rheumatic diseases with a well-documented and prominent microangiopathy, such as systemic sclerosis (SSc) and systemic lupus erythematosus (SLE). Moreover, we included the most common inflammatory arthritis, rheumatoid arthritis (RA), due to its high prevalence and established association with cardiovascular (CV) risk. Our selection was guided by both the availability of relevant studies and the strength of the association between these diseases and vascular changes.

Following the PICO framework, we considered SLE, RA and SSc, as the patient/population (P), retinal vessel examination as the intervention (I), a healthy population as the control group/comparison (C), and microangiopathy or CV risk as the outcome (O). The search was performed on PubMed and Web of Science from 14 November 2023 to 21 June 2024 with the following inclusion criteria: all relevant studies, written in English language, published after 1990. Case reports and papers with only published abstracts were excluded. We first used the key words “retinal vessel”, “cardiovascular risk”, as well as (“rheumatoid arthritis” OR “systemic lupus erythematosus” OR “systemic sclerosis”) linked with the Boolean operator AND. This yielded a total of 8 results on PubMed and 11 on Web of Science. Consequently, the search terms were modified by employing truncation in the keyword strategy, in order to expand the search results. The combination of the keywords “microvasc*” and “cardiovascular risk” in combination with “rheumatoid arthritis” OR “systemic lupus erythematosus” OR “systemic sclerosis” produced a total of 130 results on PubMed and

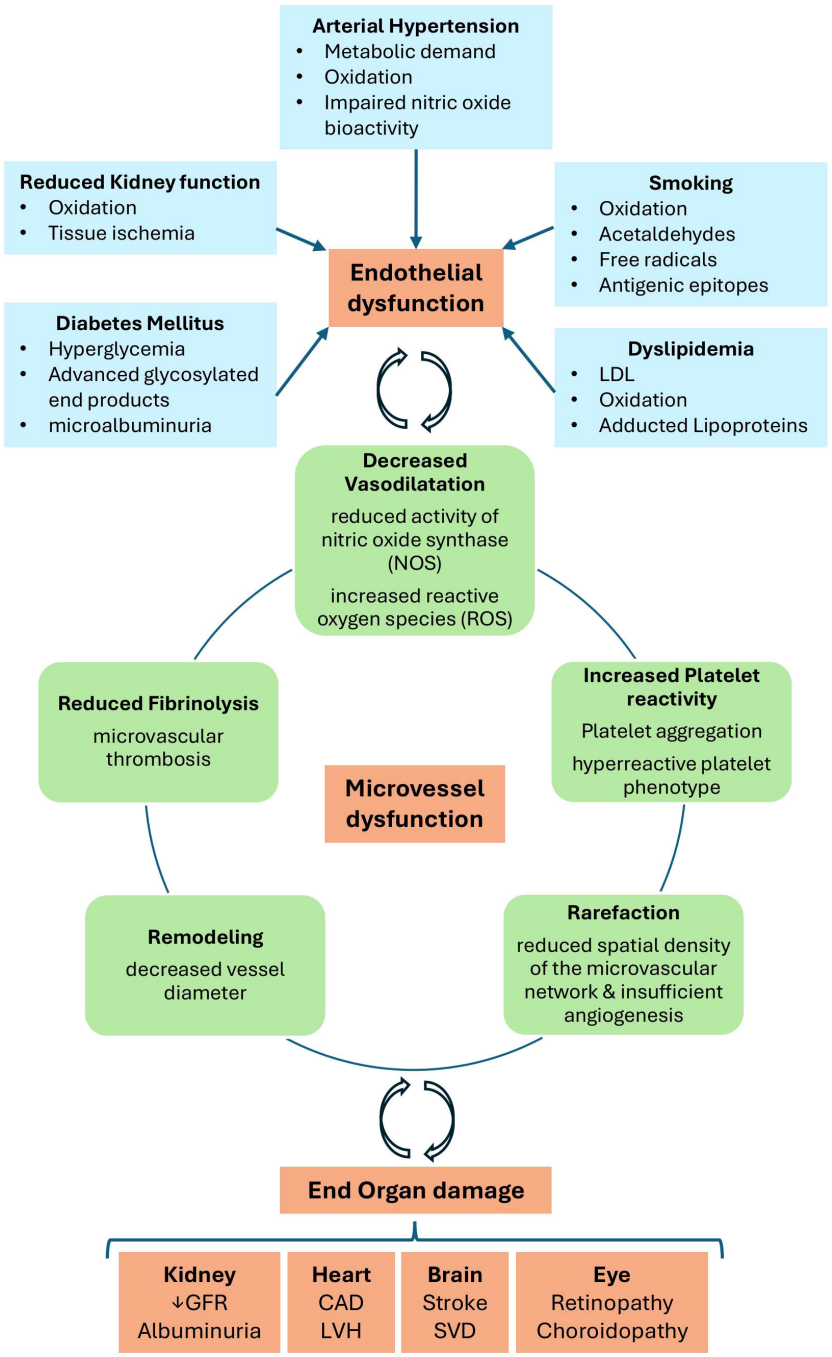

FIGURE 2
Initiation and consequences of microvascular disease (69, 70). Several factors including smoking, dyslipidemia, diabetes mellitus, arterial hypertension and reduced kidney function, contribute through multiple mechanisms to microvascular damage, ultimately leading to the development and progression of end-organ dysfunction. CAD, coronary artery disease; GFR, glomerular filtration rate; LVH, left ventricular hypertrophy; SVD, small vessel disease (adapted from Farrah et al., 2020).

267 on Web of Science. Restricting the research to results published in the last two decades and including only full-text publications in English yielded 123 publications on PubMed and 218 on Web of Science, respectively. Subsequently, the keyword combination was modified, in order to retrieve further useful results. This involved exchanging "microvasc*" with "ocular" or "retinal", resulting in additional 74 results. Following manual exclusion of duplicate records and unretrieved items, a total of 253 records were subjected to further analysis. After excluding results that did not meet inclusion criteria or were irrelevant, 29 full-text articles were identified, of which 3 could not be retrieved. In total, 26 articles and studies were included in this review.

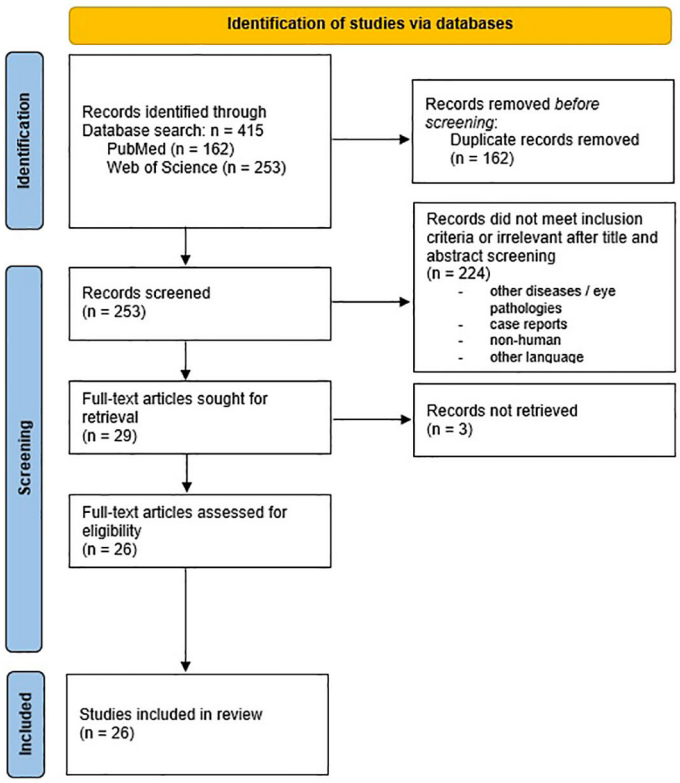

FIGURE 3
PRISMA 2020 flow diagram (125).

4 Methods of assessment of ocular microangiopathy markers

4.1 Retinal vessel analysis (RVA)

4.1.1 Definition of RVA

RVA is a non-invasive and non-mydriatic assessment method that employs ocular fundus vessel photography to calculate the diameters of retinal arterioles and venules. It involves the examination and measurement of the smallest blood vessels in the retina. Using a dedicated camera, RVA can be conducted either statically (capturing a single picture) (Figure 4) or dynamically (taking a series of pictures, after stimulating the regulation mechanism with a stimulus such as flicker light). Subsequently, the generated image is evaluated using specialized software, such as the "Vesselmap Analysis" (62).

The diameters of the retinal vessels are automatically measured, and vascular parameters are typically calculated using the formulas described during a large long-term epidemiologic study aimed at investigating the causes and risk factors for CVD, the ARIC study (80). This study included approximately 15,000 participants from four communities in the United States and documented various traditional CV risk factors, including high blood pressure, diabetes, and lifestyle habits to evaluate the diagnostic value of RVA in the assessment of the risk for myocardial infarction, stroke, and other CVD (80). The study found an important association between mean arterial pressure (MAP) with AVR which decreased after every 10 mmHg increase in MAP. The diameters of the retinal vessels were calculated in accordance with the dimensions and hemodynamics of the retinal microvasculature, employing a formula to quantify vessel narrowing as an arteriolar-venular ratio (AVR) (80, 81). To facilitate comparison of arteries across different eyes, the width of the central retinal artery (CRA), considered as the main trunk, was calculated based on measurements of all retinal arteries. Similar measures were performed for the venous caliber (81). These parameters are commonly expressed as central retinal venular equivalent (CRVE), central retinal arteriolar equivalent (CRAE), and AVR. The ratio of CRAE and CRVE is used to calculate the AVR and these parameters are used to quantify the average of the retinal vessels. The equivalents represent the central arterial inflow and venous outflow of the retina. The AVR serves as a marker reflecting the regulatory state of the retinal microcirculation (80, 81).

Imaging of constricted retinal vessels can provide information about ocular vascular impairment, thus serving as a surrogate marker for potential subclinical arteriosclerosis in the small vessels (67, 80). Software used for analysis is presented in (Table 1).

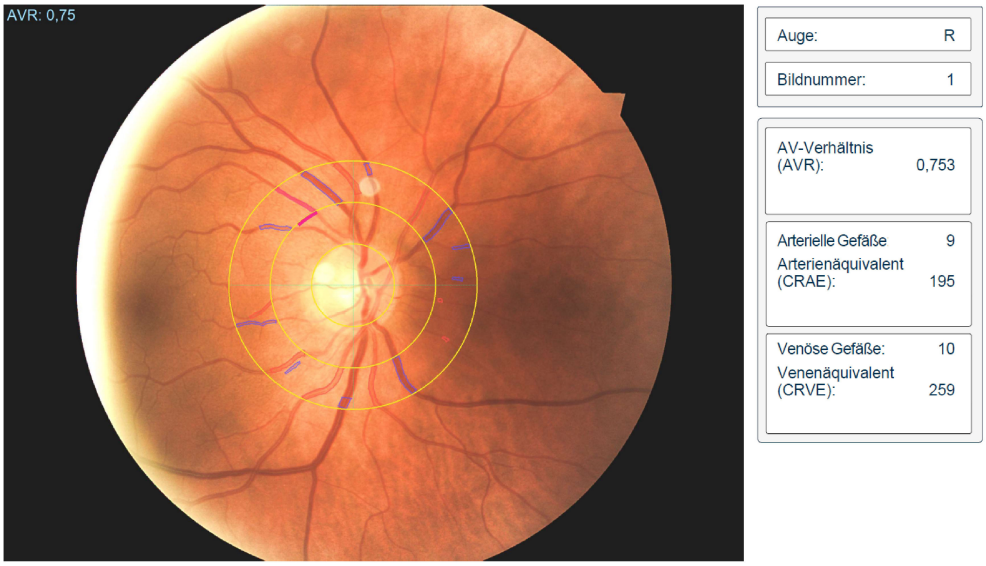

FIGURE 4
Retinal vessel analysis of a patient with systemic lupus erythematosus (AVR<0.78 associated with higher CV-Risk) (77).

4.1.2 Evidence from the general population

Hubbard et al. (80), in the population-based, cross-sectional ARIC cohort study, first described a significant correlation between retinal microvascular changes and MAP. Among 9,040 patients, focal arteriolar narrowing (OR 2.95, 95% CI 1.87–2.14) and arteriovenous nicking (OR 1.25, 95% CI 1.16–1.34) were observed in 7% and 6% of the cases, respectively. Patients with arteriolar stenosis had an 8 mmHg higher MAP, and patients with nicking showed a 3 mmHg increase (both $p < 0.0001$). During a mean follow-up of 16 years form an ARIC cohort, Seidelmann et al. (77) showed narrower retinal arteries (HR 1.06, 95% CI 1.01–1.11) and wider venules (HR 1.13, 95% CI 1.08–1.18) correlated with higher long-term risk of death and stroke. In a 15-year follow-up from a subgroup of the Inter99 study (study of CV and metabolic characteristics and lifestyle), Drobnjak et al. (82) found narrower CRAE associated with higher systolic blood pressure ($p < 0.001$), age ($p = 0.002$), and higher HDL ($p = 0.003$), while wider CRAE and CRVE were associated to smoking (both $p < 0.001$). Wong et al. (83) also confirmed in the Multi-Ethnic Study of Atherosclerosis study (MESA), within 5979 people between the ages of 45 and 84 residing in six US communities, associations between wider retinal vessels, smoking and diabetes. In a subgroup of the MESA study, Kawasaki et al. found narrower CRAE (OR 1.34) and wider CRVE (OR 1.18) were related to hypertension development after approximately 3

TABLE 1 Methods of ocular microangiopathy assessment.

	Software	Region of development
Retinal vessel analysis	Retinal Analysis (RA)	University of Wisconsin, Madison, WI
	Integrative Vessel Analysis (IVAN)	University of Wisconsin, Madison, WI
	Singapore "I" Vessel Assessment (SIVA)	National University of Singapore
	Vascular Assessment and Measurement Platform for Images of the Retina (VAMPIRE)	International collaborative project
Optical coherence tomography-angiography	AngioVue optical coherence tomography angiography	Optovue Inc., Fremont, CA, USA
	Cirrus HD-OCT Review Software	Carl Zeiss Meditec. Inc., Jena, Germany
	IMAGEnet	Topcon, Japan
	OCTAVA	National Institutes of Health in Bethesda, Maryland, USA
	ImageJ	National Institutes of Health in Bethesda, Maryland, USA
Spectral Domain Optical Coherence Tomography	Heidelberg Spectralis	Heidelberg Engineering, Heidelberg, Germany
	Cirrus HD-OCT	Carl Zeiss Meditec Inc, Dublin, CA

years of follow-up (84). Cheung et al. (74) found low HDL correlated with venous tortuosity, while high blood pressure, BMI, and age were associated with arterial tortuosity.

To summarize, RVA has been shown to correlate with CV events (e.g. stroke), CV mortality, and CV risk factors like hypertension, smoking, diabetes, age, BMI and blood lipids in the general population. It is therefore considered a non-invasive, easily reproducible method for assessing cardiovascular risk and potential disease progression.

4.1.3 Evidence in patients with autoimmune rheumatic diseases

Data on the value of RVA in rheumatic diseases are relatively scarce; most studies have employed a cross-sectional design and small sample sizes.

Lee et al. examined 50 SLE patients and an equal number of control subjects, matched for age and other CV risk factors, including BMI, arterial pressure, and cholesterol levels. The researchers observed narrower CRAE and CRVE and lower AVR in the patient group compared to controls. However, these findings did not reach statistical significance (CRAE: 89.7 ± 14.5 vs. 102.2 ± 11.3 µm, p=0.154; CRVE: 127.7 ± 14.8 144.1 ± 14.2 µm, p=0.609; AVR 0.69 ± 0.54 vs. 0.71 ± 0.66 p=0.223) (85).

Regarding association with activity indices, Babaoğlu et al. examined 47 RA patients, 32 SLE patients and 45 healthy controls by RVA after fundus photography (86). The authors found that elevated CRVE was associated with higher DAS28 values, underscoring an association between disease activity and retinal microangiopathy in the context of the disease. This can be an indicator of an association between disease activity and increased CV risk. Interestingly, this association was independent of CRP levels, indicating that angiopathy may also be found in the absence of laboratory inflammatory activity.

Larger meta-analyses, such as that of Liu et al., have sought to describe the relationship between inflammatory processes (primarily reflected in elevated CRP levels) and microcirculatory changes in the retina (87). This meta-analysis included 36 studies and tried to investigate whether there was an association between inflammation and altered retinal microvascular parameters in the general healthy population compared to patients with inflammatory diseases. The analysis included cohorts of patients with ARDs, such as RA and SSc, as well as CVD, high arterial pressure, obesity, type 2 diabetes mellitus, and acquired immunodeficiency syndrome (AIDS). A link between CRP and venous caliber was described in just over 20 studies. In summary, no evidence could be shown for the connection between retinal arteriolar caliber and CRP. However, there was a correlation between venous caliber and CRP (r = 0.09, 95% CI 0.05 to 0.12).

Interestingly, in patients with ARDs an association between elevated CRP and retinal parameters was only demonstrated in one of the two included RA studies. In this study, it was reported that CRAE was inversely associated with CRP (r = −0.293, p = 0.007). Moreover, retinal venular width correlated weakly with CRP levels (r = 0.218, p = 0.048) (88).

In another study, 26 patients with RA were examined using static RVA, alongside 13 patients with PsA and 12 patients with SpA (89). This patient cohort exhibited impairment of the retinal microvasculature. Specifically, when considering the entire cohort of rheumatic diseases, patients exhibited significantly higher CRVE values compared to a healthy control group, indicating wider venular diameters (Median 221 µm vs. 215 µm, p = 0.01 vs. 215 µm (IQR 196, 223); p = 0.01). Importantly, the patients included in this study were carefully selected to ensure the absence of any classic CV risk factors, such as arterial hypertension. Moreover, the study explored a potential relationship between physical activity (measured by a questionnaire) and vascular changes. Remarkably, just one additional hour of physical exercise per week was found to result in a notable reduction in CRVE, even after adjusting for age, gender, and BMI (CRVE of -0.59 µm; IQR -1.10, -0.08; p = 0.02). Interestingly, these patients did not show any abnormalities in large artery stiffness. Thus, it was postulated that retinal vessel analysis could be a sensitive biomarker to unmask vascular impairments, even in the absence of classic CV risk factors and unremarkable large artery examinations (Table 2).

We were not able to find RVA studies specifically in patients with SSc.

To summarize, RVA is a non-invasive method for assessing microvascular health by measuring the diameters of retinal arterioles and venules. It provides important insights into CV risk, as retinal vessel changes, such as narrowed arterioles (expressed by lower values of CRAE) and widened venules (expressed by higher values of CRVE), have been linked to elevated blood pressure, smoking, systemic inflammation, and CV surrogate markers/scores. While RVA has shown significant correlations with traditional CV risk factors in the general population, its application in ARDs remains underexplored. However, available studies suggest that retinal microvascular impairment may serve as an early marker of CV risk in these patients, particularly in relation to disease activity and inflammatory markers.

4.2 Optical Coherence Tomography Angiography (OCT-A)

4.2.1 Definition of OCT-A

OCT-A is a non-invasive method of blood flow measurement, especially the microcirculation of the posterior segment of the eye, i.e. retina and choroid. This is achieved by visualizing perfused vessels based on the flow registration of their erythrocytes, eliminating the need for injection of fluorescent substances (fluorescein angiography) (56). The perfusion can be visualized in a three-dimensional imaging (Figures 5, 6). The retinal ganglion cells (ganglion cell layer) and their nerve fibers (retinal nerve fiber layer) are supplied by the superficial vascular plexus. The deep vascular plexus is responsible for the inner plexiform, the inner nuclear and the outer plexiform layers, which contain the bipolar, amacrine and horizontal cells, connecting photoreceptors with retinal ganglion cells. The outer retinal layers, anatomically corresponding to the photoreceptors, do not include a vascular network. They are supplied by the choriocapillaris and the medium

TABLE 2 Selection of studies regarding the value of ocular microangiopathy markers in autoimmune rheumatic diseases.

Method	Authors	Number of patients	Disease	Main results	Statistical significance
RVA	Deiseroth et al. (89)	51	RA & Spondylarthritis	Patients exhibited significantly higher CRVE values compared to healthy controls [median 221 µm (interquartile range (IQR) 211, 231) vs median 215 µm (IQR 196, 223)].	p=0.01
	Anyfanti et al. (88)	87	RA	CRAE and AVR were decreased in patients compared to controls (78.8 ± 8.9 vs 90.2 ± 9.9 µm and 0.69 ± 0.09 vs 0.81 ± 0.09, respectively). CRAE and AVR were inversely associated with CRP (r=−0.293, r= −0.449, respectively). CRVE correlated positively with CRP (r = 0.218).	All, p<0.05
	Babaoğlu et al. (86)	47	RA	Elevated CRVE was associated with higher DAS28 (when DAS28>5.1, CRVE=220.4 µm, and when DAS28≤ 3.2, CRVE=214.4 µm)	p=0.03
	Lee et al. (85)	50	SLE	Narrower CRAE (89.7 ± 14.5 vs. 102.2 ± 11.3 µm) and CRVE (127.7 ± 14.8 vs. 144.1 ± 14.2 µm) and lower AVR (0.69 ± 0.54 vs. 0.71 ± 0.66) in the patient group compared to controls.	p=0.154, p=0.609, p=0.223, respectively
OCT-A	Ayar et al. (93)	106	RA	Retinal capillary plexus density in the macula of patients was lower than in healthy controls (50.99 ± 3.30 vs. 52.08 ± 2.36% in the SCP, 55.65 ± 5.73 vs. 57.53 ± 4.60% in the DCP).	Both, p<0.05
	Lee et al. (92)	12	RA	Macular retina vascular density and total microvascular density were lower in patients compared to control group.	Both, p<0.001
	Arfeen et al. (96)	20	SLE	Reduction of vessel densities in superficial and deep plexus macula regions in patients compared to controls (51.33 ± 3.48 vs. 53.19 ± 1.10% in the SCP, 52.28 ± 6.87 vs. 62.02 ± 1.89% in the DCP).	p= 0.037, p<0.001, respectively
	Ferringo et al. (98)	43	SLE	Reduced vessel density in both superficial and deep retinal vessels of patients compared to healthy controls (50.1 ± 5.6 vs. 53.0 ± 2.3% in the SCP, 55.4 ± 7.0 vs. 58.6 ± 5.4% in the DCP).QRISK3 score and IMT were identified as independent risk factors for changes in the retinal vessels	Both, p<0.05
	Carnevali et al. (99)	20	SSc	Reduced vessel density of the deep capillary plexus in patients compared to controls (47.29 ± 3.49 vs. 50.81 ± 3.71%)	p=0.00
	Hekimsoy et al. (100)	45	SSc	The vessel densities of the superficial and deep capillary plexus were lower in patients compared to controls (49.79 ± 3.47 vs. 51.49 ± 2.89% in the SCP, 51.56 ± 6.52 vs. 52.44 ± 5.43% in the DCP).	Both, p<0.05
SD-OCT	Bao et al. (58)	46	SLE	The density of the retinal capillary plexus was lower in patients than controls (5.3 ± 0.5 vs. 5.8 ± 0.5% in the SCP, 7.0 ± 0.6 vs. 7.4 ± 0.7% in the DCP).	Both, p<0.05
	Pieklarz et al. (113, 114)	33	SSc	The peripapillary choroidal vascularity index was significantly lower in patients compared to controls (64.25 ± 1.94 vs. 65.73 ± 2.12).	p<0.001
Retrobulbar color Doppler	Kal et al. (60)	20	RA	PSV and RI values of patients were higher for the ophthalmic artery and CRA than controls.	All, p<0.05
	Unal et al. (120)	25	RA	Positive correlation was observed between the RI of the ophthalmic artery and DAS 28 (r=0.199).	p=0.02
	Erdogmus et al. (121)	35	RA	Significant differences were observed in PSV, EDV, and RI of the ophthalmic artery and OA, as well as RI of the CRA between the control and patient groups.	All, p<0.05

(Continued)

TABLE 2 Continued

Method	Authors	Number of patients	Disease	Main results	Statistical significance
	Xue et al. (122)	30	SLE	Decreased blood flow velocity in patients along with increased RI and PI in the PCAs and CRA.	p<0.05
	Modrzejewska et al. (123)	43	SLE	Increase in RI in the patient group compared to the controls in all measured arteries.	p<0.01
	Wright et al. (124)	54	SLE	Difference in the morphology of the velocity waveform was observed in patients compared to controls, particularly in the ophthalmic artery and the CRA.	p<0.05

RVA, Retinal Vessel Analysis; CRVE, central retinal venular equivalent; CRAE, central retinal arteriolar equivalent; AVR, arteriolar-to-venular ratio; CRP, C-reactive protein; DAS28, disease activity score 28 joints; OCT-A, Optical Coherence Tomography Angiography; SCP, superficial capillary plexus; DCP, deep capillary plexus; SD-OCT, Spectral Domain Optical Coherence Tomography; PSV, peak systolic flow velocity; RI, resistance index; CRA, central retinal artery; EDV, end diastolic flow velocity; OA, ophthalmic artery; PI, pulsatility index; PCAs, posterior ciliary arteries.

and large vessels of the choroid. The number of volume scans taken around the fovea varies depending on the method employed (56). Software used for analysis is presented in (Table 1).

4.2.2 Evidence from the general population

In a group of patients with diabetic retinopathy, retinal vascular occlusion and age-related macular degeneration, OCT-A demonstrated consistent detection of microaneurysms (capillary saccular outpouchings, early sign for diabetic retinopathy), intraretinal microvascular abnormalities (capillary shunt vessels to provide blood flow in non-perfused areas), non-perfused areas (areas of retinal ischemia due to retinal vessel occlusion, causing neovascular disease), increase of the foveal avascular zone (FAZ) (sign of capillary occlusion around the generally avascular foveal

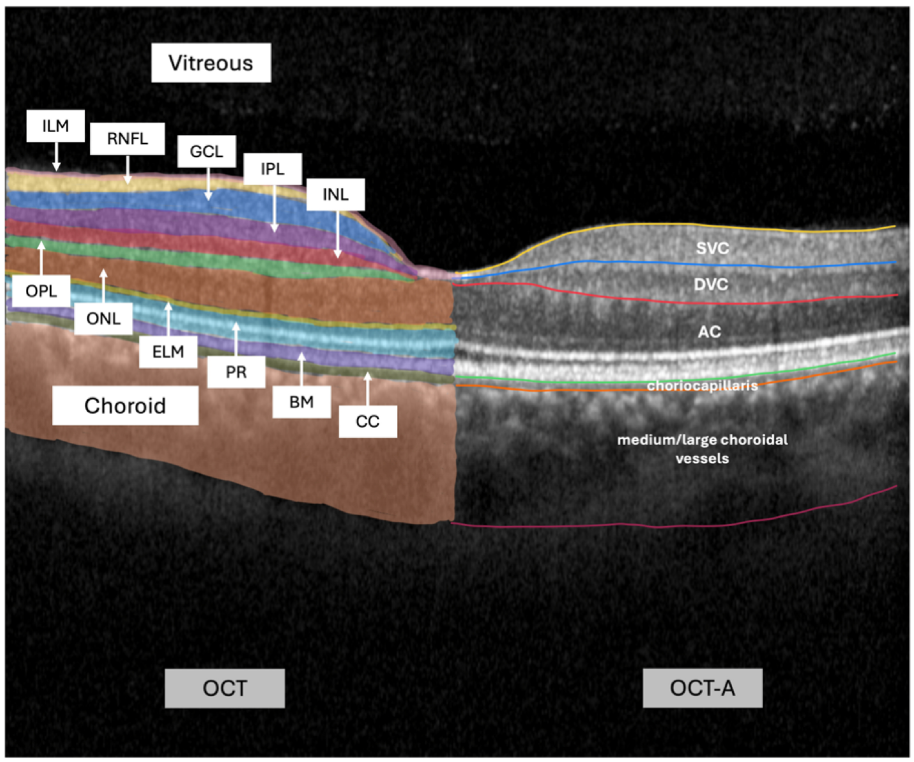

FIGURE 5
Optical coherence tomography of the macula with labeled retinal layers; left side: layers of structural optical coherence tomography (OCT); right side: layers of optical coherence tomography-angiography (OCT-A). Abbreviations, listed from inner to outer layers, from left section (OCT) to right section (OCT-A): ILM, internal limiting membrane; RNFL, retinal nerve fiber layer; GCL, ganglion cell layer; IPL, internal plexiform layer; INL, inner nuclear layer; OPL, outer plexiform layer; ONL, outer nuclear layer; ELM, external limiting membrane; PR, photoreceptor layers; BM, Bruch membrane; CC, choriocapillaris; SVC, superficial vascular complex/plexus; DVC, deep vascular complex/plexus; AC, avascular complex.

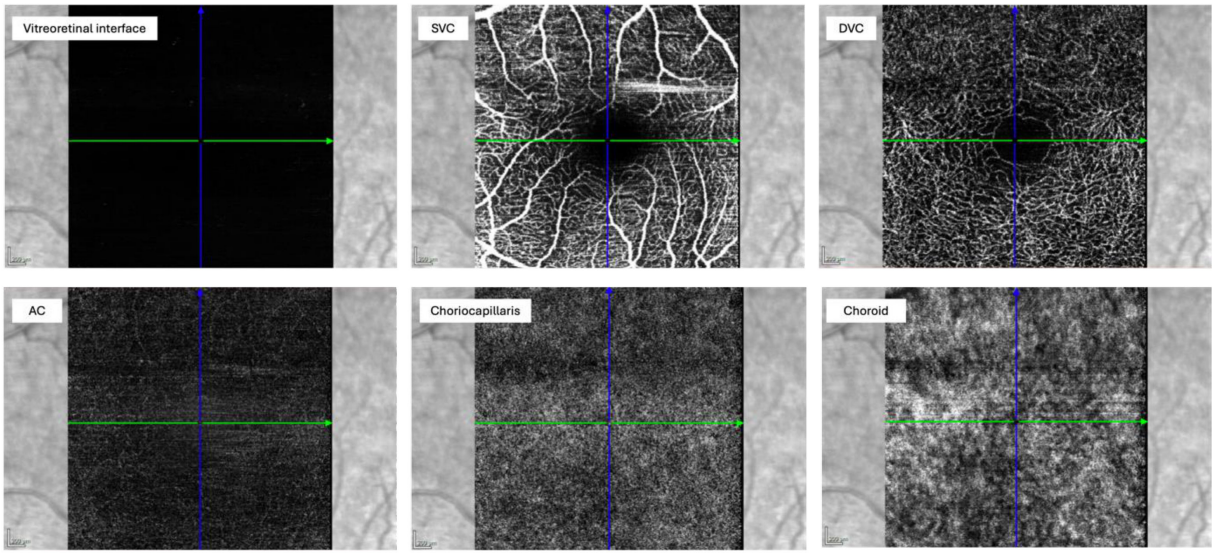

FIGURE 6
En-face view of the different layers in OCT-A. Abbreviations: SVC, superficial vascular complex/plexus; DVC, deep vascular complex/plexus; AC, avascular complex.

zone) and neovascularization (retinal-choroidal hypoxia leads to vascular ingrowth by release of vascular growth factors) (56).

Sun et al. conducted a case-control study involving 94 eyes from participants with systemic hypertension and 46 eyes from healthy controls. The study found that hypertensive subjects exhibited a significant reduction in macular vessel density in both the superficial [OR 0.02; 95% CI, 0 to 0.64; p = 0.027] and deep venous plexuses [OR 0.03; 95% CI, 0 to 0.41; p = 0.009], along with an enlargement of the deep avascular zone of the fovea compared to controls. These findings suggest that hypertension is associated with reduced retinal vessel density and an increased avascular zone, particularly in the deep venous plexus, as observed using OCT-A. This highlights OCT-A as a promising clinical tool for monitoring hypertensive damage and identifying patients at risk (90).

Importantly, these associations have also been seen in the context of further explorations and ultimately in a meta-analysis evaluating the results of 11 studies on the topic (84). In this meta-analysis it could be shown that the eyes of patients with systemic hypertension have a significantly lower superficial and deep vessel density in the macula compared to healthy control groups. These findings indicate that the OCT measurement approach may offer insights into preclinical microvascular alterations and a connection to an important modifiable CV-risk factor.

To conclude, OCT-A findings in the small retinal vessels could potentially serve as biomarkers for CVD risk stratification related to hypertensive damage in end organs such as the brain, heart, and kidneys (91).

4.2.3 Evidence in patients with autoimmune rheumatic diseases

4.2.3.1 Rheumatoid arthritis

Lee et al. conducted a cross-sectional study in 12 RA patients, demonstrating that macular retina vascular density in various subregional superficial retinal layers, as measured by OCT-A, was lower compared to an age- and sex-matched control group (superficial microvascular density: 1.72 ± 0.07 vs 1.88 ± 0.017 and total microvascular density: 1.71 ± 0.052 vs. 1.78 ± 0.027; both $p < 0.001$). Moreover, a reduction in vessel density was observed in the deeper retinal layers (92).

Ayar et al. employed a comparable methodology, examining the correlation between OCT-A outcomes and RA disease activity in a cross-sectional study comprising 106 RA patient eyes and 71 healthy control eyes (93). They found that retinal capillary plexus density (CPD) in the macula of RA patients was lower than in healthy controls (50.99 ± 3.30% in RA vs. 52.08 ± 2.36% in HC, p = 0.013). No significant difference was found between active and inactive RA patients (51.01 ± 2.92% in active vs. 50.97 ± 3.73% in inactive RA, p = 0.947).

The clinical relevance of the above observations is not yet clear. The lower vessel density might be a precursor for retinal vasculitis, which however is a rare complication in RA (94). It further may serve as an early biomarker to detect RA-related ocular involvement (92). Still, RA-related complications need to be distinguished from medication side effects, as hydroxychloroquine/chloroquine may cause retinopathy, which may be accompanied by increased FAZ and decreased vessel density in OCT-A (94, 95).

4.2.3.2 Systemic lupus erythematosus

In a cross-sectional observational study, Arfeen et al. evaluated retinal microvascular density in 20 female SLE patients and 20 female control subjects, after excluding patients exhibiting signs of retinopathy (96). The objective was to correlate vascular density with disease activity and damage risk. The findings revealed no statistically significant differences in central foveal thickness (CFT) and FAZ between SLE patients and controls ($p > 0.05$). Nevertheless, a slight reduction in vessel densities in both

superficial and deep plexus macula regions was observed in the SLE patient group (superficial (whole): 51.33 ± 3.48 vs. 53.19 ± 1.10, p = 0.037; deep (whole): 52.28 ± 6.87 vs. 62.02 ± 1.89, p < 0.001). Additionally, an inverse correlation between the SLICC/ACR SDI and vessel density in some macula sectors (p > 0.05) was found. The study concluded that OCT-A can non-invasively assess retinal vessel density, allowing for early detection of altered retinal circulation. The authors suggested that OCT-A could be useful in evaluating disease activity and damage score in SLE patients.

Conigliaro et al. compared a total of 52 eyes of SLE patients to 40 eyes of healthy controls via OCT-A and found reduced retinal microvascular density in SLE patients, particularly in those with kidney involvement (p = 0.02 and p = 0.008) (97). They concluded that vessel density could serve as a quantitative metric for capillary network health, with correlations observed between vessel density and age, best-corrected visual acuity, as well as SLE disease activity and damage accrual. Additionally, the authors proposed that hydroxychloroquine may confer a protective effect on microvascular structures.

In a further cross-sectional study, Ferringo et al. highlighted the increased CV risk in 43 SLE patients, assessed using ACC/AHA and FRS guidelines, and its impact on vascular density measured with OCT-A (98). A negative correlation was observed between deep vessel density and systolic blood pressure (p = 0.011), cIMT (p = 0.027), age (p = 0.001) and QRISK3 Score (p < 0.001). An age- and sex-adjusted multivariate analysis verified that QRISK3 score (p = 0.049) and IMT (p = 0.039) were independent risk factors for reduced retinal vessel density. Additionally, they found higher triglycerides (p = 0.019), FRS (p = 0.008) and reduced vessel density in both superficial (p < 0.001) and deep (p = 0.005) retinal vessels compared to healthy controls (n=34). Importantly, the authors assume that despite low or moderate QRISK3 and FRS levels, SLE patients show striking retinal vascular changes that correlate with subclinical atherosclerosis. These findings suggest that optical OCT-A could play an important role in assessing preclinical cardiovascular involvement in SLE that classic risk scores possibly underestimate.

4.2.3.3 Systemic Sclerosis (SSc)

In a study comprising 20 SSc patients and 20 healthy subjects, Carnevali et al. showed a significantly reduced vessel density of the deep capillary plexus DCP-VD in the SSc group in the whole scan (mean (S.D.) = 47.29 (3.49), p < 0,01) and in the perifoveal (mean (S.D.) = 49.07 (3.02), p < 0,01), superior (mean (S.D.) = 49.41 (3.21), p = 0,02), inferior (mean (S.D.) = 48.72 (3.04), p < 0,01), nasal (mean (S.D.) = 49.46 (3.10), p = 0,01) and temporal (mean (S.D.) = 49.53 (3.33), p = 0,02) regions (99).

In accordance with these findings, Hekimsoy et al. conducted a study involving 45 SSc patients and 45 control subjects (100). The results demonstrated a significant reduction in subfoveal choroidal thickness (SFCT) in SSc patient's eyes on OCT when compared to healthy subjects (274.47 ± 35.88 vs. 300.95 ± 28.06 p < 0,001). This further supports the effectiveness of OCT-A in visualizing microvascular changes.

In accordance with the aforementioned findings, Mihailovic et al. were able to replicate these results in 22 patients with SSc and 22 healthy controls. The vascular density of the superficial OCT angiogram (OCTA-SCP), and the choriocapillaris (OCTA-CCP) was significantly lower in SSc patients (OCTA-SCP: SSc group: 43.10%, control group: 45.25%, p = 0.036; OCTA-CC: SSc group: 111.07%, control group: 116.96%, p = 0.001). Interestingly, they also reported an association between nailfold capillaroscopy results and vascular density. Their correlation analysis demonstrated a negative correlation between skin score and vascular density of OCTA-SCP (p < 0.05) and a positive correlation between nailfold capillaroscopy and vascular density of OCTA-CC (rho = 0.456, p < 0.05) (101).

A recently published study by Cutolo et al. highlighted the link between peripheral vascular damages (as assessed by nailfold video capillaroscopy (NVC) for morphological microvascular statuses and laser speckle contrast analysis (LASCA) to assess the functional perfusion) and ocular vascular changes detected by OCT-A. An important finding was the direct correlation between the mean capillary count at NVC and the retinal perfusion values of the superficial and deep vascular plexus (SVP and DVP) in OCT-A (r = 0.3, p = 0.01 and r = 0.28, p = 0.01) in 32 SSc patients when compared to 27 sex- and age-matched healthy controls. The mean peripheral perfusion, assessed by LASCA, showed a positive correlation with both the retinal (DVP) and choroidal (choriocapillaris slab, CC) perfusion (r = 0.29 (DVP) and r = 0.28 (CC), both p = 0.01) (102).

A further possible utility of OCT-A seems to be in the distinction between primary Raynaud's phenomenon (PRP) and SSc, as shown in a cross-sectional study by Erturk et al. (103). A group of 38 SSc patients was included and further divided into very early SSc (VEDOSS), limited cutaneous SSc (lcSSc) and diffuse cutaneous SSC (dcSSC). Herein, it was found that the PRP group exhibited significantly higher whole, parafoveal, and perifoveal SCP and DCP vascular density values compared to the SSc subgroups (all; p < 0.001). In contrast, the lcSSc group had significantly lower foveal SCP vascular density than both the PRP and VEDOSS groups (p < 0.001). Additionally, the dcSSc group showed significantly lower foveal SCP vascular density than the PRP group (p < 0.001). However, the perifoveal SCP vascular density values were found to be significantly higher in the dcSSc group compared to the lcSSc group (p < 0.001). Lastly, the FAZ perimeter in the lcSSc group was significantly greater than that in the VEDOSS group (p = 0.017) (Table 2).

To summarize, OCT-A provides a non-invasive method for visualizing and quantifying microvascular structures in the retina and choroid. It has demonstrated significant utility in detecting early signs of diseases such as diabetic retinopathy, retinal vascular occlusion, and age-related macular degeneration, offering valuable insights into microvascular changes without the need for invasive dye injections. Additionally, OCT-A has shown promise in assessing microvascular alterations in patients with systemic diseases with evidence suggesting its potential use in evaluating disease activity, early ocular involvement, and medication side effects. Importantly, different associations between OCT-A values and CV-risk factors could be found in patients with ARDs (e.g. negative associations of vessel density with systolic blood pressure, cIMT (98), and age (97)). Moreover, abnormal QRISK3 score and

cIMT values were identified as independent risk factors for changes in the retinal vessels (98). These findings suggest that OCT-A may hold diagnostic value in cardiovascular screening and the detection of microangiopathy in ARDs. However, systematic data and consistent longitudinal examinations of its utility in ARDs are still scarce.

4.3 Spectral Domain Optical Coherence Tomography (SD-OCT)

4.3.1 Definition of SD-OCT

This method utilizes a spectrometer to simultaneously measure multiple wavelengths of light. This provides faster and more efficient data acquisition of the tissue layers of the retina, while reducing artifacts and improving the resolution of the generated images in comparison to traditional OCT (57, 104). OCT enables a structural examination of the retinal layers and potential diseases. The high axial resolution of 3 to 5 µm allows a precise diagnosis and the possibility to detect early changes in follow-up examinations (105). Figure 4 shows the different retinal layers at the macula provided by SD-OCT (left section).

4.3.2 Evidence from the general population

A meta-analysis of 12 studies from Salehi et al. (106) included various SD-OCT parameters to measure the choroidal thickness of patients with obesity (634 patients and 569 controls) and reported thinner ocular layers in isolated regions of the retina in patients with higher BMI than in controls (sub-foveal region (standardized mean difference SMD: -0.24, $p = 0.05$), region 1.0 mm nasal to fovea (SMD: -0.38, $p<0.01$; region 1.0 mm temporal to fovea (SMD: -0.38, $p = 0.05$). In another systemic review from the same authors (107) which included 25 studies with 1,632 cases of age-related macular degeneration and 1,445 healthy controls, a significant thinner subfoveal choroidal thickness in obese individuals was also found (SMD, -0.62, $p = 0.0077$). In different retinal regions like nasal and temporal to the fovea, they also found significant decreased choroid thickness. These abnormalities could impact the visual function.

Furthermore, OCT of the choroid has a high diagnostic value for various ophthalmological entities. The group of pachychoroid spectrum diseases (among others central serous retinopathy, pachychoroid neovasculopathy and polypoidal choroidal vasculopathy) exhibit dilated choroidal vessels, the so-called pachyvessels, and an increased choroidal thickness, which can be detected by OCT. On the other hand, age-related macular degeneration (108), severe diabetic retinopathy (proliferative or diabetic macular edema) (109) and acute anterior ischemic optic neuropathy (110) are associated with a thin choroidal thickness.

Aydin et al. evaluated in a prospective cross-sectional study the SD-OCT parameters central macular thickness (CMT) and choroidal thickness (CT) in 92 patients with CV-risk factors (measured via SCORE) and 21 healthy individuals. CT was significantly lower at the subfoveal location in all study groups ($p < 0.05$), as well as in the nasal and temporal quadrants of the high CV-risk and coronary arterial disease group ($p < 0.05$) (111). This indicates that ocular microvascular changes could be used as a promising new biomarker for predicting the occurrence of coronary heart disease in the future.

A further cross-sectional study compared advanced SD-OCT and OCT-A parameters in chronic hypertension, severe hypertensive retinopathy, and healthy controls (112). The hypertensive group (n = 45 eyes) showed significantly lower OCT parameters compared to healthy controls (n = 50 eyes). Notably, a significant correlation was found between OCT-A and SD-OCT parameters in the hypertensive group, but not in controls. OCT-A also revealed reduced vascular and perfusion density and a significantly larger FAZ area in hypertensive patients. These findings suggest that chronic hypertension or past hypertensive episodes impact retinal microcirculation, ultimately affecting retinal thickness.

To summarize, studies of SD-OCT in the general population found correlations with traditional CV risk factors like BMI and hypertension and with the SCORE system.

4.3.3 Evidence in patients with autoimmune rheumatic diseases

4.3.3.1 Systemic lupus erythematosus

In a study examining 46 SLE patients, 32 without (NLR) and 14 with lupus retinopathy (LR), Bao et al. demonstrated that the superficial retinal capillary plexus (SRCP) density was significantly lower in the NLR group than in the 50 healthy control subjects (58). Furthermore, the LR group exhibited a further reduction in density (control 5.8 ± 0.5 vs. NLR 5.6 ± 0.4, $p = 0.007$; vs. LR 5.3 ± 0.5, $p < 0.001$). The authors hypothesized that this could be an early indicator of alterations in ocular structures, as well as a potential marker for disease progression (58).

4.3.3.2 Systemic sclerosis

Pieklarz et al. compared in two studies (2023 and 2024) 33 SSc patients to 40 healthy controls via SD-OCT and found that the peripapillary choroidal vascularity index was significantly lower in patients (2023: 64.25 ± 1.94 vs. 65.73 ± 2.12, $p < 0.001$ 2024: 67.26 ± 2.63 vs. 66.30 ± 2.82 $p<0,05$) (113, 114). The choroidal vascularity index (CVI) calculates the ratio of the luminal area (LA) to the total choroidal area (TCA) and thus enables a quantitative analysis. Their results place a new focus on the impairment of the choroid, which would support the vascular hypothesis for an elevated risk of glaucomatous optic neuropathy in patients with SSc.

CVI may be altered in various ocular and systemic diseases, however, so far it has only been applied in studies, validation in large population-based studies is lacking and the clinical relevance is not conceivable.

In a further study, Carnevali et al. (99) highlighted the ability of SD-OCT to detect ocular microvascular density abnormalities in patients with SSc. They analyzed the eyes of 20 SSc patients and 20 control subjects. Patients had significantly lower deep capillary plexus vessel density compared to control (47.29 (3.49) vs. 50.81 (3.71), $p = 0.00$). However, no significant difference was observed in CVI and superficial capillary plexus (SCP) (CVI: 66.58 (1.13) vs.

66.70 (1.83), p = 0.80; SCP: 45.67 (5.21) vs. 45.64 (3.22), p = 0.98) (Table 2).

To our knowledge, there are no studies examining SD-OCT in RA patients to date.

To summarize, SD-OCT is an advanced imaging technique that allows for high-resolution, non-invasive structural analysis of the retina and choroid. It has shown benefits in assessing ocular changes in various conditions, such as obesity, age-related macular degeneration, and diabetic retinopathy, where it can detect both thinning and thickening of the choroid. The few existing data on SD-OCT also suggest a possible value in identifying early microvascular alterations and potential ocular complications in ARDs like SLE and SSc. However, associations of SD-OCT with CV associated parameters have been only examined in the general population and not in patients with the included ARDs.

4.4 Retrobulbar color Doppler

4.4.1 Definition of retrobulbar color Doppler

The retrobulbar color Doppler examination is used to assess ocular blood flow, which is frequently impaired in the presence of CV disease, including carotid artery occlusion, cerebrovascular disease, heart failure, and acute coronary syndrome (61). The method allows for the visualization of the direction and speed of blood flow without providing any information about vessel diameter. Consequently, in some studies, OCT measurements are integrated to obtain comprehensive data on vessel diameter, density and anatomical course (61). The following parameters are determined: the peak systolic flow velocity (PSV), the end diastolic flow velocity (EDV), and the resistance index (RI). The RI is defined as the ratio of the difference between PSV and EDV to PSV (RI = (PSV − EDV)/PSV) (61).

4.4.2 Evidence from the general population

Retrobulbar Doppler indices were evaluated in 66 patients with transient ischemic attack (TIA) or minor stroke (115). Patients with carotid occlusive disease exhibited reduced flow velocities in the OA and CRA (all p < 0.02). In this work, it could be shown that CDI is suitable for the detection of carotid occlusion. Measuring blood flow velocities in the OA and CRA was pointed out as a valid method to identify patients with carotid stenosis, indicating its possible use to give additional information on hemodynamics of carotid arterial disease (115).

Similarly, Reynolds et al. demonstrated that Doppler ultrasound is an effective diagnostic tool for detecting ipsilateral stenosis or occlusion of the ACI. In a study of 152 patients, a reversed flow direction in the orbital artery on one side was found to be a highly specific (100%) marker for high-grade ipsilateral carotid artery stenosis or occlusion (116).

In another study of 18 patients with chronic heart failure symptoms and left ventricle ejection fraction below 55% compared to 21 healthy controls, Almeida-Freitas et al. (117) found that patients revealed significantly lower mean diastolic velocities (5.14 ± 2.4 cm/s vs. 7.44 ± 3.5 cm/s, p = 0.007) and higher RI (0.76 ± 0.08 vs. 0.70 ± 0.08, p=0.04) of the ophthalmic artery (OA). Additionally, they showed a negative correlation between systolic blood pressure and the RI of the OA (r = -0.47, p = 0.007), as well as a positive correlation between diastolic velocity of the OA and systolic blood pressure (r = 0.44, p = 0.02). The authors concluded a possible association to low cardiac output.

Meng et al. summarized data of changes in retrobulbar blood flow measured with retrobulbar color Doppler in a relevant meta-analysis (118). They investigated 13 prospective studies involving 912 eyes from diabetic patients and 553 eyes from healthy controls. The comparison revealed significant differences in color Doppler ultrasound between diabetic eyes without retinopathy and healthy eyes. Specifically, PSV and RI of the ophthalmic artery were elevated (mean difference PSV: 2.25, 95% CI 0.80-3.71, p = 0.002; RI: 0.03, 95% CI 0.01-0.66, p = 0.02). Additionally, both the PSV and EDV of the CRA were decreased (mean difference PSV: -2.44, 95% CI -2.41 to -0.66; EDV: -0.65, 95% CI -1.13 to -0.18; p = 0.07 for both). Furthermore, significant differences were observed between patients with diabetic retinopathy and healthy controls in the following parameters: EDV of the OA and the CRA were significantly reduced in patients (mean difference OA: –1.59, 95% CI –2.46 to –0.72; CRA: –1.18, 95% CI –1.52 to –0.84; both p < 0.001). Moreover, the RI of the OA was higher in the patient cohort compared to the control group (mean difference RI: 0.05, 95% CI 0.02 to 0.08; p = 0.008). These findings suggest that retrobulbar color Doppler could potentially be a valuable diagnostic tool for evaluating microangiopathy in diabetic patients.

Karami et al. conducted a comparative analysis of hemodynamic changes in retrobulbar vessels between diabetic retinopathy patients (n = 98) and a healthy control group (n = 25). They found a significantly higher RI (p = 0.009) and pulsatility index (PI, p = 0.029) in the ophthalmic arteries of diabetic retinopathy patients than in controls (119).

4.4.3 Evidence in patients with autoimmune rheumatic diseases

4.4.3.1 Rheumatoid arthritis

Kal et al. have examined ocular blood flow in patients with RA (60). A total of 20 RA patients and 20 healthy control subjects were included in the study. In each eye, the OA and the CRA were examined with retrobulbar color Doppler ultrasound using a 7.5-MHz linear phase probe. The following parameters were determined: PSV, EDV, and RI. The PSV values of the patients were significantly higher for the OA (p = 0.001; p < 0.001) and the CRA (p = 0.020; p = 0.004). Similarly, the RI values of patients from the ophthalmic (p = 0.001) and CRA (p = 0.005) were significantly higher. In addition, OCT revealed that the perifoveal and subfoveal choroidal thickness were reduced in the patient group.

Unal et al. conducted similar Doppler examinations in a RA and a control group, analyzing 25 patients with active RA and comparing them with 24 healthy subjects (120). A significant positive correlation was observed between the RI of the OA and the Disease Activity Score (DAS 28) (p = 0.02, r = 0.199). Additionally, median RI values of the OA, posterior ciliary artery

(PCA), and CRA differed significantly between patients with active RA (evaluated by DAS 28) and the control group ($p < 0.05$).

These findings are consistent with those of Erdogmus et al., who also utilized Doppler sonography to investigate orbital blood flow in 35 RA patients compared to 35 healthy subjects (121). Significant differences were observed in PSV, EDV, and RI of the ophthalmic artery and OA, as well as RI of the CRA between the control and RA patient groups. Importantly, a slightly lower ocular blood flow was observed in RA patients compared to controls.

4.4.3.2 Systemic lupus erythematosus

Xue et al. demonstrated significant alterations in retrobulbar vessel blood flow in patients with SLE (122). By employing color Doppler ultrasound and evaluating the same arteries and parameters as described above, a correlation was identified between disease activity and the PI values of the ophthalmic arteries. The authors reported decreased blood flow velocity in SLE patients along with increased RI and PI in the PCA and CRA ($p < 0.05$).

Modrzejewska et al. found retrobulbar resistance disturbances in a study of 43 female SLE patients and a 43 female controls measured by RI in various arteries (123). The color Doppler ultrasound in all measured arteries, the OA, the CRA, the posterior lateral ciliary artery (LPCA) and the medial posterior ciliary artery (MPCA), showed a significant increase in RI in the patient group compared to the controls (mean values; ophthalmic artery 0,73 vs. 0,68; CRA 0,67 vs. 0,64; LPCA 0,67 vs. 0,61; MPCA 0,66 vs 0,60; all $p < 0.01$). In addition, correlations were identified between age and the CRA-RI of SLE patients ($p = 0.0376$).

Similarly, Wright et al. (124) utilized Doppler sonography to investigate changes in microangiography in 54 SLE patients and 32 control subjects. They examined the OA, CRA and common carotid artery (CA) for changes in the morphology of the flow velocity waveforms and tested the correlation with RI. No significant difference was observed between the groups with regard to RI in any of the evaluated arteries (OA 0.71 ± 0.08 vs 0.70 ± 0.10; CRA 0.68 ± 0.11 vs 0.70 ± 0.09; CA 0.69 ± 0.10 vs 0.69 ± 0.11). However, the morphology of the flow curves showed different dynamics in the microvasculature of the ocular vessels in the SLE patients. Moreover, a significant difference was observed in the morphology of the velocity waveform within the low frequency range (1.0–1.8 Hz) in SLE patients compared to controls, particularly in the OA and the CRA ($p < 0.05$) (Table 2).

To summarize, retrobulbar color Doppler ultrasound is a valuable diagnostic tool for assessing ocular blood flow in systemic diseases. It allows for measuring the PSV, EDV, RI and PI in key ocular vessels such as the OA and the CRA. Current studies revealed promising insights into autoimmune diseases like RA and SLE by identifying changes in blood flow and vascular resistance in ocular and other vessels. Given that alterations in ultrasound indices in the general population are often linked to increased CV risk or past CV events, it is possible that similar associations exist in rheumatic diseases. However, large longitudinal studies with follow-up are needed to further explore and clarify these associations.

5 Discussion

It is well established that patients with ARDs are at an elevated risk of developing CV disease (e.g. stroke, coronary artery occlusion myocardial infarction). Therefore, early detection of CV risk factors and pathological vascular changes is crucial in these patient populations. Nevertheless, current evidence supporting the effective stratification and early detection of CV risk remains limited, and traditional CV risk scores have been shown to underestimate risk in ARDs. Several surrogate markers have been proposed as potential means of identifying high-risk patients in the early stages. However, these markers are not yet used routinely in clinical settings.

Microangiopathy has been described to lead to an increased vascular resistance and therefore reduced blood flow to the end organs. Consequently, the eye, often referred to as the "window to the heart," appears to be a valuable organ for assessing microvascular changes. Ocular analyses seem to be able to reveal CV risk before other surrogate parameters do. The non-invasiveness of the measurements is particularly favorable. In particular, OCT-A appears to be a highly promising technique, offering a relatively simple and highly reproducible approach. Another advantage is the standardized evaluation of results, which is based on automated software. SD-OCT also enables faster and more efficient data collection of the retina while reducing artifacts compared to conventional OCT. Additionally, RVA offers several advantages, including cost-effectiveness, the absence of radioactive radiation, and robust inter-examiner reproducibility. The advantages of retrobulbar color imaging include its accessibility in numerous clinical settings and its capacity to evaluate vascular conditions and detect other ocular pathologies, which can be readily identified by trained personnel. In this review, we provided a comprehensive overview of these markers, examining their associations with key CV risk factors, disease activity, surrogate CV parameters, and traditional CV risk scores.

The studies discussed herein have however several limitations. First, small sample sizes and heterogeneity in methodologies and measured parameters limit the generalizability of results and prevent the recommendation of a standardized approach for incorporating these markers into CV risk stratification strategies. On the other hand, these markers have demonstrated predictive value for CV events in the general population, and initial data in ARDs show promising potential. Second, the studies did not allow for prognostic conclusions regarding the value of the included CV surrogate markers in predicting actual mortality or morbidity in ARDs, as most were not conducted in a longitudinal manner. Future research should focus on larger patient populations and establish associations between these surrogate markers and hard CV outcomes through well-designed follow-up studies.

In conclusion, this review underscores the opportunities provided by various methods for assessing the eye's microvascular status in patients with ARDs. We also aimed to highlight the significance of early detection of risk factors and pathological

vascular changes in these patient populations. Looking ahead, artificial intelligence holds the potential to significantly enhance the evaluation of ocular imaging, offering a promising approach for the early detection of CV risk. As early microvascular lesions can be reversed, incorporating diagnostic methods such as OCT-A with advanced imaging techniques, RVA, and retrobulbar color Doppler into regular check-ups could facilitate early diagnosis, prevent CV events, and ultimately improve patient outcomes and quality of life.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Author contributions

BS: Investigation, Visualization, Writing – original draft, Writing – review & editing. ALZ: Investigation, Visualization, Writing – original draft, Writing – review & editing. JS: Investigation, Writing – review & editing. RHF: Methodology, Writing – review & editing. AF: Methodology, Writing – review & editing. AS: Project administration, Resources, Supervision, Validation, Writing – review & editing. CG: Investigation, Supervision, Validation, Writing – review & editing. JW-M: Project administration, Resources, Supervision, Validation, Writing – review & editing. MA: Investigation, Visualization, Writing – review & editing. KT: Conceptualization, Methodology, Supervision, Validation, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

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frontiers | Frontiers in Immunology

TYPE Original Research
PUBLISHED 24 April 2025
DOI 10.3389/fimmu.2025.1509941

OPEN ACCESS

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RECEIVED 11 October 2024
ACCEPTED 31 March 2025
PUBLISHED 24 April 2025

CITATION
Zhang T, Gentry CA, Kuderer NM, Lyman GH, Ng B and Michailidou D (2025) Association of SSRI and SNRI use with incidence of cardiovascular events in veterans with giant cell arteritis and polymyalgia rheumatica. *Front. Immunol.* 16:1509941. doi: 10.3389/fimmu.2025.1509941

Association of SSRI and SNRI use with incidence of cardiovascular events in veterans with giant cell arteritis and polymyalgia rheumatica

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The leading cause of death in patients with giant cell arteritis (GCA) and polymyalgia rheumatica (PMR) is cardiovascular disease. The objective of this study was to determine whether the use of selective serotonin reuptake inhibitors (SSRI) and serotonin norepinephrine reuptake inhibitors (SNRI) in veterans with GCA and PMR could have a cardio-modulatory effect as compared to nonuse. Patients with GCA and PMR were identified through the Veterans Affairs Informatics and Computing Infrastructure. After a 2:1 propensity score matching for SSRI or SNRI users, we identified nonusers with similar covariates. We then applied a multivariate logistic regression (MLR), to calculate the odds ratio (OR) for cardiovascular event (CVE) outcomes within 5 years after the index date. Related hazard ratios (HR) were also calculated to validate the discovery of our findings. We identified 2249 patients with GCA and 3906 patients with PMR. Among patients with GCA, 174 (27%) SSRI users had incident cardiovascular disease as compared to 47 (28%) SNRI users and 277 (19%) nonusers; in the PMR cohort, 108 (13%) were SSRI users compared to 71 (15%) SNRI users and 255 (11%) nonusers. The adjusted ORs of the CVE outcome associated with venlafaxine (2.44, p=0.01) and sertraline (1.45, p=0.04) were significantly greater than 1 in GCA, with similar results observed in the PMR cohort (2.01, p=0.02, and 1.45, p=0.04, respectively). Cox-regression analysis was also conducted, and the hazard ratios were qualitatively consistent with the MLR analysis. In conclusion, the adjusted risk of CVE in patients with GCA or PMR using either venlafaxine or sertraline was higher than that in the non-exposed groups.

KEYWORDS

giant cell arteritis, polymyalgia rheumatica, SSRI, SNRI, ischemic stroke, TIA, myocardial infarction, angina

Introduction

Giant cell arteritis (GCA) and polymyalgia rheumatica (PMR) are chronic idiopathic inflammatory conditions of unclear etiology (1) with significant implications for cardiovascular morbidity and/or mortality. Both conditions are characterized by increased activated platelet activation, with circulating levels of the platelet marker thrombospondin-1 (TSP-1) recently demonstrated to be significantly higher in patients with GCA and PMR as compared to healthy controls (2–4). Activated platelets undergo degranulation resulting in the release of dense and alpha granules that contain serotonin and other platelet activating factors (5). Upon interaction with other platelets, they contribute to coagulation promoting atherosclerosis that is complicated by arterial thrombosis, myocardial infarction, and ischemic stroke (6). Patients with GCA are at higher risk of developing cardiovascular events (CVE) compared to non-GCA patients, with the highest risk of these events occurring within the first year of GCA diagnosis (7). A recent study demonstrated that patients with GCA experienced myocardial infarct (MI) that was mainly type 2 due to systemic inflammation (8). However, in other studies, there was no increased risk of acute coronary syndrome in GCA (9). Patients with PMR also have a higher risk of cardiovascular events, with that risk being greatest in patients who are younger than 60 years at the time of diagnosis (10).

Selective serotonin reuptake inhibitors (SSRI) and serotonin norepinephrine reuptake inhibitors (SNRI) could have a beneficial effect on the cardiovascular system by inhibiting platelet aggregation and therefore reducing cardiovascular mortality and morbidity (11). Some of the newest SSRI such as sertraline, can improve insulin resistance, dyslipidemia, and have anti-inflammatory action reducing C-reactive protein and interleukin-6 (12). Duloxetine, an SNRI was found to have antiplatelet and thrombo-protective properties (13). Studies investigating the risk of primary ischemic events among SSRI users have been inconclusive. Because SSRI inhibit serotonin uptake into platelets, there could be a reduction in the risk of ischemic heart events (14–16). In a randomized, double-blind placebo-controlled trial that recruited patients with depression within 30 days of hospitalization for acute MI or unstable angina, patients were randomly assigned to receive either sertraline or a placebo for 24 weeks. Overall, severe CVE was less with sertraline compared to placebo (14.5% vs 22.4%) though not statistically significant (17). Other studies have shown no difference in the cardiovascular risk in depressed patients treated with SSRI compared to non-depressed patients who did not use any anti-depressants (18).

The incidence and risk of cardiovascular events in patients with GCA and PMR who use SSRI and SNRI have not been carefully investigated. The objective of our retrospective study was to evaluate the association of SSRI or SNRI users with cardiovascular outcomes defined to include ischemic stroke, transient ischemic attack (TIA), myocardial infarction, and angina in patients with GCA and PMR within a veteran-based population.

Abbreviations: GCA, giant cell arteritis; PMR, polymyalgia rheumatica; SSRI, selective serotonin reuptake inhibitors; SNRI, serotonin norepinephrine reuptake inhibitors; MLR, multivariate logistic regression; CVE, cardiovascular event; TIA, transient ischemic attack; MI, myocardial infarct; OR, odds ratio; VINCI, Veterans Affairs Informatics and Computing Infrastructure; HTN, hypertension; ICD-9-CM, International Classification of Diseases Ninth Revision; ICD-10-CM, International Classification of Diseases Tenth Revision; TSP-1, thrombospondin-1; BMI, body mass index; SD, standard deviation; HR, hazard ratio; CI, confidence intervals; TNF- α,tumor necrosis factor alpha; IL-6, interleukin-6.

Methods

Data sources and study population

In this retrospective study approved by our institutional review board, patients with GCA and PMR, were identified between January 1999 and September 2023, and extracted through the Veterans Affairs Informatics and Computing Infrastructure (VINCI). Cardiovascular events were identified using diagnostic codes to search hospital admissions and outpatient visits within the Veterans Health Administration system, and linkage with the Centers for Medicare and Medicaid administrative data, as previously performed by our group (19, 20). VINCI also provides information about outpatient pharmacy dispensing that allowed us to identify SSRI (citalopram, escitalopram, fluoxetine, paroxetine, sertraline, vortioxetine, and fluvoxamine) and SNRI (duloxetine, venlafaxine, desvenlafaxine, milnacipran) users among GCA and PMR patients.

Study design and data collection

Matched cohort analyses were conducted for incident CVE among patients with GCA or PMR who used SSRI or SNRI, and findings were compared to patients with GCA or PMR who did not use any anti-depressants. The comparison cohort was created by matching two individuals with GCA or PMR who did not use SSRI or SNRI to each GCA or PMR patient who used SSRI or SNRI within 6 weeks before diagnosis of GCA or PMR with total use of at least 365 days. Initiation of SSRI or SNRI was confirmed by more than one filled prescription of either brand or generic drug names. We included in our database patients who had been on other antidepressants such as clomipramine, amoxapine, desipramine, trazodone, doxepin, imipramine, phenelzine, mirtazapine, bupropion, bupropion/naltrexone, or clomiphene prior to the index date (date of GCA or PMR diagnosis). The matching was performed based on gender, age at the time of disease diagnosis, race, glucocorticoid use for at least 150 days, hypertension (HTN), smoking, diagnosis of vasculitis or PMR in the outpatient or inpatient setting, and average Charlson's comorbidity score 5 years prior to the index date.

The GCA cohort included patients: (a) aged ≥50 years; (b) classified with at least one GCA clinical modification code from the

International Classification of Diseases Ninth or Tenth Revision (ICD-9-CM or ICD-10-CM) (Supplementary Table 1), and (c) on glucocorticoid therapy and/or other immunosuppressive therapy for at least 150 days, starting within 30 days before diagnosis or within 365 days after diagnosis. Similarly, the PMR cohort included patients: a) aged ≥ 50 years; b) classified with the ICD-9-CM or ICD-10-CM codes for PMR (Supplementary Table 1), and (c) on glucocorticoid therapy and/or other immunosuppressive therapy for least 150 days, starting within 1 month prior to diagnosis or within the first year of diagnosis. Identification of patients with GCA and PMR by using ICD-CM codes and administrative databases has similarly been applied in the literature before (19–22). Our study participants were followed up until the date of a cardiovascular outcome (ischemic stroke, TIA, myocardial infarction, angina), the end of the 5-year observation period, death, or the end of our study (30 September 2023), whichever happened first.

Study outcome of interest

The outcome of interest was the first incidence of cardiovascular events (ischemic stroke, TIA, myocardial infarction, angina) after the index date among the study cohorts. Cardiovascular events were defined by using ICD-9 and ICD-10 procedural codes (Supplementary Table 1). We included patients who had a prior history of cardiovascular events for at least 12 months prior to the index date. However, we excluded patients who had a prior history of cardiovascular events and had been on dual anti-platelet therapy (aspirin plus clopidogrel, aspirin plus dipyridamole, aspirin plus prasugrel, or aspirin plus ticagrelor) for at least 6 months prior to the index date. We also excluded patients who had deep venous thrombosis and/or pulmonary embolism and had been on heparin, warfarin, apixaban, dabigatran, edoxaban, or rivaroxaban within 6 months prior to the index date.

Use of covariates

Covariates were considered potential confounders that are recognized as independent risk factors for cardiovascular events, including, HTN, body mass index (BMI), and smoking. HTN was identified using the ICD-9 and ICD-10 codes (Supplementary Table 1) and assessed at baseline. Baseline BMI and smoking status prior to the start of the disease cohort follow-up were also included as covariates. BMI is known to be a confounder for cardiovascular events (23), whereas smoking is a well-characterized risk factor for cardiovascular disease (24). Basic demographic information such as age, gender, race/ethnicity, and information about the initial diagnosis of GCA in the outpatient or inpatient setting were also included as potential confounders. Patients with malignancy were excluded from this study after identifying at least two encounters for ICD-9 or ICD-10 codes for malignancy within 6 months prior to the index date, because of the association between heart disease and malignancy (25). As a comorbidity index score, we used the Charlson comorbidity score that was calculated based on 19 medical conditions including diabetes, heart disease, and cancer using data up to 5 years prior to the index date (26).

Statistical analysis

Baseline demographic characteristics were detailed based on the stratification with or without SSRI or SNRI use for the GCA and PMR cohorts. Mean ± standard deviation (SD) for quantitative variables is reported, whereas for categorical variables, proportions expressed as a percentage (based on non-missing values) are presented. Descriptive statistics for the frequency of CVE were also calculated after matching based on the same stratification among the two cohorts. After performing a 2:1 propensity score matching for confounding control, we identified pairs of SSRI and/or SNRI users as well as nonusers among the two patient cohorts and applied a multivariate logistic regression (MLR) over the matched data, to calculate the odds ratio (OR) for any CVE outcome within 5 years after the date of cohort entry (index date) in each SSRI or SNRI medication.

Multivariable Cox hazard regression models were also implemented to assess hazard ratios (HR) and the estimates are reported with 95% confidence intervals (CIs). The censoring events in the time-to-event analysis were death, end of the study (30 September 2023), and malignancy that some of the patients might have developed during their disease. Multivariable Cox regression analysis was adjusted for BMI, gender, age at time of disease diagnosis, race, smoking, HTN, disease diagnosis in the outpatient or inpatient setting, and 5-year average Charlson's score.

For all analyses, p-values < 0.05, were considered statistically significant. All statistical analyses were performed using the R software (version 3.6.3, http://www.r-project.org/).

Results

Baseline demographic characteristics of the study populations

After matching, a total of 2249 patients with GCA and 3906 patients with PMR were included in our study. Within the GCA cohort, 653 were SSRI users, 168 were SNRI users, and 1428 were nonusers. Among the PMR cohort, 815 and 487 were SSRI and SNRI users respectively, whereas 2604 were nonusers. Most of the patients were male and white in both cohorts. The mean age of patients with GCA at the time of diagnosis ranged between 68 to 74 years, whereas in the PMR cohort was above 70 years (Table 1). Less than one-fourth of the patients were smokers both in the GCA and PMR cohorts. The mean BMI ranged between 28 to 30 in the GCA and PMR cohorts. The frequency of HTN, which is a known risk factor for cardiovascular events (27) was higher in patients with GCA and was observed in more than half of the patients. A possible explanation for this observation is that patients with GCA are

10.3389/fimmu.2025.1509941

TABLE 1 Baseline demographic characteristics of SSRI, SNRI and nonusers in the GCA and PMR cohorts. .

	GCA, N= 2249			PMR, N=3906		
	Nonusers N=1428	SSRI users N=653	SNRI users N=168	Nonusers N=2604	SSRI users N=815	SNRI users N=487
Age, years (mean, IQR)	74 (50-97)	71 (50-97)	68 (51-96)	72 (50-97)	72 (50-97)	71 (50-97)
Sex (male), N (%)	1339 (94%)	603 (92%)	149 (89%)	2506 (96%)	764 (94%)	444 (91%)
Race/Ethnicity, N (%)						
White	1017 (71%)	471 (72%)	125 (74%)	2184 (84%)	669 (82.08%)	398 (82%)
African American	142 (10%)	74 (11%)	19 (11%)	144 (5.5%)	46 (5.64%)	41 (8%)
Native American	12 (0.9%)	4 (0.5%)	1 (0.6%)	21 (0.5%)	8 (0.98%)	2 (0.4%)
Hispanic or Latino	61 (4%)	23 (3.5%)	7 (4%)	76 (3%)	27 (3.31%)	17 (3.5%)
Asian	2 (0.1%)	0 (0%)	1 (0.6%)	18 (0.5%)	3 (0.37%)	1 (0.2%)
Unknown	178 (13%)	75 (12%)	15 (9%)	144 (5.5%)	52 (6.38%)	22 (4.5%)
Native Hawaiian	16 (1%)	6 (1%))	0 (0%)	27 (1%)	10 (1.22)	6 (1.2%)
Smoking, N (%)	262 (18%)	131 (20%)	41 (24%)	430 (17%)	146 (18%)	78 (16%)
BMI, (mean, IQR)	27.93 (14.26-58.71)	28.93 (15.37-62.10)	30.34 (16.23-51.50)	29.05 (10.04-61.76)	29.69 (17.60-60.71)	30.47 (17.07-53.08)
Charlson (mean, IQR)	4.68 (0.4-14.2)	4.75 (0.2-16.2)	4.9 (0.4-13.6)	4.64(0.2-15.4)	4.84 (0.2-13.4)	4.75 (0.2-13)
HTN, N (%)	846 (59%)	430 (66%)	77 (46%)	1141(44%)	396 (48%)	198 (41%)
Steroid use, N (%)	1374 (96%)	636 (97%)	157 (93%)	2603 (99.9%)	815 (100%)	487 (100%)
Other IMT, N (%)	8 (0.6%)	23 (3%)	14 (8%)	1 (0.1%)	0 (0%)	0 (0%)
Dx as outpatient, N (%)	1260 (88%)	557 (85%)	142 (85%)	2504 (96%)	778 (95%)	459 (94%)
Ischemic stroke, N (%)	43 (3%)	38 (6%)	6 (4%)	8 (0.3%)	5 (1%)	6 (1%)
TIA, N (%)	104 (7%)	59 (9%)	13 (8%)	76 (3%)	27 (3%)	13 (3%)
MI, N (%)	88 (6%)	39 (6%)	15 (9%)	87 (3%)	45 (5%)	26 (5%)
Angina, N (%)	101 (7%)	80 (12%)	23 (14%)	127 (5%)	51 (6%)	38 (8%)
Prior CV event, N (%)	63 (4%)	40 (6%)	10 (6%)	53 (2%)	12 (2%)	11 (2%)
Anti-coag w6m, N (%)	144 (10%)	57 (8%)	17 (10%)	232 (9%)	88 (11%)	65 (13%)
Dual aPLT w6m, N (%)	105 (7%)	68 (10%)	17 (10%)	121(5%)	56 (7%)	19 (4%)
*Other AD, N (%)						
Bupropion	22 (2%)	24 (4%)	9 (5%)	30(1%)	47 (6%)	15 (3%)
Doxepin	2 (0.14%)	4 (0.6%)	0 (0%)	3(0.1%)	4 (0.5%)	3 (0.6%)
Imipramine	2 (0.14%)	0 (0%)	0 (0%)	2 (0.1%)	–	–
Mirtazapine	18 (1%)	24 (4%)	3 (2%)	30 (1%)	28 (3%)	18 (4%)
Selegiline	1 (0.1%)	0 (0%)	0 (0%)	–	–	–
Trazodone	34 (2%)	75 (11%)	32 (19%)	66 (3%)	77 (9%)	41 (8%)
Desipramine	–	–	–	–	1 (0.1%)	–

IQR, Interquartile Range (25% - 75%); IMT, immunosuppressive therapy; AD, antidepressant; CV, cardiovascular; aPLT w6m, antiplatelet therapy within 6 months; anti-coag w6m, anti-coagulation within 6 months
*Other non-SSRI or SNRI AD concomitantly administered.

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usually treated with higher doses of glucocorticoids as compared to patients with PMR.

Both cohorts had similar average 5-year Charlson scores among SSRI, SNRI and nonusers. Most patients with GCA were treated with glucocorticoids (steroids), whereas a very small percentage was treated with other immunosuppressive agents (tocilizumab or cyclophosphamide). 100% of patients with PMR were treated with oral glucocorticoids. Therefore, steroids were not used as an independent covariate in the most due to lack of contrast. The initial diagnosis of GCA or PMR, was made in the outpatient setting in more than 85% of the patients. The frequency of ischemic stroke, TIA, MI, and angina as well as prior history of CV events, and dual anti-platelet therapy within 6 months prior to the index date was slightly higher in the GCA cohort compared to the PMR cohort and varied within the groups of SSRI users, SNRI users and nonusers. A very small proportion of patients in both cohorts were on other antidepressants concurrently administered with SSRI or SNRI (Table 1).

Frequency of cardiovascular events among SSRI, SNRI users and nonusers in patients with GCA and PMR

The occurrence of cardiovascular events in patients with GCA and PMR within the groups of SSRI users, SNRI users, as well as non-users, is presented in Table 2. In the GCA cohort, 174 (27%) SSRI users had incident cardiovascular disease as compared to 47 (28%) SNRI users and 277 (19%) nonusers; within the PMR cohort, incident cardiovascular disease was noted in 108 (13%) SSRI users in comparison to 71 (15%) SNRI users and 255 (11%) nonusers (Table 2).

Association of SSRI and SNRI use with incidence of cardiovascular events in patients with GCA and PMR

The association between SSRI and SNRI use, and the incidence of CVE was then assessed in Table 3. In our adjusted main analysis that included nonusers and users of only one medication from the SSRI or SNRI group, we found venlafaxine and sertraline use was associated with a higher incidence of cardiovascular disease compared to nonusers, in both GCA and PMR subgroups. Patients with GCA who started using venlafaxine and sertraline within 6 weeks before diagnosis with use for at least a year were significantly more likely to have a higher incidence of cardiovascular events within 5 years from index date (adjusted OR for venlafaxine=2.44, 95%CI:1.23-4.84, p=0.01, and adjusted OR for sertraline=1.45, 95%CI:1.02-2.05, p=0.04). Similar results were observed in the PMR cohort (adjusted OR for venlafaxine =2.01, 95%CI:1.08-3.77, p=0.02, and adjusted OR for sertraline = 1.45, 95%CI:1.02-2.06, p=0.04). Citalopram was also associated with a higher cardiovascular incidence in the PMR cohort (adjusted OR=2.66, 95%CI:1.15-6.19, p= 0.02).

TABLE 2 Frequency of CVE in SSRI/SNRI- and non-users in GCA and PMR.

GCA, n=2249	PMR, n=3906
SSRI-users, n=653	*SSRI-users, n=815*
Fluoxetine with CVE, n=33	Fluoxetine with CVE, n=13
Fluoxetine w/o CVE, n=69	Fluoxetine w/o CVE, n=107
Sertraline with CVE, n=73	Sertraline with CVE, n=60
Sertraline w/o CVE, n=185	Sertraline w/o CVE, n=369
Citalopram with CVE, n=51	Citalopram with CVE, n=17
Citalopram w/o CVE, n=159	Citalopram w/o CVE, n=109
Paroxetine with CVE, n=9	Paroxetine with CVE, n=11
Paroxetine w/o CVE, n=44	Paroxetine w/o CVE, n=47
Escitalopram with CVE, n=7	Escitalopram with CVE, n=6
Escitalopram w/o CVE, n=21	Escitalopram w/o CVE, n=73
Fluvoxamine with CVE, n=1	Fluvoxamine with CVE, n=1
Fluvoxamine w/o CVE, n=0	Fluvoxamine w/o CVE, n=2
Vortioxetine with CVE, n=0	*SNRI-users, n=487*
Vortioxetine w/o CVE, n=1	Venlafaxine with CVE, n=25
SNRI-users, n=168	Venlafaxine w/o CVE, n=102
Venlafaxine with CVE, n=27	Duloxetine with CVE, n=45
Venlafaxine w/o CVE, n=52	Duloxetine w/o CVE, n=312
Duloxetine with CVE, n=20	Milnacipran with CVE, n=0
Duloxetine w/o CVE, n=69	Milnacipran w/o CVE, n=1
Non-SSRI or SNRI-users, n=1428	Desvenlafaxine with CVE, n=1
Nonusers with CVE, n=277	Desvenlafaxine w/o CVE, n=1
Nonusers w/o CVE, n=1151	*Non-SSRI or SNRI-users, n=2604*
	Nonusers with CVE, n=255
	Nonusers w/o CVE, n=2349

To verify the robustness of our discovery we did a sensitivity analysis by including nonusers and users of all medications from both the SSRI and SNRI groups to perform a larger scale regression (Supplementary Table 2). In the adjusted MLR, venlafaxine use remained significantly associated with the higher odds of cardiovascular incidence (adjusted OR=2.18, 95%CI:1.31-3.63, p=0.002) followed by fluoxetine (adjusted OR=1.95, 95%CI:1.25-3.07, p=0.004), and sertraline (adjusted OR=1.51, 95%CI:1.10-2.06, p=0.01) in the GCA cohort. In the PMR cohort venlafaxine use continued to be associated with higher odds of cardiovascular disease (adjusted OR=2.34, 95%CI:1.46-3.74, p<0.001) followed by sertraline (adjusted OR=1.38, 95%CI:1.01-1.88, p=0.04).

We then applied Cox proportional hazard regression models to assess the HR of CVE among SSRI or SNRI users within 5 years in the GCA and PMR cohorts adjusting for comorbidity covariates. The HR for all cardiovascular events after 2:1 matching was significantly greater than 1 for both venlafaxine (p=0.03), and

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TABLE 3 Adjusted odds ratio of CVE for individual medication users in GCA and PMR within 5 years.

*CVE OR, (95% CI), p-value	
GCA	PMR
SSRI	SSRI
Fluoxetine 1.70 (0.98-2.94), 0.06	Fluoxetine 0.79 (0.38-1.67), 0.54
Sertraline 1.45 (1.02-2.05), 0.04	Sertraline 1.45 (1.02-2.06), 0.04
Citalopram 1.48 (0.98-2.23), 0.07	Citalopram 2.66 (1.15-6.19), 0.02
Paroxetine 0.77 (0.31-1.94), 0.58	Paroxetine 2.03 (0.81-5.11), 0.13
Escitalopram 2.36 (0.65-8.62), 0.20	Escitalopram 0.63 (0.23-1.70),0.35
Fluvoxamine -	Fluvoxamine -
Vortioxetine -	
SNRI	SNRI
Venlafaxine 2.44 (1.23-4.84), 0.01	Venlafaxine 2.01 (1.08-3.77), 0.02
Duloxetine 1.08 (0.56-2.11), 0.80	Duloxetine 1.25 (0.83-1.88), 0.28
Milnacipran -	Milnacipran -
Desvenlafaxine -	Desvenlafaxine -

*Adjusted for BMI, gender, age at the time of disease diagnosis, race, smoking, HTN, disease diagnosis in the outpatient or inpatient setting, and 5-year average Charlson's score). For each regression, we included nonusers and users of only one medication.

TABLE 4 Adjusted hazard ratios of CVE in individual medication users in GCA and PMR after 2:1 matching within 5 years.

*CVE HR, (95%CI), p-value	
GCA	PMR
SSRI	SSRI
Fluoxetine 1.39 (0.80-2.43), 0.24	Fluoxetine 0.77 (0.35 -1.72), 0.53
Sertraline 1.43 (1.05-1.96), 0.02	Sertraline 1.51 (1.08-2.10), 0.01
Citalopram 1.24 (0.86-1.78), 0.24	Citalopram 0.87 (0.45-1.69), 0.69
Paroxetine 2.41 (1.09-5.33), 0.03	Paroxetine 0.81 (0.29-2.26), 0.68
Escitalopram 0.63 (0.16-2.48), 0.51	Escitalopram 1.99 (0.89-4.47), 0.09
Fluvoxamine -	Fluvoxamine -
Vortioxetine -	
SNRI	SNRI
Venlafaxine 1.77 (1.06-2.94), 0.03	Venlafaxine 2.39 (1.35-4.23), p=0.003
Duloxetine 0.86 (0.44-1.68), 0.67	Duloxetine 1.09 (0.74-1.62), 0.64
Milnacipran -	Milnacipran -
Desvenlafaxine -	Desvenlafaxine -

*Adjusted for BMI, gender, age at time of disease diagnosis, race, smoking, HTN, disease diagnosis in the outpatient or inpatient setting, and 5-year average Charlson's score. For each HR, we included nonusers and users of only one medication.

sertraline (p=0.02) in the GCA cohort, as well as in patients with PMR (p=0.003 and p=0.01 respectively) (Table 4). Paroxetine use was associated with the highest risk of developing cardiovascular disease in the GCA cohort (adjusted HR:2.41, 95%CI:1.09-5.33, p=0.03). However, due to the small number of patients under paroxetine, we believe the validity of this positive result needs further examination. Our results indicate that venlafaxine and sertraline users are at high risk of developing CVE in both GCA and PMR cohorts within 5 years of their disease course (Table 4).

Using all SSRI and SNRI medications in our Cox regression analysis, sertraline and venlafaxine use remained significantly associated with a high risk of CVE in the GCA cohort (adjusted HR:1.33, 95%CI:1.02-1.75, p=0.04, and adjusted HR:1.95, 95% CI:1.33-2.87, p<0.001 respectively), but not paroxetine use (adjusted HR:1.34, 95%CI:0.76-2.35, p=0.30) (Supplementary Table 3). For the PMR cohort, the use of sertraline and venlafaxine also continued to be associated with a higher risk of CVE (adjusted HR:1.43, 95%CI:1.08-1.91, p=0.01, and adjusted HR:2.09, 95% CI:1.39-3.15, p<0.001 respectively) (Supplementary Table 3).

We also compared the HRs among patients with SSRI or SNRI use to further eliminate any potential unmeasured confounders, to better validate the association between certain medications and observed higher incidence rates. These HRs are reported in Supplementary Table 4. For example, the HR of CVE among venlafaxine users in the PMR cohort is for comparing patients with venlafaxine use and PMR diagnosis to patients with any SSRI or SNRI use and PMR diagnosis. Non-users were not involved in this analysis. Interestingly, only venlafaxine use was associated with a higher risk of cardiovascular disease for both the GCA and PMR cohorts (Supplementary Table 4).

The median duration of each SSRI or SNRI medication after the beginning of the study among the GCA and PMR cohorts is presented in Supplementary Table 5. The median duration of the SSRI medications varied between 299 to 454 days in the GCA cohort, whereas for the PMR patients was between 392 to 692. With regards to the SNRI medications, the median duration was between 364 to 478, and 214 to 720 days for the GCA and PMR cohorts respectively.

We also present stratified Kaplan-Meier curves for the cardiovascular outcomes in GCA (Figures 1A, B) and PMR (Figures 2A, B). As shown in these figures, patients with GCA and PMR, stratified as venlafaxine or sertraline users, have a distinct time-to-event incidence of CVE events compared to non-users. The x-axis represents the time in days after each individual's index date, whereas the y-axis shows the estimated probability of patients with GCA or PMR without developing cardiovascular events. For example, at 250 days after the diagnosis of GCA, the predicted probability of having CVE is around 12% for the nonusers, whereas the venlafaxine users have approximately 50% more chance of experiencing CVE in the GCA group (Figure 1A). As supplementary material we also present the predicted probability of experiencing cardiovascular outcomes among users of paroxetine and duloxetine compared to non-users in the GCA and PMR cohorts (Supplementary Figures 1, 2 respectively).

Discussion

In this retrospective observational study, we observed a higher incidence of cardiovascular events among patients with GCA and

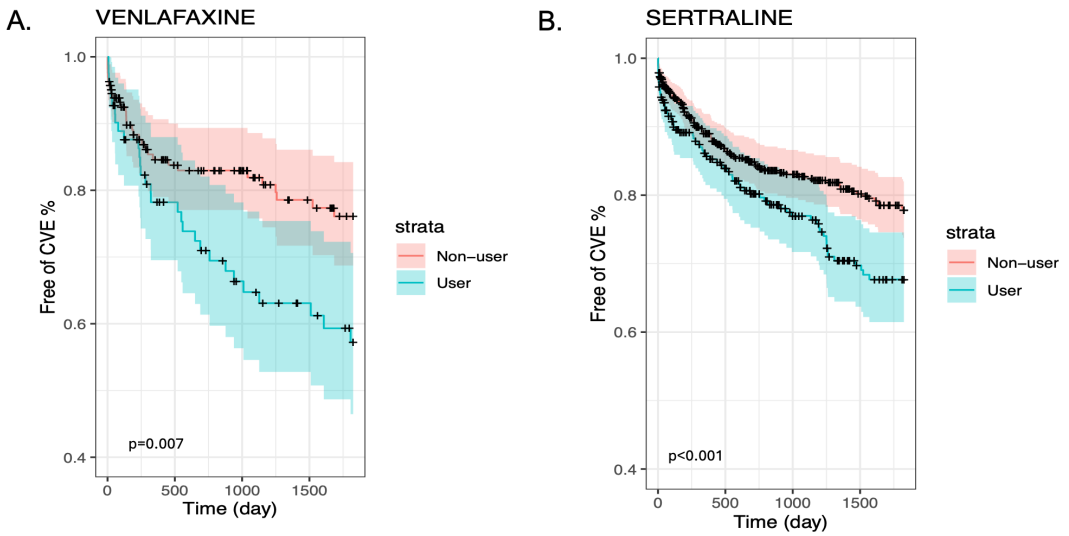

FIGURE 1
Kaplan-Meier plots for the time to CVE from the time of diagnosis of GCA stratified by medication user and non-user (blue and red lines respectively) after matching and including non-users and users of Venlafaxine **(A)** or Sertraline **(B)**.

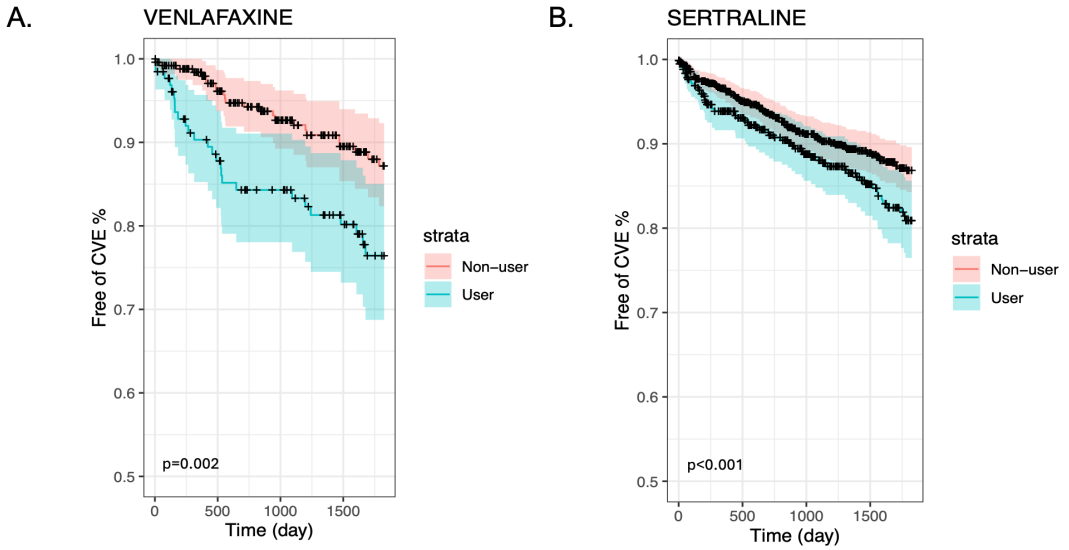

FIGURE 2
Kaplan-Meier plots for the time to CVE from the time of diagnosis of PMR stratified by medication user and non-user (blue and red lines respectively) after matching and including non-users and users of Venlafaxine **(A)** or Sertraline **(B)**.

PMR using the antidepressants venlafaxine or sertraline compared to nonuse. We also found a high risk of cardiovascular disease among venlafaxine and sertraline users in both the GCA and PMR cohorts. This observation may imply a harmful role of venlafaxine and sertraline use, increasing the risk for cardiovascular events among patients with GCA and PMR. We also recognize that depression which is common among patients with GCA and PMR (28, 29), is an independent risk factor for incident cardiovascular disease (30, 31).

To the best of our knowledge, there are no data on the impact of SSRI or SRNI use on cardiovascular burden in inflammatory diseases such as GCA and PMR. Patients with GCA are known to have increased mortality due to cardiovascular events including ischemic heart disease as shown in two independent studies conducted in northern (32) and southern Sweden (33) and verified by postmortem studies showing persistent vascular inflammation (34). However, in patients with PMR there was no association between cardiovascular events and mortality (35), despite some studies showing an increased risk of all types of cardiovascular events early in their disease course within the first six months after diagnosis (10).

An increasing amount of evidence suggests that platelet activation persists despite glucocorticoid therapy in patients with

GCA and PMR (2, 3). Persistently elevated levels of von Willebrand factor that is produced by both endothelial cells and megakaryocytes (36, 37), as well as TSP-1 in the circulation of patients with GCA and PMR (3, 4), considered to be in clinical and biochemical remission, may indicate a constant procoagulant state. This prothrombotic effect could be modified by antidepressants that inhibit serotonin reuptake, in particular SSRI and SNRI, via depletion and/or decrease in levels of intraplatelet serotonin. Indeed, in the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART) study, treatment with sertraline resulted in substantially less release of platelet (P-selectin, platelet factor 4, and thromboxane B2) and endothelial markers (vascular cell adhesion molecule-1 and E-selectin) as compared to placebo, in patients that suffered depression post-MI (38). However, evidence that these biochemical changes could have relevant cardiovascular significance remains unclear.

Interestingly, some studies indicate that sertraline use in depressed primates after an 18-month treatment period, may result in 4.9 times and 6.5 times higher coronary artery atherosclerosis extent compared to untreated depressed monkeys, and non-depressed monkeys respectively (39, 40), suggesting that both chronic sertraline use, and depression could be proatherogenic. Other preclinical studies have shown that chronic use of the SSRI fluoxetine enhanced the formation of atherosclerotic lesions in apolipoprotein E-deficient mice via increasing integrin activity on neutrophils and monocytes, potentially increasing the risk of cardiovascular events (41). In our sensitivity analyses, fluoxetine was also associated with a higher incidence of cardiovascular disease.

With regards to venlafaxine, it was shown that its use was associated with higher rates of stroke and TIA compared to other antidepressants among older people (42). Venlafaxine may promote inflammation and cytokine production, as its use is associated with elevated levels of tumor necrosis factor alpha (TNF- α), and interleukin-6 (IL-6), especially at higher doses of 150 mg daily due to its pro-norepinephrinergic effect (43, 44). IL-6 is an inflammatory cytokine with a known pro-atherogenic role (45). Of note, continued elevated plasma, and temporal artery tissue IL-6 levels reflecting ongoing vascular inflammation despite glucocorticoid therapy, has been reported in some patients with GCA (46). A subset of patients with PMR were also found to have elevated plasma IL-6 levels despite glucocorticoid therapy for a month (47). Further complicating matters, persistent systemic, and vascular inflammation in patients with PMR and GCA could be contributing to accelerated atherosclerosis and vascular remodeling leading to arterial stenosis and aneurysms (48, 49).

In a recent meta-analysis, SSRI use was associated with an increased risk of ischemic stroke (aOR 1.48; 95% CI 1.08–2.02), probably via its atherosclerotic effect on the cerebral vasculature (50). In our own study, we found that the aOR of cardiovascular events for sertraline use among patients with GCA and PMR was 1.46 and 1.45 respectively. In another study, SSRI use was also associated with an increased carotid intima-media thickness that is a predictor of myocardial infarction in a study of middle-aged veteran twins from the Vietnam Era Twin registry (51). Interestingly, in a propensity score-matched population-based study conducted in Canada there was a higher risk of acute MI, stroke, or cardiovascular related hospitalization among SNRI users compared to SSRI users within one year of drug initiation (52).

Our study has several limitations. Firstly, depression itself is a risk factor for cardiovascular events and could be a confounding factor by indication. Apart from indication bias, possible selection bias due to the retrospective nature of our study, and misclassification are also other limitations. We may have excluded patients with severe GCA or PMR disease as they may not have survived up to 150 days to be considered for immunosuppressive therapy or may have had a fatal cardiovascular event. Another limitation of our study is that the diagnosis of GCA and PMR was based on ICD codes. Also, inflammatory markers, histologic evidence of temporal arteritis for the diagnosis of GCA, imaging studies such as ultrasound of temporal arteries, magnetic resonance angiography and fluorodeoxyglucose (FDG)-positron emission tomography that is frequently used for diagnostic purposes, as well as disease severity and activity status, were not recorded for this study. Another limitation is that most patients with GCA and PMR were on glucocorticoid therapy, whereas only a very small proportion of patients with GCA were also on the IL-6 inhibitor tocilizumab, which could have a potential vascular protective role (45).

Additionally, information about the degree of physical activity and dietary preferences are not available for this study given its retrospective nature, and residual confounding is another limitation. Further, although our cohorts were large, the number of cardiovascular events was low which restricted the power of our study. Also, we did not use ICD codes for depression to identify patients who were depressed, and its severity, as we assumed that those on antidepressants had depression as an indication. Additionally, we did not use codes suggesting potential non medication adherence and/or codes associated with adverse effects of anti-depressants, resulting in discontinuation. Finally, it is unclear to what extent our results can be generalized to other autoimmune diseases such as rheumatoid arthritis and lupus that are independent risk factors for cardiovascular disease, or the general population in the presence of traditional risk factors, as there is a heavy representation of men in the military population.

However, our study has some strengths. This is the first large study that suggests that venlafaxine and sertraline use could be associated with a high incidence and risk of cardiovascular disease validated within two different disease cohorts, that share some common pathophysiological features. Another strength is that the reported adjusted OR and HR of cardiovascular events for venlafaxine and sertraline users demonstrated similar trends in both disease cohorts, enhancing further the robustness of our study findings. Although our findings suggest a cardio-harmful effect of venlafaxine and sertraline use, among these high-risk cardiovascular disease inflammatory conditions, our results need

to be further validated by larger multicenter prospective clinical studies. Future research should explore the mechanisms by which specific antidepressants may influence cardiovascular health and assess the dose and duration of the effect of these pharmaceutical interventions on cardiovascular risk over time among patients with inflammatory disorders.

In conclusion, our study uncovers critical insights into how antidepressant pharmacotherapy, and particularly venlafaxine and sertraline can significantly modify cardiovascular risk profiles in patients with GCA and PMR. Given the widespread prescription of these medications for depression, it is imperative that clinicians and patients remain vigilant about the potential cardiovascular risks associated with their use. A careful assessment of the benefits versus risks is essential in guiding treatment decisions for these vulnerable populations in clinical practice. By prioritizing cardiovascular health, providers can improve clinical outcomes and quality of care for those affected by these inflammatory conditions.

Data availability statement

All data relevant to this study are included in this article. The dataset presented in this article is not readily available due to ethical/privacy restrictions. Requests to access the datasets should be directed to chris.gentry@va.gov.

Ethics statement

The Research and Development Committee from the Department of Veterans Affairs approved the study (IRB#16548). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

TZ: Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. CG: Data curation, Formal analysis, Methodology, Resources, Software, Supervision, Writing – review & editing. NK: Conceptualization, Methodology, Supervision, Writing – review & editing. GL: Conceptualization, Methodology, Supervision, Writing – review & editing. BN: Methodology, Supervision, Writing – review & editing. DM: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research and/or publication of this article.

Acknowledgments

I would like to acknowledge Dr. George Dale, Emeritus Professor, Department of Medicine, University of Oklahoma Health Sciences Center, for inspiring me to conduct this study.

Conflict of interest

Dr. NK reported receiving consulting fees from AstraZeneca, Janssen, Pfizer Inc., Bristol Myers Squibb, Beyond Spring Inc., G1 Therapeutics Inc., Sandoz, Seagen Inc., and Fresenius Kabi outside the submitted work. Dr. GL reported personal fees from AstraZeneca, Sandoz, G1 Therapeutics Inc., Beyond Spring Inc., Fresenius Kabi, Merck & Co Inc., Bristol Myers Squibb, and Samsung Biologics outside the submitted work. Dr. DM received the Pfizer US Pharmaceuticals Group grant 53857367 outside the submitted work and funding body did not play any role in this study.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2025.1509941/full#supplementary-material

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frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 21 May 2025
DOI 10.3389/fmed.2025.1547518

OPEN ACCESS

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RECEIVED 18 December 2024
ACCEPTED 21 April 2025
PUBLISHED 21 May 2025

CITATION
Alsing CL, Igland J, Nystad TW, Gjesdal CG, Næss H, Tell GS and Fevang BT (2025) Trends in stroke occurrence in rheumatoid arthritis: a retrospective cohort study from Western Norway, 1972 through 2020.
Front. Med. 12:1547518.
doi: 10.3389/fmed.2025.1547518

Trends in stroke occurrence in rheumatoid arthritis: a retrospective cohort study from Western Norway, 1972 through 2020

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Objectives: To investigate stroke occurrence in patients with rheumatoid arthritis (RA) diagnosed from 1972 through 2013 compared with the total population.

Methods: We included 1821 patients diagnosed with RA from 1972 through 2013 at Haukeland University Hospital in Norway. The patients were divided into three inception cohorts by time of RA diagnosis (1972–1998, 1999–2006, and 2007–2013), based on major changes in RA treatment. The total population of the same county was used as a comparison cohort. Both cohorts were followed from 1972 through 2020. Annual change in stroke event rates were calculated by Poisson regression with adjustment for age and sex. Hazard ratios were estimated by Cox regression with adjustment for age, sex, smoking, BMI, diabetes and serological status. Standardized event ratios (SER) were estimated by Poisson regression as a measure of excess stroke events in patients with RA compared with the total population.

Results: In total 156, 70, and 31 stroke events occurred in the first, middle, and last inception cohorts during, respectively, 17,110, 9,561, and 4,098 person-years of observation. From 1999 to 2020 stroke event rates declined by 4.8% (95% CI 2.7–6.9) per year in the RA cohort and by 3.4% (95% CI 3.1–3.7) per year in the comparison cohort. There was a trend towards lower stroke risk across inception cohorts, with a statistically significant reduction only observed among women in the last cohort compared to the first cohort (hazard ratio 0.30, 95% CI 0.12–0.76). Despite this reduction, the last inception cohort had the highest excess of stroke events (SER 1.58, 95% CI 1.03–2.43), compared with the total population. However, this excess stroke occurrence was only observed in men with RA and not in women with RA.

Conclusion: Despite an overall decline in stroke occurrence over time, men with RA diagnosed after 2007 had a residual excess stroke occurrence compared to the total population. No excess stroke occurrence was observed in women with RA from the same time period. Our findings highlight the continued need of targeted stroke prevention in patients with RA, particularly for men.

KEYWORDS

rheumatoid arthritis, cardiovascular, epidemiology, observational, comorbidity/multimorbidity, stroke

1 Introduction

Rheumatoid arthritis (RA) is the most common chronic inflammatory joint disease, affecting 0.5–1% of the population (1). Previous studies have shown an increased risk of cardiovascular disease (CVD) in RA compared with the general population and patients with RA have a 60% increased risk of stroke (2), possibly higher in young and anti-citrullinated protein antibodies (ACPA) positive patients (3–5).

Excess CVD in RA is caused by a combination of traditional CVD risk factors and systemic inflammation. Among the known risk factors, smoking is highly prevalent in patients with RA, and hypertension is often undertreated (6, 7). Inflammation is known to accelerate atherosclerosis, while specific anti-inflammatory treatment prevents cardiovascular events (8). In patients with RA, high disease activity correlates with high CVD risk (9, 10), and remission, on the other hand, is associated with lower CVD risk (11, 12). Furthermore, atrial fibrillation, a common cause of stroke, has been linked to inflammation and is more frequent in patients with RA compared with the general population (13).

RA management has improved significantly during the 21st century. The two most important milestones are arguably the introduction of biologic disease-modifying anti-rheumatic drugs (DMARDs) in 1998 and the treat-to-target strategy from 2004 and onwards (14). With modern treatment, a higher proportion of patients achieve remission, and consequently fewer experience joint destruction leading to less joint replacement surgery (15). Several observational studies report lower CVD and stroke risk in patients with RA treated with methotrexate and biological DMARDs (16, 17).

Recent studies on CVD in RA diagnosed during the 21st century show conflicting results. Both Løgstrup and Baviera have found a persistent excess stroke occurrence in patients with RA diagnosed during 1997–2017 and 2005–2017 compared with the general population (18, 19). Other studies, however, have found a decline or no excess stroke occurrence in patients with RA diagnosed during equivalent time periods (20, 21). Several studies have found a persistence of excess myocardial infarction in patients with RA compared with the general population (22–24). However, other studies, including a study published by our research group, found no excess occurrence of myocardial infarction in patients with RA diagnosed in the 21st century (25, 26).

Few studies have investigated stroke occurrence in relation to the time of RA diagnosis, comparing before and after the major improvements in RA treatment. We therefore aim to investigate stroke occurrence in patients with RA diagnosed during different treatment eras compared with the general population.

2 Materials and methods

2.1 Study design and settings

We performed a retrospective cohort study of 1821 patients with RA diagnosed at the Department of Rheumatology, Haukeland University Hospital during 1972–2013. There are currently only 2 rheumatologists in private practice in the county, hence almost all patients with RA are treated at the hospital. The total population of the same county (Hordaland) was used as a comparison cohort. Individual data were available for the RA cohort, while data for the comparison cohort were available as aggregated counts by 5-year age group, sex, and calendar year. Both cohorts were followed from 1972 through 2020.

The study complies with the Declaration of Helsinki and the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement and was approved by the Regional Committee for Medical and Health Research Ethics, Health Region West (2014/1932) and the institutional review board (27).

2.2 Patients with RA

Full details of the selection and inclusion of patients with RA, including a flowchart and a comparison of included and excluded participants, have been published previously (24). In summary, we searched the hospital patient administrative system for patients with an outpatient contact or hospital admission with an RA diagnosis during 1972–2013 at the Department of Rheumatology, Haukeland University Hospital. Then, consent for inclusion was acquired either by letter of consent or through the Norwegian Arthritis Registry. Exemption of consent was allowed for deceased patients ($n = 979$). The medical records of the included individuals were reviewed by two physicians. RA was defined as present if diagnosed by the treating rheumatologist, and this was mandatory for inclusion. Participants were excluded if the final diagnosis during follow-up was not RA. Data on characteristics of patients with RA (Table 1) were derived from the medical records.

Patients with RA were divided into three inception cohorts by year of RA diagnosis: 1972–1998, 1999–2007, and 2008–2013. The chosen time periods reflect improvements in RA management: in 1998 the introduction of biological DMARDs; in 2007 the universal adoption of the treat-to-target strategy at our department.

2.3 Comparison cohort

All inhabitants in Hordaland County (378,261 in 1972 to 524,495 in 2019), including patients with RA, were used as a comparison cohort. Aggregated counts of the population per calendar year, 5-year age group, and sex were obtained from the Western Norway Cardiovascular Registry (WENOCARD) (1972–2006) and the Cardiovascular Diseases in Norway project (CVDNOR) (2007–2014). During 2015–2020 population counts were obtained from Statistics Norway. WENOCARD and CVDNOR have been described in detail previously (25, 28, 29). We did not have

10.3389/fmed.2025.1547518

TABLE 1 Characteristics of 1821 patients with rheumatoid arthritis (RA), Hordaland County, Norway 1972–2013.

Characteristics	Time of RA diagnosis		
	1972–1998 (*N* = 771)	1999–2007 (*N* = 642)	2008–2013 (*N* = 408)
Women, *n* (%)	559 (72.5%)	445 (69.3%)	261 (64.0%)
Age at RA diagnosis, years	54 (15.4)	56.2 (16.1)	55.8 (15.5)
BMI[a], kg/m^2; mean (SD)	24.9 (4.3)	25.5 (4.5)	25.7 (4.4)
Missing, *n* (%)	77 (10.0%)	43 (6.7%)	1 (0.3%)
Smoking status at RA diagnosis			
Missing, *n* (%)	45 (5.8%)	3 (0.5%)	1 (0.2%)
Non-smoker, *n* (%)	372 (51.2%)	264 (41.3%)	161 (39.6%)
Former smoker, *n* (%)	121 (16.7%)	198 (31.0%)	141 (34.6%)
Smoker, *n* (%)	233 (32.1%)	177 (27.7%)	105 (25.8%)
Comorbidities[b]			
Previous AMI, *n* (%)	36 (4.7%)	35 (5.5%)	19 (4.7%)
Previous stroke, *n* (%)	14 (1.8%)	22 (3.4%)	11 (2.7%)
Diabetes, *n* (%)	20 (2.6%)	38 (5.9%)	30 (7.4%)
Angina, *n* (%)	50 (6.5%)	40 (6.2%)	17 (4.2%)
Antihypertensive drug use, *n* (%)	88 (11.4%)	141 (22.0%)	106 (26.0%)
Statin use, *n* (%)	8 (1.0%)	89 (13.9%)	42 (10.3%)
ACR/EULAR criteria fulfilled[c], *n* (%)	654 (84.8%)	563 (87.7%)	370 (90.7%)
RF/ACPA positive[a], *n* (%)	480 (62.4%)	418 (65.2%)	301 (73.8%)
ESR[d], mm/h; mean (SD)	51.4 (31.5)	46.4 (26.1)	39.4 (25.1)
CRP[d], mg/l; mean (SD)	44.4 (44.4)	42.8 (47.3)	30.0 (37.6)
Missing, *n* (%)	300 (39%)	1 (0%)	0 (0%)
Involvement of large joints, *n* (%)	546 (70.8%)	441 (68.7%)	232 (56.9%)
Radiographic erosions[a], *n* (%)	577 (76.3%)	288 (46.1%)	137 (33.7%)

ACPA, anti-citrullinated protein antibodies; ACR, American College of Rheumatology; AMI, acute myocardial infarction; BMI, body mass index; CRP, c-reactive protein; DMARD, disease-modifying anti-rheumatic drug; ESR, erythrocyte sedimentation rate; EULAR, European Alliance of Associations for Rheumatology; NSAID, non-steroidal anti-inflammatory drug; PVD, peripheral vascular disease; RA, rheumatoid arthritis; RF, rheumatoid factor; SD: standard deviation.

[a]During follow-up. BMI was calculated using the available height and weight measurements from medical records nearest in time to RA diagnosis.

[b]Before and 1 year after RA diagnosis.

[c]The 2010 ACR/EULAR criteria were used for all patients.

[d]The highest value within 1 year before and 2 years after the diagnosis of RA.

additional data on cardiovascular risk factors for the comparison cohort.

2.4 Outcomes

A stroke event was defined as a hospitalization with stroke (ICD-8; 430, 433, 431, 434, 436, ICD-9; 430, 431, 434, 436 and ICD-10; I60, I61, I63, I64) as a primary or secondary diagnosis. Recurrent events were counted if more than 28 days passed between discharge and the next admission. An incident event was defined as the first hospitalization with stroke as a primary or secondary diagnosis after RA diagnosis.

Data on stroke events during 1972–2006 were obtained from WENOCARD for both patients with RA and the comparison cohort. Outcomes were obtained from CVDNOR (2007–2014) and the Norwegian Cardiovascular Disease Registry (NCDR) (2015–2020) for the comparison cohort and by review of hospital patient administrative systems (2007–2020) for the RA cohort. The data from CVDNOR and NCDR both originate from discharge codes in the hospitals' patient administrative systems.

2.5 Statistical analysis

Characteristics of patients with RA were compared across three inception cohorts (Table 1) and furthermore stratified by sex (Supplementary Tables 1 and 2). The time of RA diagnosis was defined as the first of January in the year RA was diagnosed by the treating rheumatologist. The follow-up time used to count stroke events was defined as the time between the time of RA diagnosis and death or the end of the study (31st of December 2020). However, for calculating incidence rates and time-to-event analyses, the study end was extended to 31st December, 2022, due to supplementary RA cohort data. Continuous variables are presented as means with standard deviations and categorical variables as numbers and proportions. Missing data are reported when present in more than 2% of the inception cohort. Welch's t-test was used to test for statistically

significant differences between groups for continuous variables and chi-square test for categorical variables.

Crude rates of stroke incidence and events were estimated per year for the RA cohort and comparison cohort to delineate changes from 1972 to 2022. Cubic splines with 3 knots were fitted to show trends due to fluctuations in stroke rates in the RA cohort. Annual age-adjusted stroke event rates were calculated using direct standardization, with the 2013 European Standard Population as the reference population. This analysis was restricted to the comparison cohort due to lack of statistical power in the RA cohort.

Annual changes in event and incidence rates were estimated by Poisson regression models with calendar year as a continuous predictor and person-time as an offset. Separate estimates were calculated for 1972–2020 and 1999–2020 to address the biphasic trend in observed stroke rates in both cohorts due to secular changes in the definition and diagnosis of stroke. The exponentiated coefficient for calendar year represents the incidence rate ratio (IRR) corresponding to the average annual relative change in incidence rates. The annual change can be calculated by subtracting the IRR from one. The analyses were performed unadjusted and adjusted for age, sex, BMI, diabetes, smoking and serological status.

Time-to-event analyses were performed for the RA cohort to investigate stroke incidence. Patients with stroke before RA diagnosis were excluded from these analyses. We created cumulative incidence functions adjusted for competing risk of death prior to stroke. Hazard ratios were estimated using Cox regression with inception cohorts as a categorical predictor, adjusting for age, sex, smoking, BMI, diabetes and serological status. The proportional hazards assumption was verified by statistical testing of Schoenfeld residuals.

We estimated standardized event ratios (SER) as a measure of excess stroke events in patients with RA compared with the general population for each inception cohort and across subgroups. Reference rates were calculated per 5-year age group, sex, and calendar year using counts of stroke events and mid-year population at risk in the comparison cohort. Counts of stroke events in the RA cohort were aggregated according to the same strata as the comparison cohort. We then calculated the expected counts of stroke events for each stratum in the RA cohort using the population at risk and the reference rates. The expected counts were included as an offset in a Poisson model with counts of stroke events as the dependent variable and standardized event ratios as the output. All Poisson regression analyses are reported using robust 95% confidence intervals to adjust for overdispersion. There were no missing data in the regression analyses. Sensitivity analyses were performed setting the baseline to 1st of January 1 year after RA was diagnosed.

Analyses were conducted using Stata Statistical Software (release 17 or later; StataCorp LP, College Station, TX) and R (version 3.6.3 or later). A p-value below 0.05 was considered significant and the p-values are not adjusted for multiple testing.

3 Results

Three thousand and seventy-six patients were identified using the electronic patient administrative system. Four hundred and twenty-nine patients did not consent to inclusion. Among consenting individuals, eight hundred and twenty-eight patients were excluded mainly due to incorrect RA diagnosis ($n = 279$), incomplete medical records ($n = 282$), receiving follow-up by a private practicing rheumatologist ($n = 89$) or being diagnosed with RA prior to 1972 or after 2013 ($n = 178$). Thus, a total of 1821 patients with RA were included in this study across three inception cohorts according to the year of RA diagnosis: 771 patients during 1972–1998; 642 patients during 1999–2007 and 408 patients during 2008–2013. The comparison cohort included on average 325,537, 394,509 and 437,656 inhabitants during 1972–1998, 1999–2007 and 2008–2020, respectively.

3.1 Patient characteristics

Patients with RA in the two latest inception cohorts were on average older at baseline, had higher BMI, more frequently diabetes, and were more likely to use antihypertensives or statins (Table 1) compared with patients diagnosed before 1999. Manifestations of radiographic erosions during follow-up were more prevalent in the first inception cohort (76.3%) compared with the later inception cohorts (respectively 46.1 and 33.7%). Patients with RA diagnosed in the last inception cohort had the lowest levels of ESR or CRP at baseline. Smoking prevalence declined from 32 to 25.8% from the first to last inception cohort.

Men and women had similar characteristics across inception cohorts (Supplementary Tables 1 and 2), except for persistently lower smoking rates (respectively 33 and 26%) and lower levels of diabetes (respectively 7.7 and 3.6%) in women. Comparing the middle inception cohort to the latest cohort revealed several changes specific to women: mean CRP levels decreased significantly (mean difference 16, 95% CI 9.81–22.15, $p < 0.001$); the prevalence of radiographic arthritis decreased from 49.4% in the middle cohort to 31.5% in the latest cohort ($p < 0.001$); angina at baseline decreased from 6.1% in the middle cohort to 1.9% in the latest ($p = 0.018$). These particular characteristics did not significantly differ between the middle and latest cohorts among men. Lastly, DMARD use within the first year of RA was similar among men and women, although a higher proportion of men received biologic DMARDs in the latest cohort (10.3% of men vs. 5.4% of women).

3.2 Stroke incidence and time-to-event analyses

Annual stroke incidence declined on average 3.2% (95% CI 0.8–5.6) in the RA cohort, after adjusting for sex, age, BMI, diabetes, smoking and serological status (Supplementary Table 3). The 20-year cumulative incidence of stroke was similar in the first (10.9%) and middle (10.8%) inception cohorts (Figure 1). However, there was a trend towards lower stroke incidence in the latest inception cohort, diverging from earlier cohorts from 5 years after RA diagnosis and onwards. There was no statistically significant difference in stroke risk compared to the first cohort (HR 0.65, 95% CI 0.38–1.11, $p = 0.11$) after adjusting for age, sex, smoking, BMI, diabetes and serological status. In contrast, stratified analysis by sex revealed a significantly lower stroke risk among women in the latest cohort (HR 0.30, 95% CI 0.12–0.76, $p = 0.01$), but no significant difference for men (HR 1.19, 95% CI 0.59–2.39, $p = 0.48$).

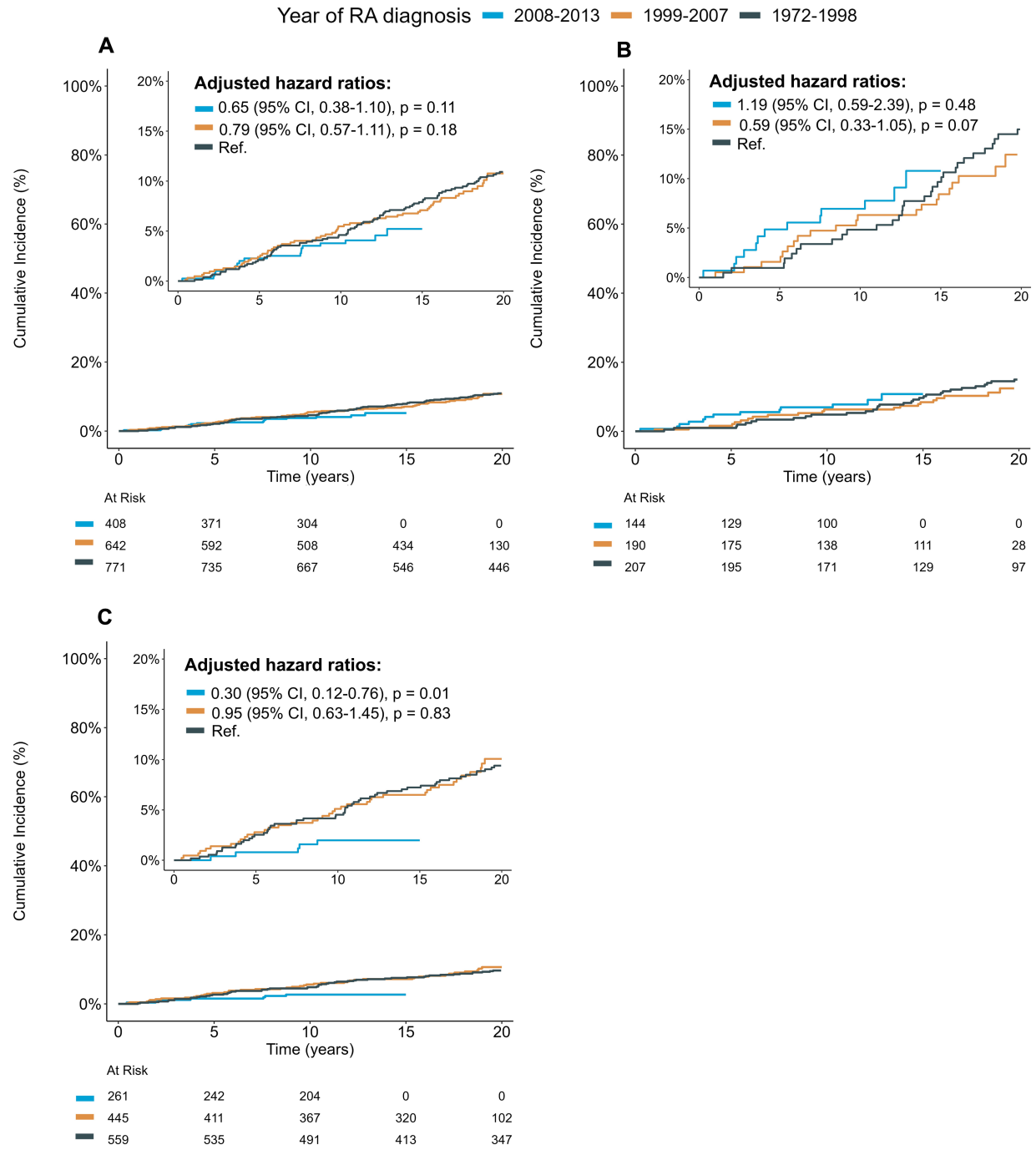

FIGURE 1
Cumulative incidence functions showing time to first stroke hospitalization for the total RA cohort **(A)**, for men **(B)**, and women **(C)** stratified by time of RA diagnosis. The cumulative incidence was adjusted for competing risk of death. Patients with stroke prior to RA diagnosis were excluded from the analyses. Reported hazard ratios were estimated by cox regression, with adjustment for age, sex, smoking, BMI, diabetes and serological status. CI; Confidence interval; RA, rheumatoid arthritis.

3.3 Stroke events

In total, 156 stroke events occurred in 109 patients diagnosed with RA during 1972–1998 over 17,110 person-years of follow-up, 70 stroke events occurred in 55 patients with RA diagnosed during 1999–2007 over 9,561 person-years of follow-up and 31 stroke events occurred in 20 patients with RA diagnosed during 2008–2013 over 4,098 person-years of follow-up. In the comparison cohort 21,210, 12,152 and 14,451 stroke events occurred during, respectively, 1972–1998, 1999–2007 and 2008–2020.

The overall temporal trend for crude event rates of stroke appeared biphasic for both the comparison and RA cohort, declining from 2000 and onwards, likely reflecting shifts in case definition and diagnosis over time (Supplementary Figure 1). From 1999 and onwards there was an annual decline of 4.8% (95% CI 2.7–6.9,

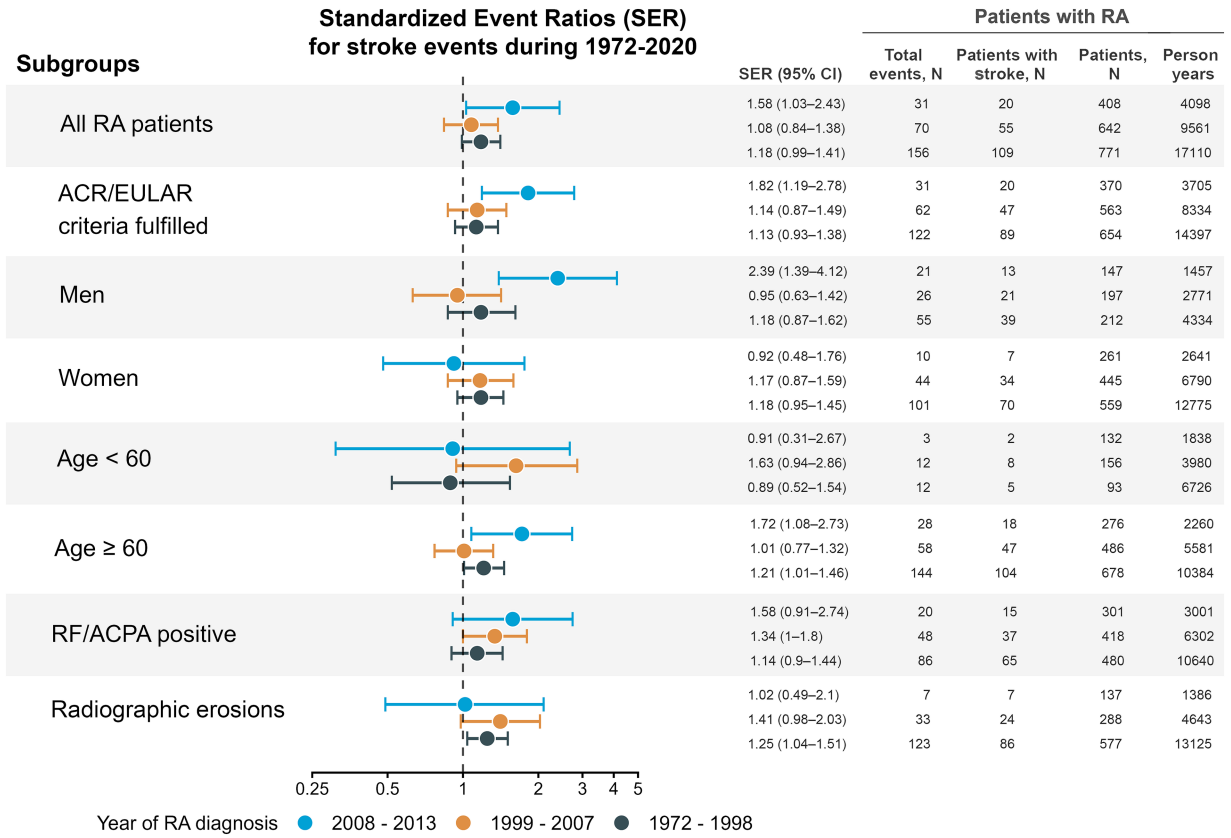

FIGURE 2
Standardized event ratios comparing stroke events in rheumatoid arthritis (RA) patients with the general population. Only inhabitants of Hordaland, Norway were included in the estimates. Point estimates are given with 95% robust confidence intervals. Separate estimates were calculated for the entire RA cohort and 6 RA subgroups defined by age, sex, positive rheumatoid factor or ACPA, fulfilment of the 2010 ACR/EULAR criteria, and radiographic erosions during follow-up. Counts of events, persons with stroke, and person-years of follow-up are shown only for the RA cohort, not the total population. Recurrent events were counted if more than 28 days between discharge to next admission. Person-years were estimated from the year of RA diagnosis to death or 31st December 2020. ACPA, anti-citrullinated protein antibodies; ACR, American College of Rheumatology; EULAR, European Alliance of Associations for Rheumatology; RA, rheumatoid arthritis; RF, rheumatoid factor; SER, standardized event ratio.

$p < 0.001$) in age- and sex-adjusted stroke rates in the RA cohort, and 3.4% (95% CI 3.1–3.7, $p < 0.001$) in the comparison cohort (Supplementary Table 3).

There was a general tendency of a moderate excess of stroke events across the RA subgroups (Figure 2). However, only patients with RA in the latest inception cohort had a statistically significant excess occurrence of stroke events (SER 1.58, 95% CI 1.03–2.43) compared with the total population and adjusted for year of event, sex, and age group. The excess exclusively observed in the male RA subgroup (SER 2.39, 95% CI 1.39–4.12), and no statistically significant excess was observed for female RA patients.

In the first inception cohort, we found an excess occurrence of stroke events of 18% (SER 1.18, 95% CI 0.99–1.41, $p = 0.066$), compared with the total population. Some subgroups of the first inception cohort had a significant excess of stroke events: patients older than 60 years (SER 1.21, 95% CI 1.01–1.46) and those with radiographic erosions (SER 1.25, 95% CI 1.04–1.51). In the middle inception cohort, only the RF/ACPA positive subgroup had a significant excess occurrence of stroke events (SER 1.34, 95% CI 1.00–1.80, Figure 2). Sensitivity analyses (Supplementary Table 4), revealed similar results, although a slightly lower estimate of excess stroke occurrence in the latest inception cohort.

4 Discussion

In this study, we compared stroke occurrence in patients with RA with the total population in the Hordaland municipality, Western Norway, stratified by the time period of RA diagnosis and adjusted for age, sex, and calendar year. We found a decline in stroke events over time in both the RA and comparison cohorts. However, a significant excess of stroke events was observed in male patients with RA, diagnosed between 2008 and 2013, but not in female patients. There was a trend towards excess stroke occurrence in patients diagnosed during 1972–1998, although not statistically significant and with similar estimates for men and women.

Surprisingly the most recent inception cohort had the highest estimated excess stroke occurrence compared with the general population. This excess stroke occurrence, however, was exclusively observed in male patients with RA, with no corresponding excess in female patients. This sex-specific discrepancy aligns with findings by Kerola et al., who found that RA conferred a significant stroke risk primarily in men, despite adjustment for cardiovascular risk factors (30).

Our study extends these observations by looking at temporal patterns. Unlike the study by Kerola et al., who only examined a

contemporary RA cohort, our longitudinal analysis across multiple inception cohorts reveals that this discrepancy in stroke occurrence is a recent development, not mirrored in the general population. While the cause of this discrepancy remains unclear, this recent emergence suggests that the discrepancy is less likely driven by inherent biological sex differences. More likely, the disparities could be driven by non-biological factors, such as differences in health behaviors, including lifestyle factors, RA management, or possibly cardiovascular prevention.

Supporting these findings are the significant improvements in markers of RA disease activity across inception cohorts, specific to female patients with RA. Women in the latest inception cohort had lower average CRP, less radiographic arthritis, and less angina at baseline, and this trend did not extend to male patients with RA. These improvements occurred despite the observation of similar use of non-biological and even more frequent use of biological DMARDs in male patients with RA.

Notably, we found no significant differences between men and women regarding the use of statins or antihypertensives across inception cohorts. Disparities in the use of cardiovascular prevention are therefore an unlikely explanation for the observed sex-specific discrepancy.

Several factors could explain why the estimated excess was most prominent in the last inception cohort. Misclassification of stroke events likely occurred more frequently in earlier inception cohorts due to less accurate diagnostics, potentially obscuring excess stroke occurrence in these periods. Competing risk from higher mortality in RA could also influence our estimates, causing potentially lower estimates of stroke events in the earlier inception cohorts with longer follow-up periods.

Our findings of excess stroke occurrence in a contemporary RA cohort is in line with several previous studies. Løgstrup et al. recently found a 22% increased risk of stroke in RA diagnosed during 1996–2017 who were prescribed DMARDs during a 10-year follow-up period. Baviera et al. found a 39% increased risk of stroke in a RA cohort diagnosed during 2005–2017 identified from co-payment exemption codes (18, 19). Our study corroborates these findings by investigating patients with RA with a diagnosis established by a rheumatologist, not registry codes, which adds clinical value. We also compared the same RA cohort before and after improvements in RA treatment and investigated subgroups defined by RA characteristics, such as RF/ACPA-positive patients.

In contrast to our findings, Holmqvist et al. did not find excess stroke risk in an incident RA cohort diagnosed during 1997–2009 in Sweden (HR 1.11, 95% CI 0.95–1.30) (21). However, when stratified by RA disease duration, the risk was detectable after 10 or more years from RA diagnosis. Our study included stroke recurrence and patients with a stroke before RA diagnosis, while these were excluded from Holmqvist's study. The follow-up period and period of RA diagnosis (1997–2009) overlapped in Holmqvist's study, and therefore patients with RA with a diagnosis closer to the end of the study had a substantially shorter follow-up period than in our study.

Few previous studies have investigated stroke occurrence in RA inception cohorts over time compared with the general population. In accordance with our findings, Myasoedova et al. found a persistent excess stroke incidence in a study of 905 patients with RA diagnosed during 1980–2009 compared with 904 patients without RA stratified by the decade of RA diagnosis (26). Also, a retrospective cohort study from Spain found increasing stroke hospitalizations in patients with RA during 1999–2015 but did not compare with the general population (31). Our study corroborates these findings by investigating a larger RA cohort compared with the total population from the same geographical area.

In contrast to our findings, Yazdani et al. found a decline in ischemic stroke risk over time in a RA cohort diagnosed from 1999 up to 2004 compared with matched controls (20). Notably, they did not report sex-specific estimates. Several differences between our studies could explain the diverging results. Our study used the total population for comparison instead of matching, which is preferable to avoid possible selection bias. In addition, the definition of RA in our cohort was more stringent: We initially identified cases using ICD-codes, similar to Yazdani et al. but excluded 11% after a review of medical records finding a diagnosis of osteoarthritis or other inflammatory joint diseases than rheumatoid arthritis.

Our study has some limitations. We did not have data on traditional cardiovascular risk factors for the comparison cohort, and were subsequently unable to adjust the analyses on excess stroke occurrence for these confounders. Consequently the cause of the continued excess in stroke occurrence could not be established. The outcome included both hemorrhagic and ischemic stroke, which have different risk factors and mechanisms. We did not have data on race and ethnicity. Our cohort likely resembles that of the general Norwegian population, of which immigrants made up 17.3% of the total population in 2025, almost all of these from Nordic or European countries (32). Substantially fewer patients were included in the first RA inception cohort, which is likely due to an increase in referrals to secondary care along with improvements in RA management. Finally, we did not have data on incident events for the comparison cohort.

The key strengths of this study are the long follow-up period and the inclusion of patients diagnosed before and after improvements in RA treatment. Furthermore, patients with RA were compared with the total population instead of using a matched comparison cohort, which could lead to selection bias. The included patients also had an RA diagnosis of high certainty, and patients with other inflammatory joint diseases or osteoarthritis, who have a CVD risk different from that of patients with RA, were excluded from our cohort. Using registry or equivalent data sources also ensured the completeness of follow-up data and a high level of sensitivity in identifying stroke events.

5 Conclusion

Despite substantial declines in overall stroke rates over time, our findings suggest a residual excess stroke occurrence in patients with RA diagnosed after 2007 compared to the general population. Notably, this contemporary excess stroke burden was specific to male patients with RA. While the lack of excess stroke occurrence in women could reflect differences in benefits of improved RA management or cardiovascular care over time, our findings highlight the continued need of targeted stroke prevention for patients with RA, particularly in men.

Data availability statement

The datasets presented in this article are not readily available because the datasets analyzed for this study cannot be shared publicly since the approval by the regional ethics committee does not allow sharing of de-identified patient data. Aggregated data may be shared

upon request, but further aggregation will be needed to ensure anonymity in the RA cohort. Requests to access the datasets should be directed to Christian Alsing, chr.alsing@gmail.com.

Ethics statement

The studies involving humans were approved by Regional Committee for Medical and Health Research Ethics, Health Region West. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

CA: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. JI: Conceptualization, Data curation, Methodology, Resources, Software, Supervision, Validation, Writing – review & editing. TN: Investigation, Resources, Supervision, Writing – review & editing. CG: Conceptualization, Methodology, Supervision, Writing – review & editing. HN: Supervision, Writing – review & editing. GT: Conceptualization, Methodology, Supervision, Writing – review & editing. B-TF: Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Visualization, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. This work was supported by the Western Norway Regional Health Authority, Marit Hansen's Memorial Fund, and Aslaug Andersen's Memorial Fund.

Acknowledgments

The authors thank Tomislav Dimoski, The Norwegian Institute of Public Health, Oslo, Norway, for his contribution by developing the software necessary for obtaining data, conducting the data collection, and quality assurance of the data of the CVDNOR project.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2025.1547518/full#supplementary-material

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frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 10 June 2025
DOI 10.3389/fmed.2025.1538710

OPEN ACCESS

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RECEIVED 03 December 2024
ACCEPTED 20 May 2025
PUBLISHED 10 June 2025

CITATION
Liu Y, Liu Y, Fan S, Yang J, Xu M, Zhao L, Liu C, Xing Y and Kong X (2025) Correlation between CBC-derived inflammatory indicators and all-cause mortality with rheumatoid arthritis: a population-based study.
Front. Med. 12:1538710.
doi: 10.3389/fmed.2025.1538710

Correlation between CBC-derived inflammatory indicators and all-cause mortality with rheumatoid arthritis: a population-based study

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Objectives: We investigated the relationship between inflammatory indicators derived from complete blood cell (CBC) counts and all-cause mortality in individuals with rheumatoid arthritis (RA).

Methods: Data were collected from the National Health and Nutrition Examination Survey (NHANES) database from 2007 to 2018, with a median follow-up duration of 78 months. The inflammatory indicators derived from CBC included several types: the systemic inflammatory response index (SIRI), the systemic immune-inflammation index (SII), the neutrophil-to-lymphocyte ratio (NLR), the platelet-to-lymphocyte ratio (PLR), and the monocyte-to-lymphocyte ratio (MLR). The multiple COX regression models were used to estimate adjusted hazard ratios (HRs) and 95% CIs concerning all-cause mortality of participants with RA, which focused on CBC-derived inflammatory indicators. Additionally, restricted cubic spline (RCS) curve was utilized to investigate non-linear associations.

Results: The research comprised a cohort of 1,314 individuals, among whom 246 with RA succumbed during a median follow-up duration of 78 months. After adjusting for key covariates, the mortality rate in patients with RA who had high SIRI, NLR, and MLR levels was considerably higher than in those with medium or low SIRI, NLR, and MLR levels. Compared with the lowest tertile, the highest tertiles of SIRI (HR 1.87, 95% CI: 1.12–3.13), NLR (HR 1.79, 95% CI: 1.10–2.92), and MLR (HR 1.88, 95% CI: 1.17–3.02) were associated with an increased risk of all-cause mortality. The Kaplan-Meier analysis indicated a significant decrease in the survival probability among individuals with elevated SIRI, NLR, and MLR levels. The RCS analysis revealed a linear association between SIRI, NLR, MLR, and RA-related all-cause mortality, whereas a non-linear relationship was identified between the SII, PLR, and mortality.

Conclusion: This investigation revealed that the SIRI, NLR, and MLR are novel, valuable, and convenient inflammatory indicators. In the United States adults with RA, higher SIRI, NLR, and MLR were independently associated with an increased long-term mortality risk. These findings not only assist in uncovering

the potential utility of predicting RA outcomes but also provide rheumatologists valuable guidance for disease management.

KEYWORDS

rheumatoid arthritis, mortality, NHANES, systemic inflammatory response index, neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio

1 Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disorder with excessive synovial tissue growth, pannus formation, and gradual bone and cartilage deterioration (1). Undoubtedly, RA has a high prevalence rate and continues to pose a significant global public health issue. Worldwide, the disease burden of RA has increased and will persist in growing. Prevention and early intervention are crucial in preventing disease flares and reducing the enormous burden associated with RA (2). Predictions indicate that the burden of RA will keep on increasing to the extent that the global prevalence of disease will reach 31.7 million by 2050 (3). Identifying the impacts influencing RA morbidity and mortality is essential for developing effective management strategies and interventions. The observed increase in RA mortality rates during the follow-up period enhances our comprehension of disease progression and its consequences (4). It is well-established that specific autoantibodies in RA play a notable role in diagnosing disease activity and predicting prognosis (5). However, recent research has shifted focused toward inflammatory indicators for disease evaluation and prognosis (6). Multiple researches have emphasized the crucial role of inflammation in the progression and pathogenesis of RA (7). While Inflammatory indicators are commonly used for RA diagnosis and disease assessment, there is a lack of data about their association with mortality. Moreover, novel inflammatory indicators derived from routine blood tests have shown potential for monitoring RA-related mortality and aiding in disease management. Consequently, rheumatologists are actively seeking other accessible inflammatory indicators that can be utilized to manage and evaluate the entire course of RA.

Recent studies have reported notably elevated levels of inflammatory indicator in RA patients compared to healthy controls. Furthermore, these inflammatory indicator levels, derived from complete blood analysis results, have proven to be easily obtainable and cost-effective indicators of RA disease activity. The biomarkers include neutrophils, lymphocytes, platelets, and monocytes. In addition, inflammatory indicators derived from CBCs, such as the systemic inflammatory response index (SIRI), systemic immune-inflammation index (SII), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR), are implicated in various diseases (8). These indicators are crucial inflammatory cells that secrete cytokines, chemokines, proteases, and angiogenic factors during chronic inflammation (9). Numerous composite blood scores have been proposed to evaluate disease activity for this purpose. Recently, several studies have been demonstrated a correlation between the NLR and PLR with RA disease activity (10). Nonetheless, it exists a gap in the literature concerning a systematic and comprehensive investigation of the association between CBC-derived inflammatory indicators in RA patients and all-cause mortality.

Overall, research has established a connection between inflammatory indicators derived from CBC and the manifestation of RA in individuals (11). The SIRI has demonstrated potential as a non-invasive and effective biomarker for diagnosing and evaluating RA activity, predicting RA-associated interstitial lung disease (RA-ILD), and assessing tumor development (12). Similarly, the SII is recognized as a novel inflammatory marker associated with RA disease activity (13). Commonly, inflammatory indicators derived from CBCs, such as the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and Disease Activity Score 28 (DAS28), are utilized to evaluate RA activity (14). The NLR is an emerging biomarker that provides insights into immune system activation and systemic inflammation (15). Consequently, an elevated NLR serves as a reliable and cost-effective prognostic indicator of cardiovascular and overall mortality in individuals with RA (16). Additionally, the PLR can be used as a potential marker of systemic bone loss in patients with RA (17). The MLR may be employed as a supplementary diagnostic indicator in patients with undifferentiated inflammatory arthritis (18). For now, several articles have reported links between CBC-derived inflammatory indicators and mortality in patients with conditions such as psoriatic arthritis (19) and asthma (20). However, several investigations have the limitation of small sample sizes. Although a limited number of papers have explored the correlation between inflammatory indicators derived from CBC and the activity and morbidity associated with RA, there is a paucity of research on the relationship between these Inflammatory indicators and the survival outcomes of RA patients. Identifying independent risk factors related to the survival status of RA patients is crucial for effective disease management and prognosis assessment.

To date, the potential association between inflammatory indicators identified in CBCs, using data from the National Health and Nutrition Examination Survey (NHANES), and all-cause mortality in RA patients remains largely unexplored. From 2007 and 2018, an analysis was conducted involving 1,314 individuals with RA to investigate the associations between SIRI, SII, NLR, PLR, and MLR with all-cause mortality. Our investigation aimed to identify a cost-effective and readily available prognostic indicator for individuals with RA.

2 Materials and methods

2.1 Study design and population

Using NHANES, the National Center for Health Statistics evaluates the nutritional and health conditions of non-institutionalized civilians. The NCHS Institutional Review

Board granted approval to the NHANES proposal, and all survey participants have provided informed consent and signed a consent form. This study included 1,794 persons diagnosed with RA during six consecutive cycles from 2007–2008 to 2017–2018. Among these individuals, two were pregnant and 478 had missing data on core covariates (131 PIR deletions, one marital status deletion, two education status deletions, two smoking status deletions, 269 alcohol use deletions, 21 BMI deletions, and 52 cell blood count deletions). In summary, the case study ultimately included a total of 1,314 participants (Figure 1).

2.2 A comprehensive evaluation of RA

Individuals' circumstances were assessed using self-report questionnaire. The survey comprises three inquiries: Have you ever received a diagnosis of arthritis from a doctor or any other healthcare professional? At what age were you initially diagnosed with arthritis? What is the specific type of arthritis? Based on the aforementioned three screening questions, participants who had received a diagnosis of RA were selected for inclusion in the assesses. It has been reported that the coincidence rate between self-reported diagnosis and clinical diagnosis is more than 85% (7, 21, 22).

2.3 Evaluation of inflammatory indicators generated from CBC

By measuring the whole blood cell count using an automated hematology analyzer, various blood components, including red blood cells, white blood cells, and platelets, were quantified for the given volume of blood. Below are formulas for the CBC-derived inflammatory indicators:

$$\text{SIRI} = \frac{\text{neutrophil count} * \text{monocyte count}}{\text{lymphocyte count}}$$

$$\text{SII} = \frac{\text{neutrophil count} * \text{platelet count}}{\text{lymphocyte count}}$$

$$\text{NLR} = \frac{\text{neutrophil count}}{\text{lymphocyte count}}$$

$$\text{PLR} = \frac{\text{platelet count}}{\text{lymphocyte count}}$$

$$\text{MLR} = \frac{\text{monocyte count}}{\text{lymphocyte count}}$$

2.4 Covariates

Factors that could confound the association between inflammatory indicators obtained from CBCs and mortality in RA were carefully managed, taking into account the literature and pertinent clinical expertise. The primary covariates are listed as follows: According to the World Health Organization classification of age, the age variable was divided into two groups: young (under 60 years) and elderly (60 years and older). There are two categories for gender: male and female. Four categories exist for race: Mexican-Americans, non-Hispanic blacks, non-Hispanic whites and other. Divorced, separated, or never married are the various categories of marital status. Three categories make up the poverty-income ratio (PIR): The low-income group includes people or families with incomes of 1.35% or less; the moderate group includes people or families with incomes of 1.35%–3.5%; and the high group includes people or families with incomes of 3.5% or more. There are two categories of body mass index (BMI): normal (BMI < 25.0 kg/m^2) and obese (BMI ≥ 25.0 kg/m^2). Alcohol intake is divided into two categories: never (less than 12 drinks in a person's lifetime) and ever/current (12 or more drinks in a person's lifetime). In terms of smoking status, there are two categories: never smokers and former/current smokers (≥ 100 cigarettes in a lifetime). It is possible to diagnose hypertension based on the self-reported medical history, blood pressure readings greater than 140/90 mm Hg annually, or the use of antihypertensive medications. Having an HbA1c level of at least 6.5%, a random blood glucose level of at least 11.1 mmo1/L, a fasting plasma glucose level of at least 7.0 mmo1/L, or self-reported use of insulin or other diabetes medications indicates that an individual has diabetes.

2.5 Statistical analysis

To accurately represent the Correlation between the selected samples and the actual population, and to mitigate the effects of missing samples, oversampling, and differences in sample selection on the overall analysis, we employed a complex sampling analysis method and applied weight to the samples. The population was stratified into tertiles based on the indicators under study within the included population. Kaplan-Meier curves were generated to visually depict the survival probabilities associated with several categories of inflammatory indicators derived from complete blood counts. Cox proportional hazards models, calculated using both univariate and multivariate weights, were utilized to analyze the correlation between inflammatory indicators from CBC and all-cause mortality in RA patients. Three distinct models were constructed: Model 1 adjusts only for age and gender; Model 2 incorporated additional considers for race/ethnicity, marital status, poverty-to-income ratio, and body mass index; Model 3 further adjusted for factors such as diabetes, hypertension, smoking status, drinking status, among others. To investigate whether there was a non-linear relationship between all-cause mortality from RA and inflammatory biomarkers collected from CBC, we used restricted cubic spline (RCS) analysis. The entire statistical analysis was conducted by R statistical software, specifically version 4.3.1.

3 Results

3.1 Characteristics of the RA participants

Based on the information for SIRI, SII, NLR, PLR, and MLR ternaries presented in Supplementary Table 1, the study population demonstrated the following weighted demographic

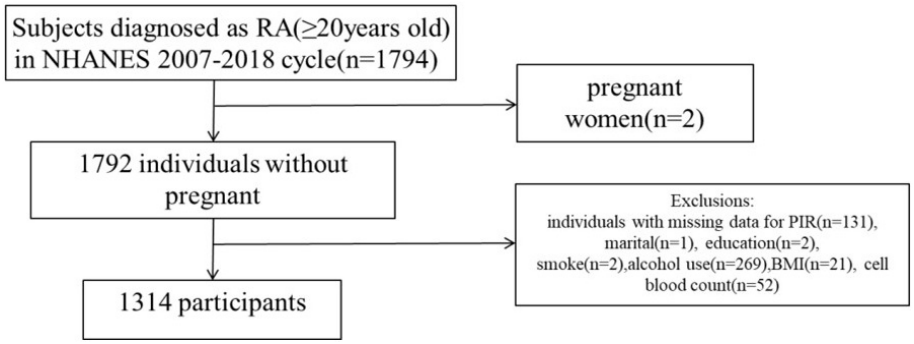

FIGURE 1
National Health and Nutrition Examination Survey (NHANES) 2007–2018 study flow chart.

baseline characteristics. The data in Supplementary Table 1a indicate that the high SIRI group was significantly overrepresented by male patients compared to the low and medium SIRI groups. Additionally, the high SIRI subgroup had a higher percentage of adults aged 60 and above as well as a greater percentage of individuals with hypertension. According to Supplementary Table 1b, the prevalence of hypertension was notably greater among patients in the high SII subgroup compared to those in the other two subgroups. Supplementary Table 1c reveals that the population with a high NLR had a greater proportion of individuals aged 60 years and older contrasted with the low and middle NLR groups, and the prevalence of hypertension was similarly elevated in the high group. Supplementary Table 1d highlights a notable disparity in the number of females between the high PLR population and the low and medium PLR populations. Furthermore, the number of non-drinkers in the high PLR group was significantly higher than those in the low and medium PLR groups. Supplementary Table 1e suggests that with the increase in MLR, there was a noticeable increase in the proportion of males, people over 60 years old, and persons with hypertension.

3.2 Measuring and predicting RA mortality based on CBC-derived indicators

A 78 months follow-up was conducted (range: 1–157 months), 246 (18.75%) mortality events occurred. Cox proportional hazard analysis demonstrated a significant increase in mortality rates among participants with RA in the high SIRI group versus those in the low and medium SIRI groups (HR 2.58, 95% CI: 1.61–4.12). In Model 1, the high SIRI group had a statistically significant increase in all-cause mortality when age and sex were considered. This increase was also observed in comparison to the low and medium-SIRI groups (HR 2.17, 95% CI: 1.35–3.47). Model 2 demonstrated that, even after accounting for race/ethnicity, marital status, education, and PIR, the high-SIRI group exhibited a significantly greater all-cause death rate than did the low and medium SIRI groups (HR 2.01, 95% CI: 1.22–3.30).

After additional adjustments for diabetes, hypertension, smoking status, alcohol consumption, and BMI were made in Model 3, high SIRI patients had a significantly higher death rate from all causes than those with medium SIRI. Statistics indicated that this difference was significant in statistical terms (HR 1.87, 95% CI: 1.12–3.13). Patients with RA had a notable positive correlation between the SIRI and mortality. The relationship between SII and mortality in patients with RA was studied using a Cox proportional hazard model. According to the findings presented in Table 1, the crude model results indicate a statistically significant increase in all-cause mortality in the high-SII subgroup compared to the low and medium SII subgroups (HR 1.45, 95% CI: 1.04–2.02). According to Model 1, after adjusting for age and sex, the mortality rate of RA patients with a high SII remained significantly greater (HR 1.46, 95% CI: 1.07–2.00) than that of patients with a low or medium SII, and the difference was statistically significant. In Model 2 and Model 3, subsequent to making additional adjustments for race/ethnicity, marital status, education, PIR and diabetes status, hypertension status, smoking status, alcohol usage, and BMI, the all-cause mortality rate for RA patients in the high-SII subgroup remained greater than that in the low- SII subgroup and moderate-SII subgroup. However, the difference was no longer statistically significant. Cox proportional hazard model analysis revealed that patients in the high-MLR (HR 2.69, 95% CI: 1.67–4.33) and high-NLR (HR 2.28, 95% CI: 1.40–3.68) groups had significantly greater all-cause mortality than did those in the low- and medium-MLR groups. Even after accounting for factors such as age, sex, race/ethnicity, marital status, education, income, diabetes status, hypertension status, smoking status, alcohol consumption status, and BMI, the observed differences in all-cause mortality among participants with RA remained significant. Furthermore, the mortality rate increased as the NLR increased. Moreover, we analyzed the relationship between the Cox proportional hazards model, PLR, and RA mortality. However, a significant difference was not found in mortality rates among RA patients in different PLR groups, both in the unadjusted crude model and in the model with adjusted covariates.

As shown by Kaplan-Meier analysis results in Figure 2, CBC-derived indicators were significantly associated with higher mortality rates for individuals in the high SIRI, high NLR, and high MLR groups than in low SIRI, low NLR, and low MLR groups in

TABLE 1 Association of complete blood cell (CBC)-derived indicators with mortality risk in participants with rheumatoid arthritis (RA).

	Crude model		Model 1		Model 2		Model 3	
Characteristic	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
SIRI								
Low	1 (ref)	–	1 (ref)	–	1 (ref)	–	1 (ref)	–
Medium	1.52 (0.90, 2.56)	0.11	1.46 (0.89, 2.41)	0.14	1.46 (0.88, 2.43)	0.14	1.36 (0.82, 2.28)	0.24
High	2.58 (1.61, 4.12)	< **0.001**	2.17 (1.35, 3.47)	**0.001**	2.01 (1.22, 3.30)	**0.01**	1.87 (1.12, 3.13)	**0.02**
P for trend	–	< **0.001**	–	<**0.001**	–	**0.01**	–	**0.01**
SII								
Low	1 (ref)	–	1 (ref)	–	1 (ref)	–	1 (ref)	–
Medium	1.03 (0.70, 1.53)	0.87	1.03 (0.70, 1.52)	0.89	1.09 (0.72, 1.66)	0.68	1.00 (0.64, 1.56)	0.99
High	1.45 (1.04, 2.02)	**0.03**	1.46 (1.07, 2.00)	**0.02**	1.35 (0.97, 1.86)	0.07	1.26 (0.92, 1.72)	0.15
P for trend	–	**0.02**	–	**0.01**	–	0.07	–	0.12
NLR								
Low	1 (ref)	–	1 (ref)	–	1 (ref)	–	1 (ref)	–
Medium	1.36 (0.83, 2.23)	0.23	1.27 (0.79, 2.04)	0.32	1.34 (0.82, 2.18)	0.24	1.26 (0.77, 2.06)	0.36
High	2.28 (1.40, 3.68)	< **0.001**	1.95 (1.21, 3.13)	**0.01**	1.88 (1.15, 3.08)	**0.01**	1.79 (1.10, 2.92)	**0.02**
P for trend	–	< **0.001**	–	**0.003**	–	**0.01**	–	**0.01**
PLR								
Low	1	–	1	–	1	–	1	–
Medium	0.92 (0.57, 1.48)	0.73	0.93 (0.57, 1.49)	0.75	1.05 (0.66, 1.67)	0.84	1.06 (0.66, 1.68)	0.82
High	1.34 (0.89, 2.02)	0.17	1.26 (0.84, 1.89)	0.27	1.24 (0.84, 1.83)	0.27	1.32 (0.90, 1.93)	0.15
P for trend	–	0.16	–	0.25	–	0.27	–	0.14
MLR								
Low	1 (ref)	–	1 (ref)	–	1 (ref)	–	1 (ref)	–
Medium	1.66 (1.00, 2.76)	0.05	1.41 (0.84, 2.36)	0.19	1.31 (0.79, 2.17)	0.29	1.43 (0.87, 2.37)	0.16
High	2.69 (1.67, 4.33)	< **0.001**	1.98 (1.21, 3.22)	**0.01**	1.75 (1.07, 2.85)	**0.02**	1.88 (1.17, 3.02)	**0.01**
P for trend	–	< **0.001**	–	**0.004**	–	**0.02**	–	**0.01**

Model 1: adjusted for age, gender. Model 2: additional adjustment for race/ethnicity, marital status, education, and PIR. Model 3: additional adjustment for diabetes status, hypertension status, smoking status, alcohol use status, and BMI. The bold values indicate statistical significance.

RA patients ($p < 0.001$ for all). However, the survival rates among different SII and PLR groups did not differ significantly.

3.3 The non-linear correlation between mortality and CBC-derived indicators

Figure 3 shows RCS curve of the association CBC-derived indicators with the risk of mortality rate in RA participants. A linear correlation between the SIRI, NLR, and MLR and all-cause mortality in RA patients is shown in Figures 3a, c, e. An elevated SIRI is connected to increased all-cause mortality in individuals with RA, however, there was no statistically significant non-linear correlation. In contrast, Figure 3b demonstrates a non-linear relationship between SII and all-cause mortality. Specifically, When the log of SII exceeds 5.82, all-cause mortality increases sharply with increasing SII (non-linear *P*-value = 0.03). Figure 3d reveals a non-linear correlation between the PLR and mortality in patients with RA. When the log PLR exceeds 4.68, the overall mortality rate of patients with RA decreased as the PLR increased. Conversely, while when the log PLR exceeds 4.68, the overall mortality increases with the PLR increased (non-linear *P*-value < 0.001).

3.4 Association between CBC characteristics and inflammatory indicators obtained from CBC

The relationship between CBC parameters and indicators are depicted in Figure 4. The results indicate that neutrophil count and SIRI and SII are statistically significantly correlated with 0.66 and 0.65 correlation coefficients, respectively.

4 Discussion

Over a period of 78 months, a cohort of 1,314 adult RA patients was examined to assess the potential association between inflammatory indicators derived from CBC and mortality risk.

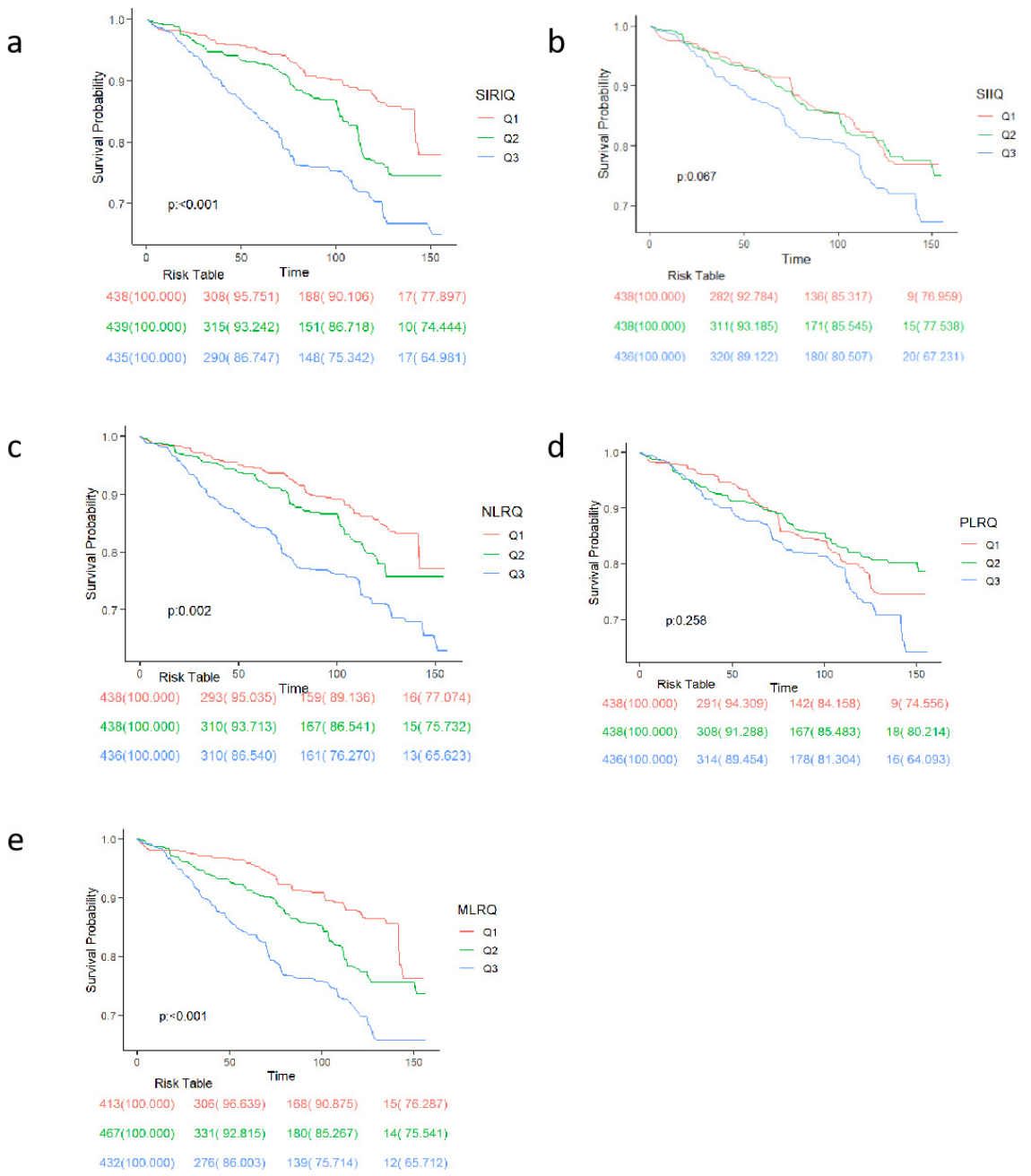

FIGURE 2
Mortality rates among participants with RA according to Kaplan–Meier curves. Kaplan–Meier curves stratified by **(a)** SII, **(b)** NLR, **(c)** NLR, **(d)** PLR, **(e)** MLR. The figure shows the survival probability trends of three groups (Q1, Q2, Q3) at different time points. The *p*-value indicates the statistical significance of survival differences among groups. The risk table below lists the remaining number of individuals and corresponding survival rates for each group at each time point.

The relationship between inflammatory indicators derived from CBC and all-cause mortality has been infrequently documented in the context of autoimmune diseases. However, recent years have witnessed a growing interest in the application of CBC-derived inflammatory indicators for evaluating disease activity in various autoimmune conditions, including systemic lupus erythematosus (23, 24), Sjogren's syndrome (25), anti-synthetase syndrome (26), and Behcet's disease (27), as well as in spondylarthritis (28) and systemic sclerosis (29). Furthermore, numerous studies also have identified associations between CBC-derived inflammatory indicators and disease complications, such as lupus nephritis (30), peripheral neuropathy in Sjogren's syndrome (31), and ocular features of Behcet's disease patients (32). CBC-derived inflammatory indicators are simple and easily available biomarkers of systemic inflammation, initially recognized for their highly sensitive as inflammatory indicators in the fields of oncology, particularly in gastric cancer (33), breast cancer (34), small cell lung cancer (35), and prostate cancer (36). CBC-derived inflammatory indicators have been validated as independent prognostic risk factors in participants with tumors, contributing

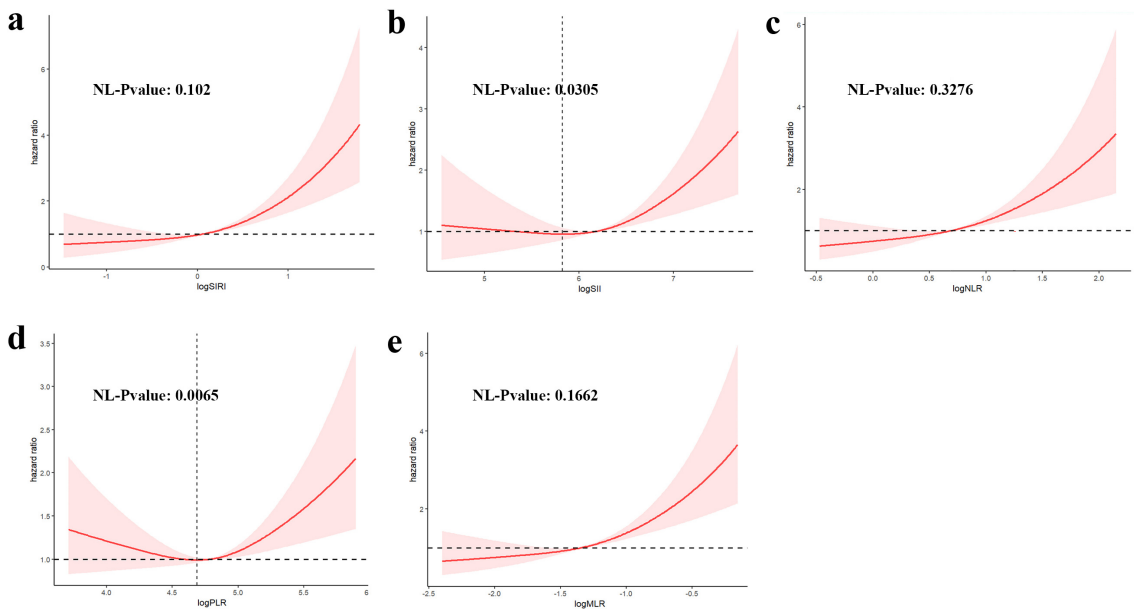

FIGURE 3
Restricted cubic spline (RCS) illustrating the correlation between indicators [**(a)** SIRI, **(b)** SII, **(c)** NLR, **(d)** PLR, **(e)** MLR] and mortality among participants with RA.

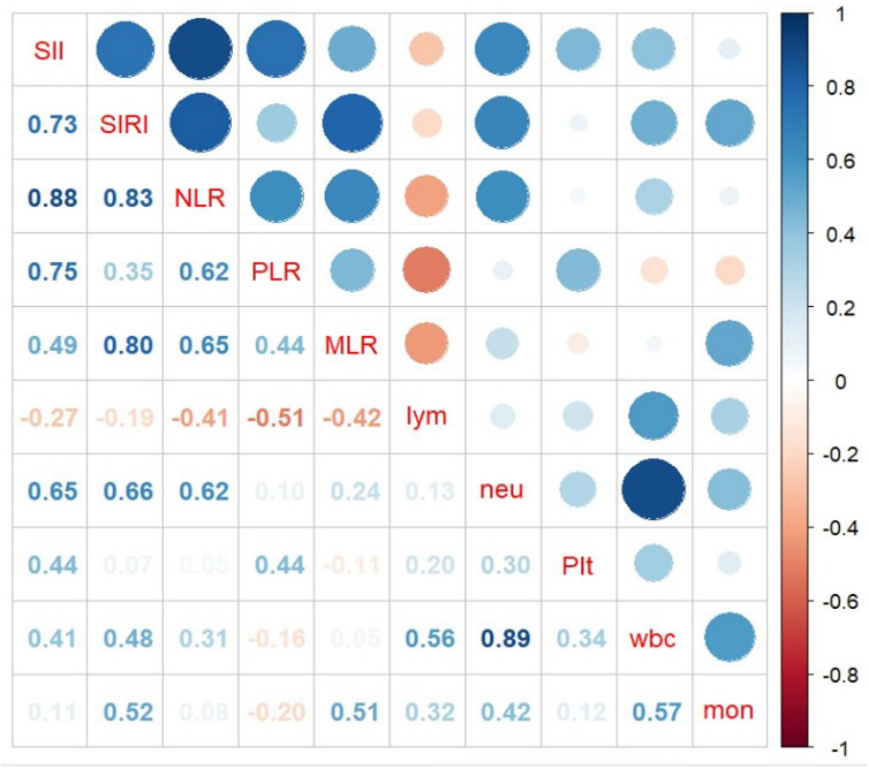

FIGURE 4
Association between complete blood cell (CBC) characteristics and inflammatory biomarkers obtained from complete blood cell (CBC).

to the prognostic assessment of disease treatment outcomes. These findings have inspired us to investigate the associations of inflammatory indicators with the prognosis and mortality of participants with RA. For the first time, our findings suggest that RA patients with high levels of SIRI, NLR, and MLR have a greater risk of mortality. K-M curves and RCS analyses demonstrated significant reductions and linear positive associations in survival probabilities for those with higher SIRI, NLR and MLR. These

findings suggest that the SIRI, NLR, and MLR, which are widely available and inexpensive indicators are linked to increased risks of mortality in patients with RA.

Data from the Baltimore Longitudinal Study of Aging (BLSA) further corroborate these findings, demonstrating that higher white blood cell counts were associated with increased mortality (37). Additionally, NLR and MLR have been identified as leukocyte-derived ratios predictive of multimorbidity and mortality within the BLSA cohort (38). Recently, the InCHIANTI study found that the NLR and MLR were reliable indicators of healthy aging and predicted changes physical resilience and mortality (39–41). Similarly, the Rotterdam Study has established an association between the NLR and mortality within the general population (42). Obviously, leukocyte derived inflammatory indicators have become a global research hotspot, and their significances in monitoring chronic diseases need to be explored further.

Inflammatory indicators are derived from the combination of neutrophils, lymphocytes, monocytes, or platelets obtained through routine blood tests. The NLR is calculated as the ratio of neutrophils to lymphocytes, reflecting the activity of cells within both the innate and adaptive immune systems. Neutrophils can produce a variety of lyases, cytokines and oxygen free radicals, which characterize the innate system as the first line of defense. In contrast, the continuous accumulation of lymphocytes in inflamed joints leads to a reduction in peripheral blood lymphocyte counts in RA patients. Lymphocytes represent the adaptive immune response. Therefore, routine blood tests are gaining attention due to decreasing peripheral blood lymphocytes and increasing neutrophil counts. Monocytes exert a regulatory influence on the immune system, engage in cytokine synthesis, and can cause bone degradation in RA. The MLR is calculated by dividing monocyte count by lymphocyte count. The SIRI reflects the interactions among neutrophils, monocytes, and lymphocytes, illustrating the intricate interplay and potential synergistic effects among these cell types. The evaluation and prognosis of rheumatoid arthritis patients involve the SIRI, NLR, and MLR due to a series of alterations in neutrophils, lymphocytes, and monocytes. The limits of CBC-derived inflammatory indicators in distinguishing patients with RA from those with other rheumatic illnesses are evident (43). However, in persons with RA, the peripheral blood contains more neutrophils and monocytes, while lymphocytes are reduced. Our research suggests that these indicators play a significant role in assessing overall mortality in individuals with RA. CBC-derived inflammatory indicators represent novel, accessible, and non-invasive tools of notable importance. Their efficacy and simplicity facilitate rheumatologists in assessing patient prognosis.

Previous researches have revealed a correlation between CBC-derived inflammatory indicators and RA. These biomarkers serve prognostic functions in rheumatic illnesses and can be employed to evaluate disease progression (15, 44). While ultrasound and magnetic resonance imaging can detect joint inflammation, these methods are complex, occasionally difficult to access, and may require specialized techniques. Conversely, although blood cell-derived indicators do not support directly diagnosis of RA, they may reflect chronic inflammatory burden associated with rheumatic diseases (43). Furthermore, correlations have been established between complex blood inflammation markers and cardiovascular risk factors, as well as subclinical atherosclerosis, in individuals diagnosed with RA (45). Numerous studies have documented the ability of CBC-derived inflammatory indicators to identify disease activity and predict disease status of patients with RA. However, few studies have reported their relationship with all-cause mortality in this population.

A measure of all-cause mortality can be employed to understand disease prevalence and assess the effectiveness of health management strategies. Therefore, it is essential to identify readily available biomarkers linked to overall mortality across various conditions. Numerous studies have documented correlations between one or two inflammatory biomarkers generated from CBCs to assess their connection with death from any cause. For instance, the SII and SIRI have been strongly related to cardiovascular mortality and all-cause mortality events, and more attention should be given to systemic immune inflammation to provide new insights into prevention (46). Moreover, the SIRI and SII independently predict all-cause and cardiovascular disease (CVD) mortality events in obese individuals. Notably, SIRI exhibits a significantly greater predictive value than SII, suggesting that it is a more meaningful marker of inflammation (47). In patients diagnosed with ANCA-associated vasculitis (AAV), the SIRI at the time of diagnosis predicts all-cause mortality during follow-up (48). Similarly, in patients with hypertension, an elevated SIRI is also correlated with increased all-cause mortality and CVD mortality (49). Additionally, the NLR has been associated with all-cause mortality with stage five chronic kidney disease (50) and with cardiovascular mortality risk in maintenance hemodialysis patients (51) and patients with RA (16). Researchers have also found a significant association between a high MLR and an elevated risk of death from chronic kidney disease and type 2 diabetes mellitus within 90 days (52). However, our study provided new strategies and supporting materials that highlight the significance of the SIRI, NLR, and MLR as independent predictors of mortality related to RA.

Patients with RA are characterized by the production of autoantibodies and systemic inflammation, which lead to the activation and release of immune cell, including neutrophils, lymphocytes and monocytes (53). Therefore, three kinds of cell counts are invaluable for understanding the inflammatory state and immune response reflected in RA. Several studies have suggested that the immunological equilibrium resulting from the interplay of leukocytes, synovial fibroblasts, chondrocytes, and osteoclasts may have a significant effect on the development of RA. One hypothesis posits that neutrophils, because their pronounced cytotoxicity, may generate degradation enzymes and reactive oxygen species that could serve as antigens in the autoimmune process, thereby affecting the underlying mechanism of the autoimmune response (54–57). An alternative hypothesis proposes that the presence of inflammation in individuals with RA may stimulate the activation of apoptotic cytokines and granulocyte colony-stimulating factor, which could promote the activation and proliferation of neutrophils, initiating the immune response through a positive feedback loop. This mechanism can ultimately contribute to the onset and progression of RA (58). Lymphocytes are a vital component of the host immune system and serve as protective factor for prognosis in RA patients (59). Moreover, monocytes have a significant impact on the pathogenesis of RA. Osteoclasts, characterized as large multinucleated cells, originate from the monocyte–macrophage lineage. Upon specific stimulation, circulating monocytes migrate

to designated sites within the bone, where they fuse with fully developed multinucleated osteoclasts and actively engage in the process of bone resorption. The process of transition from monocytes to osteoclasts is essential for joint deterioration, contributing to both in inflammation exacerbation and bone degradation in RA, despite the presence of osteoclast precursors other than monocytes (60–62). High values of the SIRI, NLR and MLR reflect both the ability of monocytes and neutrophils to mediate a strong proinflammatory response and the ability of lymphocytes to mediate a weak or inhibited anti-inflammatory response. Our study indicates that increased SIRI, NLR, and MLR are associated with greater risks of RA-related mortality. Attenuating immune inflammation emerges as a promising strategy for retarding RA progression and limiting adverse outcomes.

Our article has several advantages. Firstly, it features a substantial sample size with a representative sample selection. This study is the first to identify associations between inflammatory indicators derived from CBCs in patients suffering from RA and all-cause mortality, a large sample size was used. The analysis employed a weighted logistic regression model, adjusting for other covariates. Secondly, prior to this study, no research had comprehensively examined the relationship between inflammatory indicators derived from CBC and all-cause mortality in RA. Until now, there had been no article on the correlation between MLR and all-cause mortality in RA. It has been suggested that the MLR can serve as a complementary diagnostic indicator for the diagnosis of RA (18) and associated with disease activity and specific clinical features of RA (63). Consequently, our conclusions are more accurate and reliable. Lastly, the non-linear relationship is explored by using restricted cubic splines and smooth curve fitting, after which the inflection points are further calculated. A notable observation in our study is that the risk of mortality in RA patients increased over time, consistent with our understanding of disease-related harm. Therefore, our findings demonstrate enhanced greater persuasiveness, comprehensiveness, and robust documentation.

Meanwhile, some inevitable limitations should be acknowledged in our study. First and foremost, the cross-sectional study design was unable to determine a clear causal association between inflammatory indicators derived from CBCs in patients with RA and all-cause mortality. Moreover, CBC-derived inflammatory biomarkers were measured at a single timepoint and most likely did not reflect changes in time or intervention. Finally, given that the population in the present study was drawn from a representative sample within the United States population, a replication of our results in other racial groups is necessary.

5 Conclusion

This study suggested that increased SIRI, NLR, and MLR were associated with greater risks of RA-related mortality and can be used to measure pathological innate inflammation and protective adaptive immunity. In addition to helping to discover their potential utility in predicting RA outcomes, these findings also provide rheumatologists with guidance on disease management.

Data availability statement

The original contributions presented in this study are included in this article/Supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

YuL: Conceptualization, Investigation, Writing – original draft, Writing – review and editing. YiL: Data curation, Formal Analysis, Writing – original draft, Writing – review and editing. SF: Data curation, Formal Analysis, Methodology, Writing – original draft. JY: Data curation, Formal Analysis, Writing – original draft. MX: Investigation, Methodology, Writing – original draft. LZ: Investigation, Methodology, Writing – original draft. CL: Supervision, Validation, Writing – original draft. YX: Supervision, Validation, Writing – review and editing. XK: Funding acquisition, Resources, Supervision, Validation, Writing – review and editing.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. This work was supported by the Interdisciplinary Research Cooperation Project Team funding of Dalian Medical University (JCH22023017), the Cultivating Scientific Research Project of the Second Hospital of Dalian Medical University (XJ2023001102), and Dalian Medical Science Research Program (23Z12007).

Acknowledgments

We are grateful to the people who contributed to the NHANES database.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The authors declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2025.1538710/full#supplementary-material

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frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 19 June 2025
DOI 10.3389/fmed.2025.1556387

OPEN ACCESS

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RECEIVED 06 January 2025
ACCEPTED 26 May 2025
PUBLISHED 19 June 2025

CITATION
Fang Y, Yang K, Gao X, Gong Y, Deng Y, Xu X, Xu J, Yan L, Zeng J and Chen S (2025) Integrating ultrasound and clinical risk factors to predict carotid plaque vulnerability in gout patients: a machine learning approach.
Front. Med. 12:1556387.
doi: 10.3389/fmed.2025.1556387

Integrating ultrasound and clinical risk factors to predict carotid plaque vulnerability in gout patients: a machine learning approach

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Objectives: This study aimed to identify independent risk factors for carotid plaque (CP) vulnerability in patients with gout and to develop a predictive model incorporating both gout-specific and cardiovascular factors.

Method: This study was designed as a retrospective cohort analysis that enrolled patients with newly diagnosed gout. These patients were retrospectively followed for a period of 1 to 2 years to evaluate the incidence of CP vulnerability. CP vulnerability was assessed using standardized ultrasound examinations and graded according to the Plaque Reporting and Data System (Plaque-RADS). Multivariate ordinal logistic regression analysis was employed to identify independent risk factors associated with CP vulnerability, with a particular focus on the impact of gout-related variables. Based on these results, a random forest prediction model was developed by integrating ultrasound imaging features and clinical variables to predict CP vulnerability.

Results: Tophi (OR = 1.760, p = 0.009), power Doppler (PD) signal grades (Grade 2: OR = 1.540, p = 0.002; Grade 3: OR = 1.890, p = 0.001), and the number of gout flares in the last year (OR = 1.524, p = 0.001) were identified as independent risk factors for CP vulnerability. The random forest model showed excellent predictive performance (C-index = 0.997) and highlighted tophi, PD signal grades, and gout flare frequency as key gout-specific contributors to CP risk.

Conclusion: The presence of tophi, positive PD signals, and increased number of gout flares are significantly associated with CP vulnerability in patients with gout. The proposed machine learning model, integrating gout-specific and cardiovascular factors, provides a novel and effective approach for personalized risk stratification and management in gout patients, bridging the gap between rheumatic inflammation and cardiovascular risk assessment.

KEYWORDS

gout, risk stratification, ultrasound, carotid plaque, inflammation, prediction model, diagnosis

1 Introduction

Gout is a chronic metabolic disease defined by the accumulation of monosodium urate (MSU) crystals in joints, tendons, and surrounding tissues (1). The reported prevalence of carotid atherosclerosis in patients with gout ranges from approximately 29.1% to 48.9% (2) with nearly half showing carotid plaques (CPs) on ultrasound imaging (3). While increases in intima-media thickness and CP formation are important markers of carotid atherosclerosis, a more clinically relevant concern is plaque vulnerability, which serves as a critical predictor of cerebrovascular events, including stroke (4).

Recent studies suggest that gout contributes to carotid atherosclerosis not only via hyperuricemia but also through sustained low-grade inflammation induced by MSU crystals (5). These crystals stimulate the activation of interleukin-1β (IL-1β) and neutrophil extracellular traps (NETs), thereby exacerbating oxidative stress and endothelial dysfunction (6, 7). Despite the established link between gout and CP development, studies investigating the associations of urate crystal deposition and inflammatory markers with CP vulnerability in patients with gout remain limited.

Compared to magnetic resonance imaging (MRI) and dual-energy computed tomography (DECT), ultrasound offers notable advantages in the early diagnosis and monitoring of acute gout, particularly in detecting minute urate crystal deposits and those on cartilage surfaces (8). As a result, it has been incorporated into the latest classification criteria for gout, as outlined by the American College of Rheumatology and the European Alliance of Associations for Rheumatology (ACR/EULAR) guidelines (9). In addition, gout-specific features related to urate crystal deposition—such as the double contour sign (DCS), hyperechoic aggregates (HAG), and tophi—have been identified, facilitating the quantification of joint damage severity (10, 11).

In this study, we utilized ultrasound to evaluate joint lesions in patients with gout and explored the feasibility of developing a predictive model that integrates ultrasound and clinical features to assess CP vulnerability. This approach aims to elucidate the complex relationship between gout and cardiovascular as well as cerebrovascular events, offering a novel perspective for risk stratification.

2 Materials and methods

2.1 Patients

This retrospective cohort study was based on the database of the First Affiliated Hospital of Fujian Medical University, comprising anonymized data on medication prescriptions, diagnoses, basic clinical records, and demographic characteristics, directly retrieved from the hospital's system. The study period spanned from January 2020 to December 2022, during which participants were consecutively enrolled based on newly diagnosed cases of gout. Eligible participants were those who met the following inclusion criteria at the time of diagnosis: (1) fulfilled the 2015 ACR/EULAR gout classification criteria; (2) had at least 12 months of observation data prior to the index date and a minimum of 12 months of follow-up data after the index date. The exclusion criteria were: (1) a history of other forms of arthritis (e.g., rheumatoid arthritis, psoriatic arthritis, or spondyloarthritis); (2) a history of other crystal-related diseases; (3) a diagnosis of carotid plaques on or before the enrollment date; and (4) incomplete medical records. After applying these stringent inclusion and exclusion criteria, a total of 292 adult patients with an initial diagnosis of gout were included in the study (Figure 1).

This study was in accordance with the Ethical Standards of the Institutional Ethics Committee of First Affiliated Hospital of Fujian Medical University and with the 1964 Helsinki declaration and its later amendments or comparable Ethical Standards. Ethics batch number: MRCTA, ECFAH of FMU [2022]251. As a purely retrospective review of medical records that did not involve any personally identifiable information, the requirement for informed consent was waived.

2.2 Variables

2.2.1 Outcome variable

The outcome variable in this study was CP vulnerability assessed by ultrasonography. Carotid ultrasound assessments were performed using images acquired during examinations conducted 1–2 years after the diagnosis of gout. Atherosclerotic plaques were identified bilaterally in the common carotid artery (CCA), carotid bulb, and internal carotid artery (ICA). The presence of CPs was determined based on the Mannheim consensus (12), with only plaques exhibiting well-defined contours included. Plaque vulnerability was assessed using the Plaque-RADS classification system proposed by Saba et al. (13), and the complete criteria are presented in Figure 2. Figure 3 illustrates representative ultrasound characteristics of category 3 subtypes (3A–3C). For patients with multiple CPs, the plaque with the highest Plaque-RADS score was selected for analysis.

2.2.2 Explanatory variable

Explanatory variables were selected based on a preliminary case-control study that included a carotid plaque group (case group) and a plaque-free group (control group), matched for age and sex. A LASSO regression model based on L1 regularization was employed to analyze all candidate independent variables. Through this process, 17 non-zero coefficient variables associated with plaque formation were identified, while smoking and alcohol consumption were excluded. These variables were subsequently included as independent variables in the retrospective cohort study (Details of the pilot study are provided in the Supplementary Data 1).

The primary explanatory variables in this study focus on ultrasound findings and clinical characteristics related to gout. Musculoskeletal ultrasound assessments were conducted during the intercritical period, within 30 days of gout diagnosis, adhering to the standardized protocols outlined by the Outcome Measures in Rheumatology (OMERACT) working group (10). Ultrasound images of the first metatarsophalangeal joint (MTP1), ankle, and knee joints were re-evaluated for each patient. At the anatomical level, the assessment included: (a) key lesions of MSU crystal deposition, including the DCS, HAG, and tophi (11) (Figure 4)

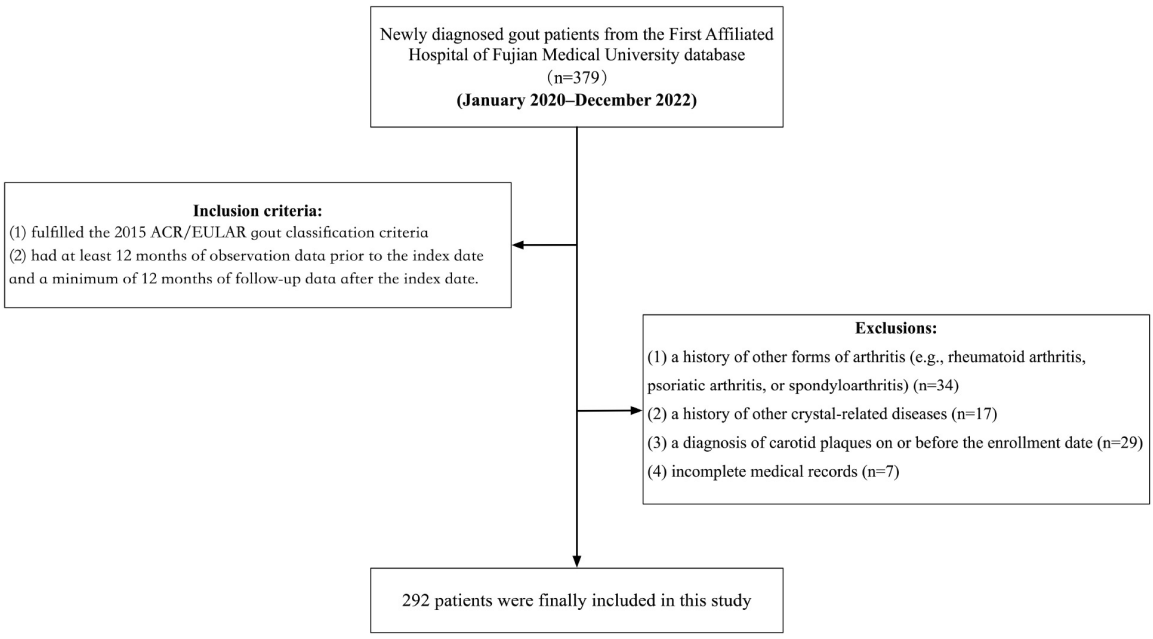

FIGURE 1
Flowchart of patients.

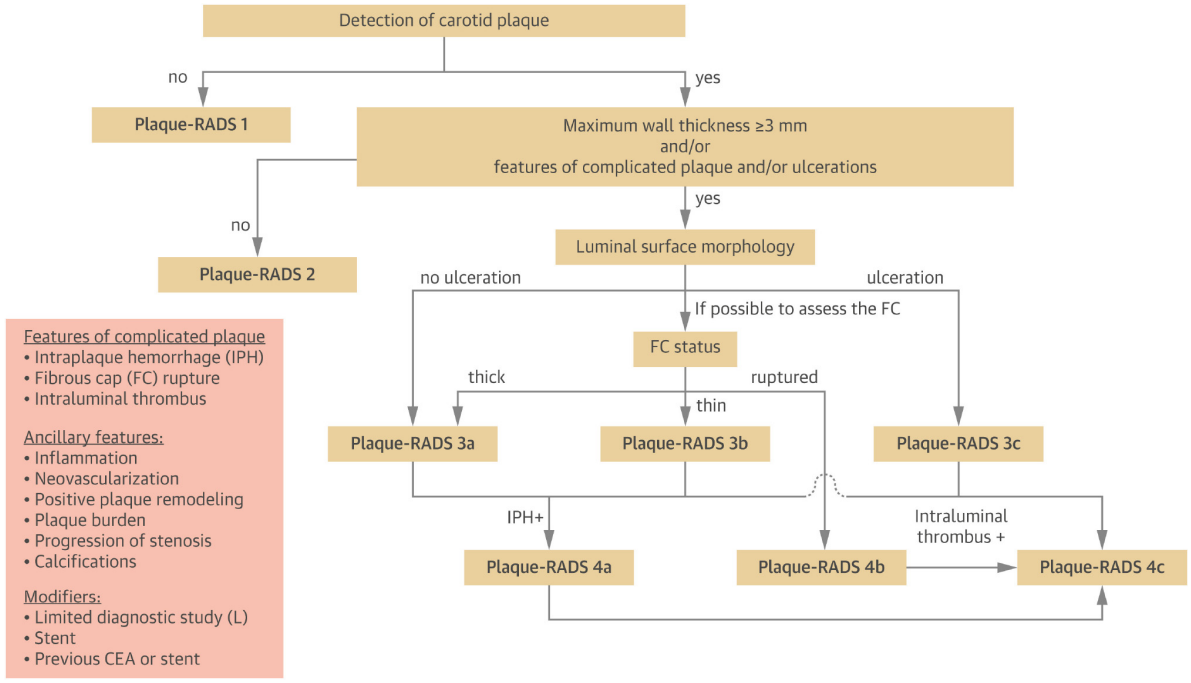

FIGURE 2
Step-by-step flow chart to classify carotid plaques into the different Plaque-RADS categories (13).

using a binary scoring system (presence/absence) as recommended by Naredo et al. (14). (b) inflammatory markers, assessed through the presence of local PD signals and bone erosion, graded using a semi-quantitative 0–3 scoring system (15) (Figure 4). Additionally, clinical features of gout were included, including the number of affected joints, the number of gout attacks in the last year, and the duration of the disease.

Secondary explanatory variables encompassed demographic and clinical characteristics, including serological test results, cardiovascular risk factors, comorbidities, and treatment regimens (Full list of explanatory variables provided in the Supplementary Data 2).

All ultrasound assessments were conducted with a standardized device model (SAMSUNG RS9 system) utilizing a high-frequency

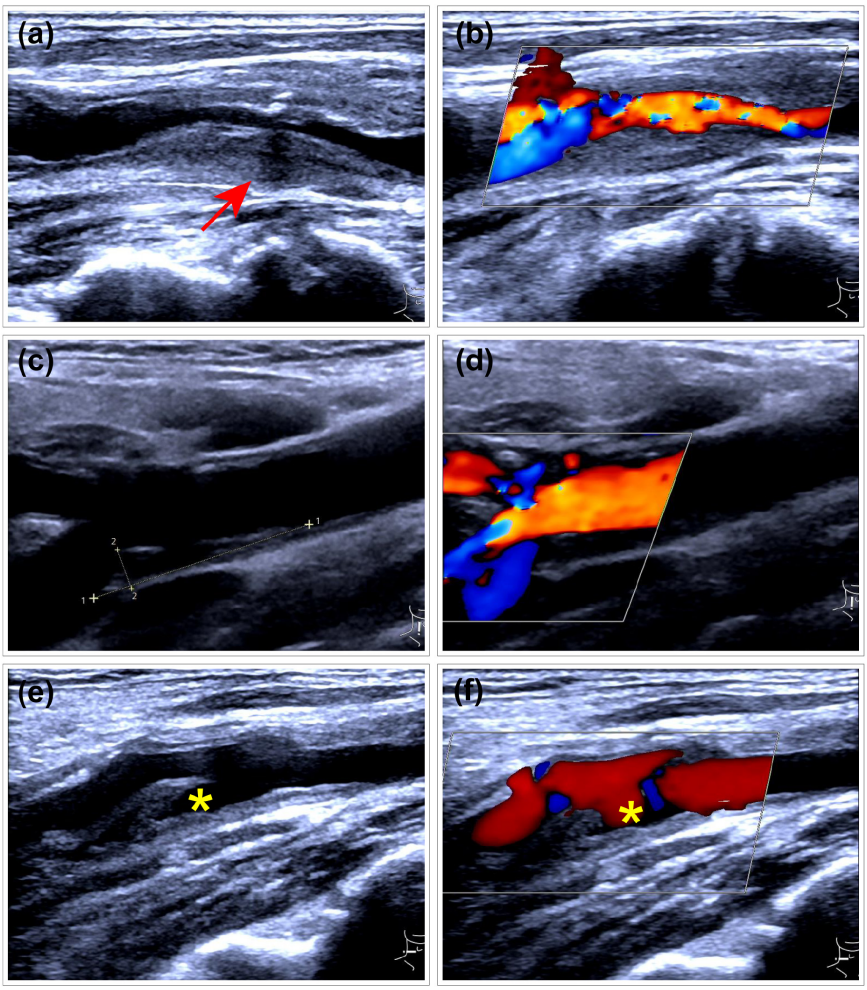

FIGURE 3
Representative ultrasound images of Plaque-RADS Category 3 subtypes (3A–3C). **(a,b)** RADS 3A plaque at the carotid bifurcation with a maximum wall thickness (MWT) greater than 3 mm. The plaque exhibits a uniform isoechoic appearance (arrow) and features a thick fibrous cap. **(a)** Gray-scale ultrasound imaging. **(b)** Doppler flow imaging. **(c,d)** RADS 3B plaque at the carotid bifurcation with a MWT greater than 3 mm. The plaque contains multiple very low echogenic areas, with most regions lacking a visible (thin) fibrous cap. **(c)** Gray-scale ultrasound imaging. **(d)** Doppler flow imaging. **(e,f)** RADS 3C plaque with a mixed hyperechoic and hypoechoic plaque at the carotid bifurcation, demonstrating ulceration (*) on both two-dimensional and Doppler imaging.

linear transducer (6–14 MHz). Stored ultrasound images were independently and blindly evaluated by two experienced sonographers, each with over 10 years of clinical practice, to ensure data reliability.

2.3 Statistical analysis

Following assessment of the normality of continuous variables and the homogeneity of variances, data were reported as means with standard deviations (SD) or medians with interquartile ranges (IQR). Categorical variables were presented as frequencies (*n*) and percentages (%).

Multivariable ordinal logistic regression combined with a stepwise backward elimination method was employed to identify independent risk factors associated with CP vulnerability. In addition, univariable logistic regression analyses were performed for smoking and alcohol consumption to inform subsequent sensitivity analyses. To evaluate the incremental predictive value of gout-specific factors, a conventional cardiovascular risk model was constructed by omitting these variables from the final model. The performance of both models was subsequently compared using cumulative receiver operating characteristic (ROC) curve analysis. The identified risk factors were subsequently used to construct a Random Forest prediction model, with variable importance assessed by the Mean Decrease in Gini Index.

Model adequacy and stability were assessed via the Akaike information criterion (AIC) and Bayesian information criterion (BIC), McFaddens' pseudo-R^2 and concordance index (C-index). Although smoking and alcohol consumption were excluded by LASSO selection due to limited statistical contribution, they were included in a sensitivity analysis given their clinical relevance as cardiovascular risk factors and potential confounders (16). Model robustness was assessed by evaluating changes in key effect estimates of primary risk factors following their inclusion.

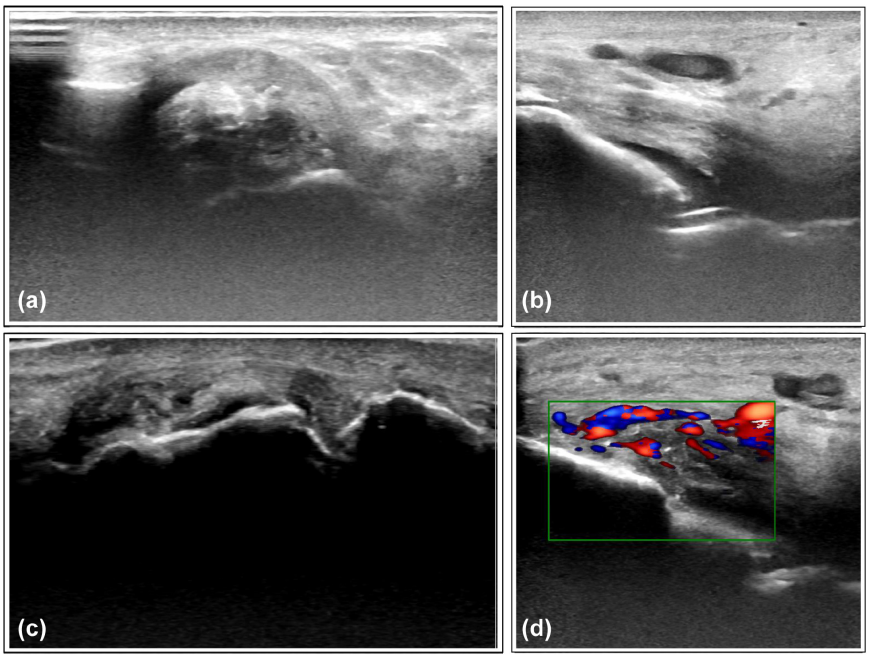

FIGURE 4
Representative ultrasound features of monosodium urate crystal deposits and associated inflammation. **(a)** Tophi observed on the lateral aspect of the ankle joint. **(b)** Double-track sign on the medial side of the ankle joint. **(c)** Scattered hyperechoic aggregates with bone erosion observed in the 1st metatarsophalangeal joint. **(d)** Intra-articular blood flow signals detected in the ankle joint capsule, suggesting synovitis.

Performance evaluation of the random forest model includes Accuracy, Precision, and Recall from the confusion matrix, and the goodness-of-fit of the model is assessed using the Mean Absolute Error (MAE).

All statistical analyses were conducted using R (version 4.1.1), with a two-sided p-value < 0.05 considered statistically significant. All participants with complete data were included in the analyses; i.e. complete case analysis.

3 Results

3.1 Clinical, demographic, and gout characteristics

A total of 292 initially diagnosed gout patients were included in the study between January 2020 and December 2022. Table 1 presents the characteristics of the enrolled participants. The cohort consisted predominantly of male patients, with a median age of 61 years. During follow-up, 167 cases (57.2%) were found to have CP. According to the Plaque-RADS classification system, 42.8% were classified as category 1, 32.2% as category 2, and the remainder were distributed across higher categories. Notably, no plaques were classified as category 4. Among the patients with CP, 56 (19.2%) experienced cerebrovascular events, such as stroke or transient ischemic attack.

Regarding the clinical characteristics of gout, the time from the first flare to diagnosis was notably prolonged (median 5 years). The number of gout flares in the year prior to diagnosis was relatively high (median 3 episodes). Additionally, 148 patients (50.7%) presented with tophi. In terms of musculoskeletal ultrasound findings, more than half of the patients exhibited evidence of the DCS (66.9%) or HAG (54.3%). PD signals were detected in 55.1% of patients, with grades 2–3 observed in 23.6%. Bone erosion was identified in 66.8% of the cases.

3.2 Association between gout and CP vulnerability

Using a LASSO regression model with L1 regularization, 17 variables with non-zero coefficients were identified. These variables were subsequently included in a multivariate logistic regression analysis employing stepwise backward elimination, which yielded a final model comprising eight variables: age, cholesterol level, number of flares in the last year, impaired renal function (GFR < 60 ml/min), diabetes, use of antihypertensive medications, the presence of gout tophi, and PD signal grade (Figure 5). Among ultrasound features, the presence of tophi (OR = 1.760, $p = 0.009$) and the degree of positive PD signals (grade 2: OR = 1.540, $p = 0.002$; grade 3: OR = 1.890, $p = 0.001$) were identified as independent risk factors of higher Plaque-RADS categories, while DCS, HAG, and bone erosion were excluded due to a lack of statistical significance ($p > 0.05$). Regarding clinical characteristics, only the number of gout flares in the last year (OR = 1.524, $p = 0.001$) was a significant risk factors, while disease duration and the number of affected joints were excluded ($p > 0.05$). Specifically, the presence of tophi increased the likelihood of plaque vulnerability by 24%, while positive PD signals were associated with a 54% increase for grade 2 and an 89% increase for grade 3.

TABLE 1 Population, clinical, and ultrasound characteristics in a gout cohort.

Characteristics	Overall (*N* = 292)
Age in years, median (IQR)	61.0 (51.0, 69.0)
Men, ***n*** (%)	245 (83.9)
BMI (kg/m^2), median (IQR)	25.0 (23.2, 26.7)
Uric acid (umol/L), median (IQR)	401.0 (359.0, 486.8)
Cholesterol (mmol/L), median (IQR)	4.4 (3.4, 5.4)
LDL (mmol/L), mean (SD)	2.7 (1.2)
CKD (GFR < 60 mL/min), ***n*** (%)	32 (11.0)
Diabetes, ***n*** (%)	112 (38.4)
Coronary heart disease, ***n*** (%)	49 (16.8)
Cerebrovascular disease, ***n*** (%)	56 (19.2)
Antiplatelet drugs, ***n*** (%)	83 (28.4)
Urate-lowering therapy, ***n*** (%)	193 (66.1)
Antihypertensive drugs, ***n*** (%)	178 (61.0)
Charlson index, n (%)	
0	20 (6.8)
1–2	128 (43.8)
3–5	103 (35.3)
≥ 6	41 (14.0)
Gout-related disease characteristics	
Number of flares last year, median (IQR)	3.0 (2.0, 5.0)
Number of involved joints, median (IQR)	3.0 (1.0, 4.0)
Disease duration, median (IQR)	5.0 (1.0, 7.0)
MSK-US findings in Gout	
Gout tophi, ***n*** (%)	148 (50.7)
DCS, ***n*** (%)	196 (66.9)
HAG, ***n*** (%)	159 (54.3)
PD signal, n (%)	
0	131 (44.9)
1	92 (31.5)
2	42 (14.4)
3	27 (9.2)
Bone erosion, n (%)	
0	97 (33.2)
1	108 (37.0)
2	55 (18.8)
3	32 (11.0)
cPP, ***n*** (%)	167 (57.2)
Plaque-RADS, n (%)	
1	125 (42.8)
2	94 (32.2)
3a	45 (15.4)
3b	24 (8.2)
3c	4 (1.4)

BMI, body mass index; IQR, interquartile range; LDL, low-density lipoprotein; SD, standard deviation; CKD, chronic kidney disease; GFR, glomerular filtration rate; MSK-US, musculoskeletal ultrasound; DCS, double contour sign; HAG, hyperechoic aggregates; PD, power Doppler; cPP, carotid plaque presence; RADS, Reporting and Data System.

Additionally, each extra gout flare per year was linked to a 52% higher risk.

When evaluating diagnostic performance, the final model—including gout-related variables—consistently outperformed the baseline cardiovascular model across all cumulative binary classification thresholds. The mean AUC values were 0.765 for the baseline model and 0.912 for the final model, demonstrating a substantial improvement in discriminative ability (Figure 6). The final model showed strong performance, with an AIC of 539.69, BIC of 591.16, McFadden's pseudo-R^2 of 0.60, and a C-index of 0.88, indicating good model fit and discrimination (see Supplementary Table 1). The univariable results for smoking and alcohol consumption are summarized in Supplementary Table 2. Sensitivity analysis results indicated that the four models exhibited similar effect sizes (β), confidence intervals, and statistical significance across eight common variables, supporting the robustness of the main findings (see Supplementary Data 3).

3.3 Random forest prediction model for CP vulnerability in gout patients

A random forest prediction model for CP vulnerability was constructed using independent risk factors identified through multivariable logistic regression analysis. The model exhibited exceptional goodness-of-fit (MAE = 0.096) and discriminative performance (C-index = 0.997). The confusion matrix results further confirmed the model's high predictive accuracy and strong generalizability in predicting carotid Plaque-RADS categories. Performance metrics were as follows: accuracy = 0.925, precision = 0.960, and recall = 0.905. Details of the confusion matrix for the random forest model are provided in Supplementary Table 3.

Variable importance in the decision tree ensemble was evaluated using the Mean Decrease in Gini index. As illustrated in Figure 7, while conventional cardiovascular risk factors—such as impaired renal function, diabetes, and antihypertensive medication use—were among the top predictors of plaque grades, gout-related factors—including musculoskeletal ultrasound findings (presence of tophi, Doppler signals) and the number of gout flares in the last year—also contributed substantially to the prediction of carotid Plaque-RADS categories.

4 Discussion

Gout is a chronic metabolic disorder resulting from urate overload and characterized by the deposition of MSU crystals. Accumulating evidence suggests that gout may contribute to increased atherosclerotic burden, which in turn predisposes individuals to a higher risk of cerebrovascular events (17). Traditionally, the assessment of plaque vulnerability has relied on ultrasound-based grading of plaque echogenicity. However, this method is highly subjective and susceptible to operator experience, resulting in limited reliability and consistency across evaluations. The Plaque-RADS classification system, a novel stroke risk stratification framework, offers a more standardized and quantitative approach to evaluating plaque

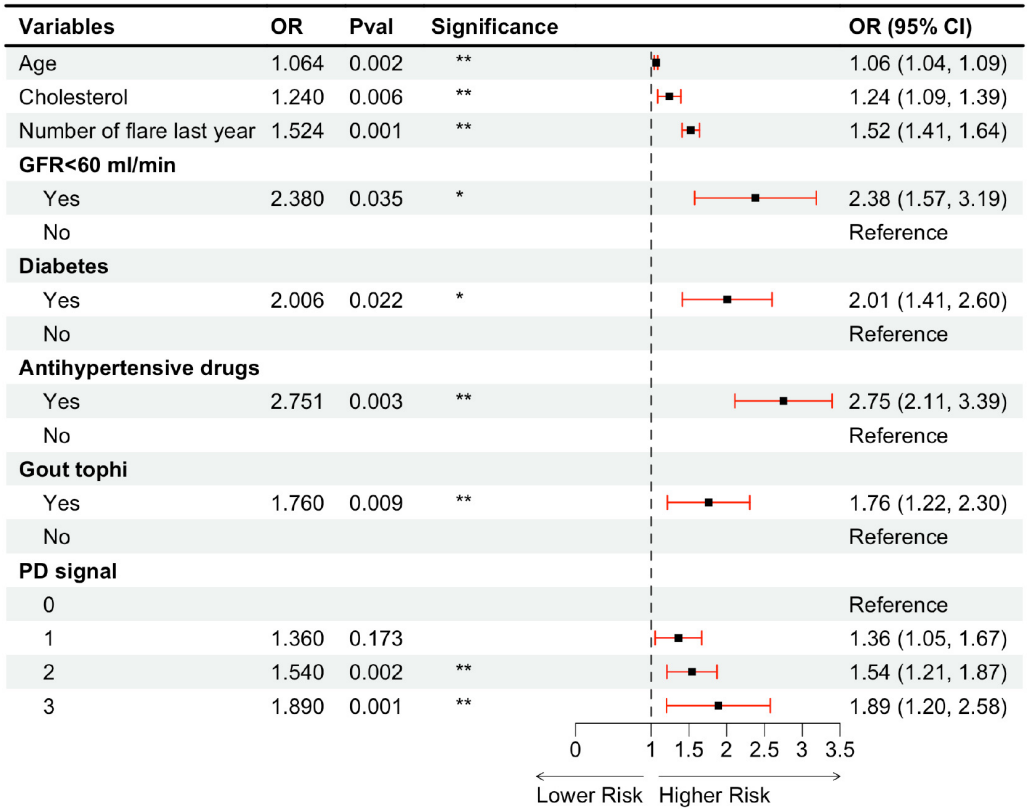

FIGURE 5
Multivariable ordinal logistic regression model assessing carotid artery plaque vulnerability in a gout cohort. OR, odds ratio; CI, confidence interval; GFR, glomerular filtration rate; PD, power Doppler. *$P < 0.05$; **$P < 0.01$.

echogenicity, thereby enhancing the objectivity and reproducibility of plaque classification.

Our study focused on carotid plaque vulnerability in patients with gout, employing the Plaque-RADS classification system as the evaluation tool. A predictive model was developed to systematically assess plaque vulnerability based on gout-specific clinical and ultrasound features. The results demonstrated significant associations between CP vulnerability and several gout-related indicators, including the presence of tophi, positive PD signals, and the number of gout flares in the last year. Furthermore, in the random forest model analysis, gout-related variables also played a substantial role in predicting plaque vulnerability. These findings underscore the potential value of incorporating gout-specific characteristics into cerebrovascular risk assessment and management strategies.

The presence of tophi in gout patients indicates advanced disease progression and a high uric acid burden, both of which are characteristic of a chronic inflammatory state that may promote plaque vulnerability (18). Previous studies have demonstrated a significant association between large tophi (> 2 mm) and the presence of carotid plaques (5), and longitudinal cohort data have identified tophi as an independent risk factors of adverse cardiovascular events, such as myocardial infarction and stroke (HR 2.12–5.25, $p < 0.05$) (19). Our study builds upon these findings by establishing a direct link between tophi and CP vulnerability, rather than merely plaque presence. Mechanistically, activation of the NLRP3 inflammasome by tophi induces neutrophil-driven acute inflammation, a process strongly implicated in atherosclerotic plaque vulnerability and rupture (20, 21). Within vulnerable plaques, activated inflammatory cells upregulate matrix-degrading enzymes (e.g., matrix metalloproteinases) and enhance oxidative stress, leading to extracellular matrix degradation and plaque destabilization (22).

The random forest model further emphasized the importance of tophi, ranking it as the top gout-specific risk factors of CP vulnerability and fourth overall among all risk factors, following traditional cardiovascular risk factors including GFR < 60 ml/min, diabetes, and antihypertensive medication use. These findings highlight the critical role of tophi in cardiovascular risk and underscore the need for personalized risk stratification and targeted management strategies in gout patients, particularly those with visible tophi.

Interestingly, no significant association was observed between CP vulnerability and the ultrasonographic features of DCS or HAG, which represent distinct types of MSU crystal deposition. This divergence may suggest that the chronicity of MSU crystal deposition plays different roles in carotid atherosclerosis progression (2, 19). HAG, for instance, may be more indicative of early vascular remodeling, as supported by a previous study that have linked it to increased carotid intima-media thickness (5). Future longitudinal studies in gout patients are needed to explore the dynamic contributions of various crystal types in the development and progression of CP.

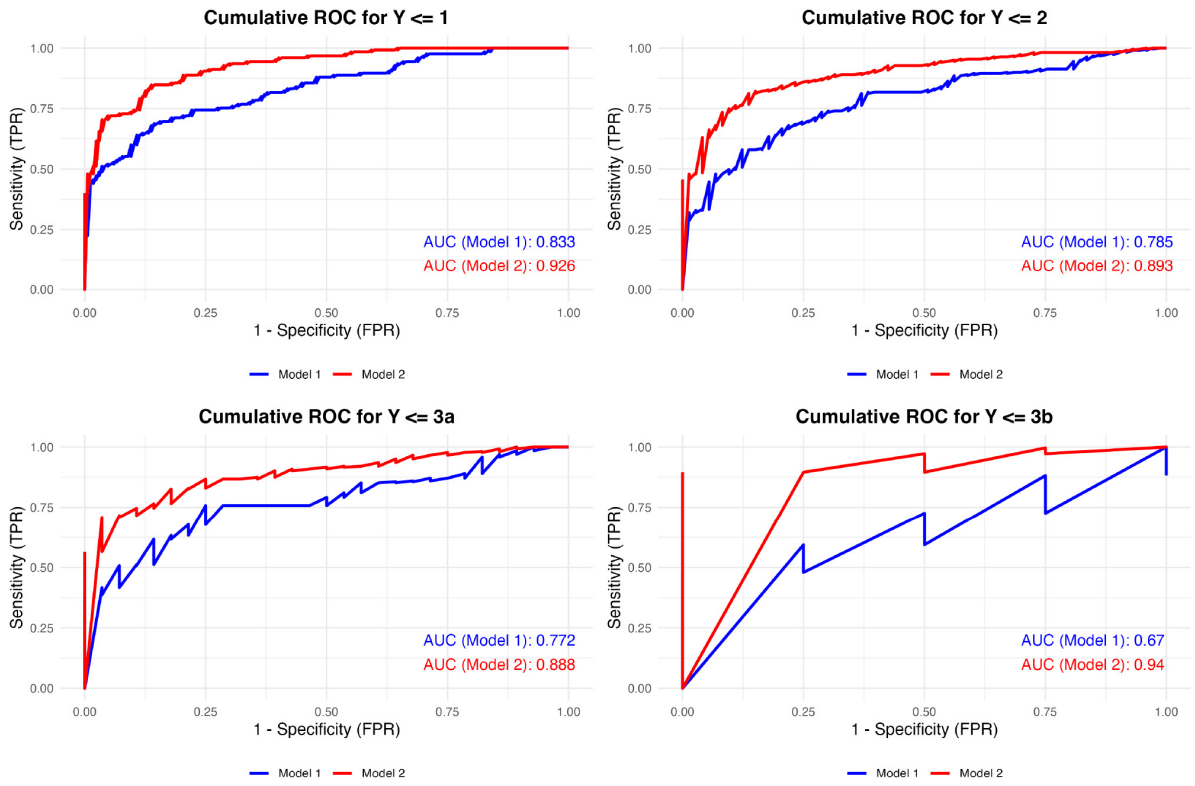

FIGURE 6
Cumulative ROC curves of the two models across different classification thresholds. Model 1 included traditional cardiovascular risk factors: age, cholesterol levels, GFR < 60 mL/min, diabetes, and antihypertensive medication use. Model 2 extended Model 1 by integrating gout-specific factors, including the presence of tophi, Doppler flow, and the number of gout flares in the last year. ROC, receiver operating characteristic; TPR, true positive rate; FPR, false positive rate.

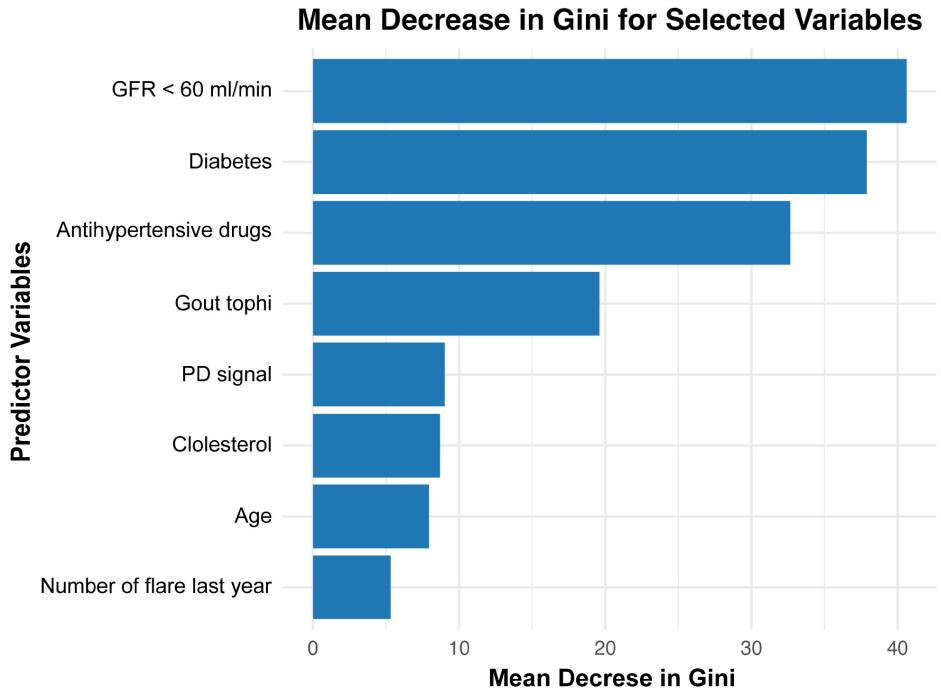

FIGURE 7
Mean decrease in Gini for feature importance in a random forest model predicting carotid plaque. GFR, glomerular filtration rate; PD, power Doppler.

Doppler technology enables the assessment of vascularization and blood flow at specific anatomical sites. In chronic inflammatory arthritis, PD signals are widely recognized as markers of inflammation and have been linked to histopathological synovitis (23). During acute gout flares, PD signal intensity is significantly elevated. Notably, persistent PD signals may also be observed during the intercritical phase, often in conjunction with progressive bone erosion (24). As a result, PD signals are considered reliable surrogate markers of crystal-mediated inflammation. Our study revealed a strong association between PD signal intensity and CP vulnerability in gout patients. Specifically, compared to PD grade 0, PD grade 3 was associated with an 89% increase in the probability of an upgraded Plaque-RADS score for CP, while PD grade 2 showed a 54% increase in vulnerability. These findings underscore the value of PD signal intensity as a novel and non-invasive indicator for evaluating cardiovascular risk in gout patients. Moreover, they highlight its potential as a therapeutic target for controlling crystal-mediated inflammation to mitigate atherosclerotic risk.

Ultrasound examination is instrumental not only for diagnosing gout but also for monitoring disease progression. Notably, ultrasound evaluation of the reduction in urate deposition can be used to predict the risk of flare recurrence after discontinuing colchicine (25). Leveraging these capabilities, our study demonstrates that ultrasound biomarkers such as tophi and PD signals are crucial in predicting CP vulnerability. By integrating these ultrasound features with clinical risk factors, our random forest prediction model achieved excellent predictive accuracy and reliability. This highlights the potential of ultrasound biomarkers to guide personalized treatment strategies, enabling more precise and effective management of gout patients with heightened cardiovascular risk.

The number of gout flares is another significant marker of systemic inflammation and uric acid-related metabolic dysfunction. Each flare represents an acute inflammatory response driven by neutrophils and pro-inflammatory cytokines, which not only aggravate local damage but also contribute to systemic endothelial dysfunction and oxidative stress (20, 26). Our study found that each additional gout flare in the preceding year was associated with a 52% increase in the likelihood of an upgraded RADS score in CP. Furthermore, the random forest model ranked the number of gout flares in the last year as a key predictor of CP vulnerability, emphasizing its contribution to the overall model performance. These findings reinforce the importance of optimizing urate-lowering therapy and implementing effective anti-inflammatory interventions to mitigate flare frequency and reduce systemic inflammatory burden. Sustained management of these factors has the potential to improve plaque stability and reduce long-term cardiovascular risks in patients with gout.

4.1 Limitations and future directions

Although this study provides valuable insights into the relationship between gout and CP vulnerability, its retrospective design presents limitations that may weaken the ability to infer causality. Secondly, Certain lifestyle variables, such as smoking and alcohol consumption, were recorded in a binary format (yes/no), without further granularity to capture frequency, intensity, or recency. This coarse classification of exposure variables may have increased the risk of residual confounding. Future studies could mitigate potential bias arising from oversimplified exposure grouping by employing more refined data collection methods. Finally, although internal cross-validation was applied to mitigate overfitting, the high C-index of the random forest model suggests potential model overtraining. Future external validation in independent gout cohorts would be valuable to further assess the model's robustness and generalizability.

5 Conclusion

This study confirms that the presence of tophi, positive PD signals, and an increased number of gout flares in the last year are significantly associated with carotid plaque vulnerability in patients with gout. Building on this, we constructed a predictive model that incorporates these gout-specific markers alongside traditional cardiovascular risk factors. The model exhibits high accuracy and reliability, providing a valuable clinical instrument for individualized risk stratification and the management of cerebrovascular events in gout patients.

Data availability statement

The original contributions presented in this study are included in this article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

This study was in accordance with the Ethical Standards of the Institutional Ethics Committee of First Affiliated Hospital of Fujian Medical University and with the 1964 Helsinki declaration and its later amendments or comparable Ethical Standards. Ethics batch number: MRCTA, ECFAH of FMU [2022]251. As a purely retrospective review of medical records that did not involve any personally identifiable information, the requirement for informed consent was waived.

Author contributions

YF: Conceptualization, Formal Analysis, Investigation, Methodology, Software, Visualization, Writing – original draft. KY: Data curation, Investigation, Visualization, Writing – original draft. XG: Data curation, Investigation, Visualization, Writing – original draft. YG: Data curation, Investigation, Visualization, Writing – original draft. YD: Data curation, Software, Visualization, Writing – original draft. XX: Data curation, Investigation, Visualization, Writing – original draft. JX: Data curation, Investigation, Visualization, Writing – original draft. LY: Data curation, Investigation, Visualization, Writing – original draft. JZ: Methodology, Project administration, Writing – review and editing. SC: Conceptualization, Funding acquisition,

Project administration, Resources, Supervision, Validation, Writing – review and editing.

Funding

The authors declare that financial support was received for the research and/or publication of this article. This study was supported by Fujian Provincial Department of Science and Technology [grant nos. 2021Y0012 and 2021Y9092] and Medical University Transformation and Special Financial Fund [grant no. 22SCZZX004].

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The authors declare that no Generative AI was used in the creation of this manuscript.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2025.1556387/full#supplementary-material

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frontiers | Frontiers in Medicine

TYPE Brief Research Report
PUBLISHED 09 July 2025
DOI 10.3389/fmed.2025.1563796

OPEN ACCESS

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RECEIVED 20 January 2025
ACCEPTED 06 June 2025
PUBLISHED 09 July 2025

CITATION
Tapken FM, Zehrfeld N, Abelmann M, Müller-Vahl AC, Benz S, Seeliger T, Skripuletz T, Witte T, Sonnenschein K, Bauersachs J, Bavendiek U, Thum T, Derda AA and Ernst D (2025) No difference in endothelial microvasculation measured by peripheral arterial tonometry in patients with Sjögren's disease and matched controls. *Front. Med.* 12:1563796. doi: 10.3389/fmed.2025.1563796

No difference in endothelial microvasculation measured by peripheral arterial tonometry in patients with Sjögren's disease and matched controls

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Sjögren's disease (SjD) is a connective tissue autoimmune disorder characterized by inflammatory infiltration of the exocrine glands, leading to symptoms such as dryness, pain, and fatigue. Additionally, up to 50% of patients may experience extraglandular manifestations. SjD patients face a higher cardiovascular risk, including severe events like myocardial infarction and strokes, partly due to an increased likelihood of subclinical atherosclerosis. Therefore, identifying SjD patients at an early stage is essential to reduce morbidity and mortality. In this study, SjD patients who met the current ACR/EULAR 2016 classification criteria were consecutively enrolled in our outpatient clinic. A control cohort was recruited through a multimedia call for participation. To assess changes in endothelial functions, a reactive hyperemia index (RHI) was calculated using peripheral arterial tonometry with the EndoPAT® measurement device. RHI values below 1.67 were considered pathological. The dataset consists of 49 SjD patients and 27 healthy controls. Both groups had similar ages and comparable cardiovascular risk factors. No differences in RHI were observed between the two cohorts. The only significant factor that was predictive for a low RHI was an increased body mass index (p = 0.036). These findings suggest that EndoPAT measurements may not be a suitable method for detecting changes in endothelial function specific to patients with SjD.

KEYWORDS

endothelial dysfunction, Sjögren's disease, cardiovascular risk, EndoPAT, peripheral arterial tonometry, miRNA, cardiovascular risk factors

Introduction

Sjögren's disease (SjD) is an autoimmune connective tissue disorder primarily marked by exocrine gland dysfunction due to lymphocytic inflammation. While it manifests with a variety of symptoms, dryness, pain, and fatigue are among the most common (1). Approximately 30%–50% of patients also exhibit systemic symptoms (2). A recent

meta-analysis estimated the prevalence of SjD to be between of 0.01% and 0.05%, identifying no geographical and temporal trends (3).

The underlying pathophysiology of SjD remains incompletely understood. However, chronic inflammation associated with SjD has been identified as an independent risk factor for accelerated atherosclerosis, leading to a notably higher prevalence of cardiovascular disease (CVD) compared to healthy controls (HC) (4–6). The elevated prevalence of CVD-related mortality among SjD patients, combined with an increased incidence of stroke, particularly in patients under 50, underscores the urgent need for early risk assessment to prevent serious long-term complications such as stroke or myocardial infarction (7–9).

Endothelial dysfunction (ED), defined as a deficiency of nitric oxide (NO) that limits the vasodilatory capacity of blood vessels, is one of the earliest detectable stages in the development of atherosclerosis (10, 11).

The present study utilizes the peripheral arterial tonometry EndoPAT® measurement to non-invasively identify microvascular endothelial changes non-invasively in SjD patients compared to HC by inducing reactive hyperemia, which is quantified as the reactive hyperemia index (RHI) (12, 13). EndoPAT® requires minimal training and its accuracy therefore remains almost independent of the examiners' experience (14). A low RHI value is associated with a higher prevalence of a combined endpoint including cardiovascular death, myocardial infarction, revascularization, or cardiac hospitalizations (15).

Thus, the aim of this study is to detect early microvascular changes in patients with SjD using EndoPAT® measurement. Additionally, the study seeks to evaluate the effectiveness of EndoPAT® as a preventive diagnostic tool.

Methods

Study design

This study is a prospective monocentric cohort study that included patients with SjD who routinely visited the rheumatological or neurological outpatient clinic of Hannover Medical School between August 2023 and April 2024. At the same time, a control cohort was recruited through a multimedia call for participation. The study consisted of 76 individuals, with 49 participants diagnosed with SjD and 27 HC, the majority of whom were German and White.

Abbreviations: ACR/EULAR, American College of Rheumatology/European League Against Rheumatism; BMI, body mass index; CRF, cardiovascular risk factors; CVD, cardiovascular disease; ED, endothelial dysfunction; EndoPAT®, endothelial peripheral arterial tone; ESSDAI EULAR's, Sjögren-syndrome disease activity index; ESSPRI EULAR's, Sjögren-syndrome patient reported index; HC, healthy controls; HDL, high density lipoprotein; LDL, low density lipoprotein; NO, nitric oxide; OI, organ involvement; RHI, reactive hyperemia index; SjD, Sjögren's disease; SSA/Ro-AB, anti-Sjögren's syndrome-related antigen A antibodies; SSB/La-AB, anti-Sjögren's syndrome-related antigen B antibodies.

Participants

All included patients met the 2016 ACR/EULAR classification criteria for SjD. Participants who had been recently pregnant, experienced a malignant cancer within the past 5 years, suffered a myocardial infarction, had a stroke, or were diagnosed with other systemic inflammatory diseases were excluded from the study. All participants provided written informed consent. The study was approved by the local authorities [Institutional Review Board of the Medical University of Hannover approval (8179_BO_S_2018)].

Data collection

The RHI was measured and automatically calculated using the EndoPAT2000® device from Itamar Medical Ltd., Caesarea, Israel. The measurements were performed in the angiological outpatient clinic of the Hannover Medical School. To minimize fluctuations caused by the circadian rhythms, all measurements were conducted at a nearly similar time in the afternoon.

The measurement protocol followed was based on the guidelines established by Axtell et al. (16). Initially, a baseline measurement of 5 min was recorded. This was followed by a 5-min occlusion of the right arm using a manual blood pressure cuff. After the occlusion, the cuff was released, and reactive hyperemia was measured for an additional 5 min. The software from Itamar Medical directly processes these measurements and independently calculates the RHI. According to the company's recommendations, a RHI value of 1.67 or below was considered pathological. A detailed methodological protocol can be found in the Supplementary Data.

Statistical and graphical analysis

Data analysis was performed using R version 4.3.1. Descriptive statistics, unless otherwise specified, are reported as median and interquartile range. The SjD patient cohort was compared to the HC group in terms of age, gender, cardiovascular risk factors (CRF), including BMI, arterial hypertension, preexisting hypercholesterolemia, preexisting diabetes, positive family history, HbA1c, serum low density lipoprotein (LDL) and high density lipoprotein (HDL) cholesterol. Continuous variables were analyzed using the Kruskal–Wallis test, while discrete variables were compared using Fisher's exact test (Table 1).

Patients with an RHI value below a threshold of 1.67 were classified as having pathological results according to the manufacturer's instructions. Furthermore, a Pearson's Chi-squared test with Yates' continuity correction was conducted to examine the relationship between two dichotomous variables group (SjD patient vs. HC) and RHI status (pathological vs. not pathological). To compare absolute RHI scores between the SjD- and HC cohort, absolute values were analyzed using a two-sample *t*-test. Fisher's exact test for count data was employed to assess the association between organ involvement and RHI abnormalities.

The association between RHI and continuous variables was examined using Spearman's rank correlations. A multiple regression analysis was conducted to determine how well absolute

TABLE 1 Baseline demographic data and cardiovascular risk factors in SjD patients and HC.

Characteristics	Control cohort $N = 27$	SjD cohort $N = 49$	p-value
Age (years)	62.7 [57.5–65.6]	61,7 [54.2–66.1]	n.s.[a]
Female gender [n, %]	22 [81.5]	44 [89.8]	n.s.[b]
Tobacco consumption (pack years)	4.43 [0–30]**	6.10 [0–40]**	n.s.[a]
Body mass index (kg/m^2)	24.22 [22.3–26.6]	24.97 [22.6–29.4]	n.s.[a]
Arterial hypertension [n, %]	6 [22.2]	19 [39.8]	n.s.[b]
Pre-known hypercholesterinemia [n, %]	6 [27.3]	16 [32.7]	n.s.[b]
Pre-known diabetes [n, %]	1 [0.04]	3 [0.06]	n.s.[b]
Positive family history* [N, %]	13 [48.1]	24 [49.0]	n.s.[b]
HbA1c (%)	5.3 [5.1–5.5]	5.4 [5.1–5.6]	n.s.[a]
Serum LDL-cholesterol (mmol/L)	3.48 [2.9–3.8]	3.12 [2.6–3.7]	n.s.[a]
Serum HDL-cholesterol (mmol/L)	1.5 [1.4–2.0]	1.7 [1.4–2.0]	n.s.[a]

Unless otherwise stated median and [inter quartile range] are reported.
[a]Kruskal–Wallis test.
[b]Fisher's exact test.
*Positive, if first degree relatives were affected by cardiovascular diseases.
**Mean value [range, min–max].

TABLE 2 Summary of disease related parameters in SjD patients.

Characteristics	N [%]
Disease related parameters	
Path. Saxon test [43]*	20 [46.5]
Path. Schirmer test [44]*	31 [70.5]
No objective dryness [49]*	12 [24.5]
Chisholm and Mason-grade ≥ 3 [25]*	21[84.0]
ESSPRI-score	5.7 [3.7–7.3]#
Laboratory values at investigation date	
ANA > 160 [47/49]*	26 [55.3]
Alpha-fodrin antibodies positive [45/49]*	1 [2.2]
Anti-SSA/Ro antibodies positive [47/49]*	30 [63.8]
ANTI-SSB/LA antibodies positive [46/49]*	6 [13.0]
Hypergammaglobulinemia positive [47/49]*	6 [12.8]
Rheumatoid factor positive [47/49]*	11 [23.4]
ESSDAI score [49/49]*	
Constitutional symptoms	4 [8.2]
Lymphadenopathy	2 [4.1]
Glandular involvement	1 [2.0]
Articular involvement	5 [10.2]
Cutaneous involvement	3 [6.1]
Pulmonary involvement	7 [14.3]
Renal involvement	2 [4.1]
Muscular involvement	0 [0.0]
Peripheral nervous system involvement	16 [32.7]
Central nervous system involvement	3 [6.1]
Hematological involvement	11 [22.4]
Biological involvement	10 [20.4]
Total score, points [IQR]	4 [0–10]#

Absolute values [relative values] or stated median and [inter quartile range] # are reported.
*Stated number of available data sets.

RHI scores can be predicted by disease-related symptoms and CRF. The significance level was set at $p < 0.05$, with all p values being two-tailed unless otherwise stated.

Figures were created using R version 4.3.1.

Results

Cohort demographics

A total of 49 SjD patients and 27 HC were included in the study population, totaling 76 individuals. The baseline demographic data are summarized in Table 1. There were no statistically significant differences in age or gender between the two groups. Furthermore, there were no relevant differences in CRF such as smoking, diabetes mellitus, and BMI, as shown in Table 2.

Disease activity and organ involvement (OI) were assessed using the EULAR Sjögren-Syndrome Disease Activity Index (ESSDAI) score (17). The median total ESSDAI score was 4 [0–10]. Among patients with OI, the peripheral nervous system was affected in 32.7% of cases. The severity of symptoms, including pain, dryness, and fatigue, was evaluated using the EULAR's Sjögren-Syndrome Patient-Reported Index (ESSPRI) (18). The median ESSPRI score was 5.67 [3.66–7.33]. Additionally, 63.8% of patients tested positive for SSA/Ro antibodies, while only 13% had a positive result for SSB/La antibodies. The median time since initial diagnosis is 54 months [35–96].

A internal, comprehensive and standardized questionnaire was employed to assess disease-specific symptoms. Alongside the high prevalence of sicca symptoms including dryness of the eyes and mouth (87.8%), the most frequently reported symptoms were arthralgia (75.5%), myalgia (73.5%), and fatigue (69.4%). Furthermore, 38.8% of participants reported experiencing Raynaud's syndrome, while 28.6% had arthritis. In addition, 22.4% of respondents indicated they had experienced inflammation of the parotid gland, 14.3% reported morning stiffness lasting over 30 min, and 10.2% had suffered from thrombosis in the past.

Results on RHI

When comparing the RHI scores of HC ($n = 27$) to those of patients with SjD ($n = 49$), there was no significant difference between the two groups ($p = 0.157$). The HC exhibited lower RHI

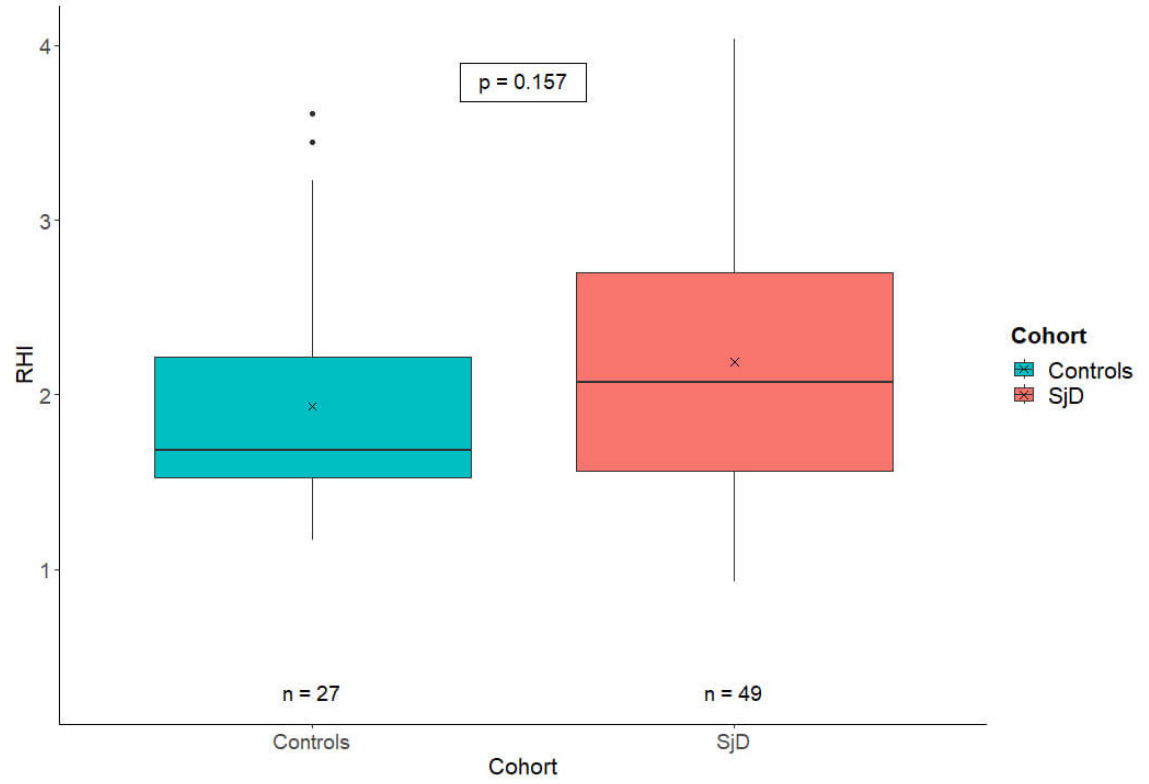

FIGURE 1
The RHI-value plot depicts the distribution of the RHI in healthy controls (blue) and SjD patients (red). The X indicates the cohort-specific RHI means, with a value of 1.93 for HC and 2.19 for SjD patients. There is only a numerically but no statistically significant difference between the two groups. RHI, reactive hyperemia index; SjD, Sjögren's disease.

values (M = 1.93; SD = 0.67) compared to the SjD cohort (M = 2.19; SD = 0.78). The results are illustrated in Figure 1.

Cardiovascular risk factors were assessed for all SjD patients and HC and are summarized in Table 1. Overall, when controlling for all other considered CRF, a significant negative association was found between the body mass index (BMI) and the RHI ($\beta = -0.04$; $p = 0.045$), as well as a significant positive association with systolic blood pressure ($\beta = -0.01$; $p = 0.029$). The negative association with BMI was also observed when only considering SjD ($\beta = -0.05$; $p = 0.038$), after controlling for all other relevant CRF including in this study.

No significant correlation was found between RHI and ESSDAI. RHI showed a tendency toward a negative association with ESSPRI, though this effect was not found to be statistically significant. Similarly, laboratory parameters including SSA/Ro-antibodies, anti-nuclear antibodies and immunoglobulin G showed no significant correlation with the RHI.

Discussion

Our study is the first to analyze ED using EndoPAT® measurements in a clearly defined cohort of SjD patients within a prospective study design.

The findings of our analysis indicate that there is no statistically significant difference between SjD and HC cohorts. However after controlling for other relevant CRF, patients with SjD and high BMI exhibited a significantly lower RHI than patients with SjD without obesity (Figure 2). In contrast, this effect was not observed in the HC group. Therefore, it is important to adjust CRF that can be controlled.

In this study, we examined SjD patients without a history of cardiovascular or cerebrovascular events. We wanted to investigate whether ED is already present in the smallest vessels as this could facilitate early identification of patients at increased cardio- and cerebrovascular risk, allowing for prevention or deceleration of atherosclerotic processes.

Sjögren's disease is associated with an increased risk of cardio- and cerebrovascular events, as well as a higher prevalence of subclinical atherosclerosis (19–21). This association is particularly evident in younger patients, often under 50, who may experience strokes at an earlier age (9). Moreover, patients with SjD exhibit abnormal profiles in novel biomarkers, including microRNAs, which further indicate an elevated cardiovascular risk profile (22).

In light of the fact that atherosclerotic end-stage diseases are a general risk for early death, a risk prevention in patients with an autoimmune disease as an additional risk factor, is highly necessary (23).

Atherosclerosis is a chronic, progressive disease that can remain asymptomatic in its early stages, including cases of ED. ED is characterized by a reduced availability of NO, which impairs the vascular system's ability to respond with vasodilation (24). This diminished vasodilatory response is reflected in a reduced RHI in the EndoPAT® measurement (16).

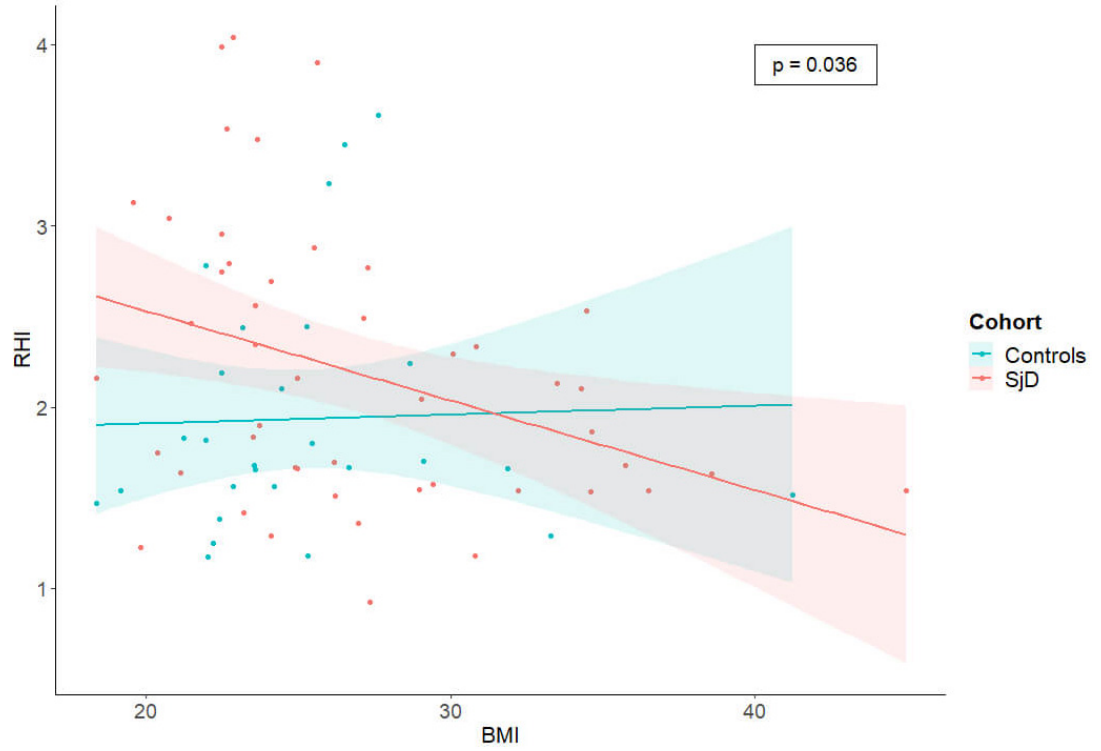

FIGURE 2
The scatter plot illustrates the correlation between RHI and BMI, with the data subdivided by cohorts. Each individual is represented by a single dot, and a linear regression line has been calculated to illustrate the differences between the cohorts and the significant negative correlation between RHI and BMI in the SjD group, when controlling for all other considered CRF. RHI, reactive hyperemia index; SjD, Sjögren's disease; BMI, body mass index.

A low RHI has shown clinical significance in relation to cardiovascular risk stratification and the early detection of ED (15).

Additionally, ED is linked to an environment that promotes inflammation, cellular proliferation, and increased coagulation, all of which contribute to the development of atherogenesis (10).

Various factors contribute to the development of atherosclerosis. Metabolic syndrome represents one relevant risk factor as a condition that includes obesity among its components, along with impaired carbohydrate metabolism, hypertension and dyslipidemia (25).

Our study has several limitations. Its monocentric design and small sample size limit the generalizability of our findings to the broader population. Additionally, we did not evaluate the impact of general medication use or glucocorticoid intake on vascular tone regulation. By excluding participants with end-stage CVDs, our study may have included patients at a too early stage to detect significant differences between SjD and HC. Consequently, further research is needed to investigate these potential influences.

This research underscores the need for a subsequent longitudinal prospective study to determine whether patients with an abnormal RHI are indeed at an increased risk of cardiovascular events.

Conclusion

In conclusion, even in the absence of evidence showing early involvement of small vessels or impaired vascular function by EndoPAT, patients with SjD have a known elevated risk for cardiovascular issues. Recognizing this is of particular importance in the context of BMI and the presence of other CRF. Based on our data, we cannot determine whether EndoPAT is unsuitable for detecting differences or if no early differences exist between patients with SjD and HC. Despite the fact that the results were negative, they therefore provide actionable insights that can help to avoid unnecessary tests and focus on more reliable diagnostic procedures such as Doppler sonography or potential biomarkers to detect patients with increased cardio- and cerebrovascular risk at an early stage and treat them preventively.

Data availability statement

The original contributions presented in this study are included in this article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Institutional Review Board of Medical University Hannover approval (8179_BO_S_2018). The studies were conducted in accordance with the local legislation and institutional requirements. The

participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

FT: Data curation, Methodology, Writing – original draft, Writing – review & editing. NZ: Conceptualization, Data curation, Writing – review & editing. MA: Writing – review & editing. AM-V: Data curation, Writing – review & editing. SB: Formal Analysis, Visualization, Writing – original draft, Writing – review & editing. TSe: Writing – review & editing. TSk: Writing – review & editing. TW: Resources, Writing – review & editing. KS: Resources, Supervision, Writing – review & editing. JB: Resources, Writing – review & editing. UB: Resources, Writing – review & editing. TT: Methodology, Resources, Writing – review & editing. AD: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing. DE: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. This work was conducted within the framework of the KlinStrucMed Program at Hannover Medical School and funded by 'Gesellschaft der Freunde der MHH e.V'.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Novartis and Itamar Medical Ltd, of Caesarea, Israel did not contribute to the study design, analyses, or data interpretation.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2025.1563796/full#supplementary-material

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frontiers | Frontiers in Medicine

TYPE Mini Review
PUBLISHED 15 August 2025
DOI 10.3389/fmed.2025.1606593

OPEN ACCESS

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RECEIVED 05 April 2025
ACCEPTED 24 July 2025
PUBLISHED 15 August 2025

CITATION
Vitale G, Colina M, Attinà D, Niro F and Ortolani P (2025) Cardiac magnetic resonance in systemic sclerosis: imaging features and potential prognostic implications. A literature review. *Front. Med.* 12:1606593. doi: 10.3389/fmed.2025.1606593

Cardiac magnetic resonance in systemic sclerosis: imaging features and potential prognostic implications. A literature review

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Systemic sclerosis (SSc) is a chronic, multisystem disorder characterized by vascular dysfunction, immune dysregulation with production of autoantibodies, fibroblasts dysfunction and consequent abnormal collagen production, leading to progressive fibrosis of the skin and various organs. Cardiac involvement is common, affecting the myocardium, pericardium, valvular structures and conduction tissue, even though it is often unrecognized. Despite this, it is a major determinant of morbidity and mortality in SSc, being responsible for about 15% of all deaths. Due to the relevant prognostic implications of cardiac involvement its early detection is mandatory. A comprehensive screening through a multimodality approach is required in all patients with SSc, even in those without overt cardiac symptoms. Cardiac magnetic resonance (CMR) is now considered the gold standard for non-invasive detection of the myocardial disease SSc related. It provides not only a morphological and functional assessment, but also offers an ultrastructural definition of the myocardium, particularly by the detection of fibrosis and myocardial inflammation (MI), unmasking an initial myocardial involvement since the early stage of disease. The aim of this review is to describe the potential spectrum of cardiac involvement in SSc, and to highlight central role of CMR in its detection, offering a comprehensive description of the imaging features and their prognostic implication.

KEYWORDS

cardiac magnetic resonance, fibrosis, systemic sclerosis, pulmonary arterial hypertension, prognostic factors, myocardial inflammation

1 Introduction

Systemic sclerosis (SSc) is a generalised autoimmune disorder of connective tissue affecting skin and internal organs. The mechanisms involved in the pathophysiology of the disease are not yet fully understood; fibrosis and microvascular occlusion characterise the pathologic findings seen in all involved organs (1). The clinical presentation can be pleomorphic, according to the organs involved, with several subsets described: limited cutaneous SSc (lcSSc), diffuse cutaneous SSc (dcSSC), and SSc *sine scleroderma*. Although SSc in an uncommon disease, it is important because it represents a paradigm for other more common medical conditions in which immunologically triggered fibrosis occurs, such as liver fibrosis and idiopathic pulmonary fibrosis. In managing patients with SSc, it is essential to routinely search for negative prognostic factors (2). Among these, cardiac involvement has a

significant impact on overall survival. The heart is commonly affected, with involvement seen in over 70% of patients, and up to 80% in autopsy studies (3, 4). Cardiac involvement is responsible for the 20–30% of unexpected deaths in SSc (5, 6). However, it is often silent, remaining unrecognized until the late stages of the disease (7). All cardiac tissues—including myocardium, pericardium, valvular structures, coronaries and conduction system—can be affected. Cardiac damage may be primary, resulting from direct vascular, fibrotic and inflammatory injury to cardiac tissue, or secondary, as a consequence of other organs disease, such as pulmonary arterial hypertension (PAH), interstitial lung disease, or scleroderma renal crisis. Ischaemic injury due to small vessel vasculopathy and MI leads to myocytes necrosis, reperfusion damage, and ultimately to myocardial fibrosis. Microvascular disease affects the media and intima layers of the small arteries and arterioles, and, in combination with coronary vasospasm—often exacerbated by cold exposure—contributes to anginal chest pain and acute coronary syndromes. Additionally, microvascular disease is a key factor in the pathogenesis of PAH. Compared to idiopathic PAH, overall survival is lower in PAH associated with SSc, despite similar hemodynamic features (8). Chronic ischaemic injury, chronic MI and consequent progressive myocardial fibrosis lead to adverse myocardial remodelling and altered ventricular compliance, resulting in both diastolic and systolic dysfunction.

2 Cardiac magnetic resonance in systemic sclerosis

Although clinical evaluation, electrocardiogram and echocardiography still represent today the first approach to assess cardiac involvement in patients with SSc, their sensitivity and specificity are relatively low, so a large number of affected patients may remain undiagnosed. The advent of cardiac magnetic resonance (CMR) has significantly impacted the epidemiology and clinical management of various diseases, including SSc. CMR, a non-radiating imaging technique, is now regarded as the gold standard for non-invasive evaluation of cardiac morphology and function. It is more accurate and reproducible than echocardiography, and offers the possibility of tissue characterization of the myocardium, particularly in terms of fibrosis and MI, providing crucial insights for clinical management. The high sensitivity of CMR enables early detection of myocardial damage, even in its preclinical stage, in particular during initial inflammatory phase, before than fibrosis or overt functional and morphological changes occur. Furthermore, its non-radiating nature ensures patient safety, making it suitable for longitudinal monitoring during follow-up. The limited availability, the costs and the potential (few) contraindications are the main limitations.

2.1 Morpho-functional evaluation and diastolic function

Myocardial involvement in SSc can present with focal hypo- or akinesia, ranging to various degrees of global left ventricular (LV) systolic dysfunction and dilatation. Myocarditis and fibrotic replacement are responsible for segmental and/or global ventricular abnormalities in the acute and chronic phases, respectively. Right ventricular (RV) hypertrophy, dilatation and dysfunction—often associated with anomalous movement of the interventricular septum—suggest the presence of PAH. These findings, particularly when they are nuanced, can be misdiagnosed by echocardiography, whereas they are more easily to detect with CMR. Specific cardiac structures, such as the right ventricle, LV apex and atrial chambers, may be challenging to approach with ultrasound. CMR overcomes the limitations of the transthoracic echocardiography, by combining different cine images, even also in not canonical cut planes, providing a more comprehensive evaluation. Recently, five distinct CMR phenotypes of cardiac SSc have been described, based on the presence of dysfunction and/or dilatation of one or both ventricular chambers: dilated right heart with RV failure, biventricular dilatation and dysfunction, normal function with large cavity sizes, normal function with normal cavity, normal function with small cavity, the latter two subsets being associated with a more favourable outcome (9). Several studies evaluated the potential correlation between morpho-functional parameters and clinical outcomes, often with conflicting results (10). Among these parameters, RV ejection fraction has been shown to independently predict all-cause mortality (9). SSc patients frequently develop signs and symptoms of heart failure (HF), regardless of systolic function. According to the results from the European Scleroderma Trials and Research (EUSTAR) registry, 36.2% of SSc patients with cardiac involvement meets diagnostic criteria for HF with preserved ejection fraction (HFpEF), while HF with reduced (HFrEF) or mildly reduced ejection fraction (HFmrEF) has been reported much less frequently, each accounting for 1.5% of cases (11). Indeed, LV systolic dysfunction has been reported in about 5.4% of cases; however, MI and fibrosis can alter biventricular myocardial relaxation and compliance, leading to elevated pulmonary venous pressures, thereby increasing RV afterload. This results in RV hypertrophy and subsequent diastolic dysfunction (DD), characterized by reduced RV filling time and prolonged isovolumic relaxation time, the latter indicating impaired active myocardial relaxation (12). As RV DD progresses, maladaptive remodeling with chamber dilatation develops, ultimately leading to RV systolic dysfunction. This, in turn, adversely affects left-sided chambers, further compromising LV filling. DD is closely associated with HFpEF, and numerous studies have evaluated it non-invasively using echocardiography. Tennøe et al. reported that 17% of 275 consecutive SSc patients had DD at baseline, with the prevalence increasing to 29% after a 3.4-year follow-up. Patients with DD were older and had higher rates of systemic hypertension, ischemic heart disease, atrial fibrillation, and pulmonary hypertension compared to those without DD. The presence of DD was associated with poorer survival (13). Accordingly, diastole should systematically be evaluated, being often the only functional detectable abnormality. While echocardiography remains the traditional approach for its non-invasive assessment, several applications of CMR imaging have demonstrated potential utility in the evaluation of both LV and RV diastolic function, including cine imaging for ventricular filling dynamics, phase-contrast sequences for transvalvular flow analysis, feature tracking for diastolic strain rates, and T1 mapping to detect myocardial fibrosis and impaired compliance, although the evidences remain limited (14–16).

2.2 Tissue characterization

MI, resulting from aberrant activation of the immune system, is common in SSc, although it is often clinically silent. Overt clinical

myocarditis is rare, whereas recent CMR studies have highlighted the critical role of subclinical inflammation in the pathogenesis of cardiac damage. Since 2009, the definition of the Lake Louis criteria has provided the foundation for non-invasive diagnosis of myocarditis (i.e., MI), based on the identification of three diagnostic criteria: edema, hyperemia, and necrosis. These criteria are derived from T2-weighted, early gadolinium enhancement, and late gadolinium enhancement (LGE) CMR images, respectively: for the diagnosis of myocarditis, at least two of the three criteria must be present (17, 18). The advent of CMR mapping imaging has advanced tissue characterization, improving sensitivity and specificity through direct measurement of T1 and T2 relaxation times. As a result, the Lake Louis diagnostic criteria have been revised in 2018 (19). Accordingly, both myocardial edema (described as regional or global increase of native T2 or T2 signal intensity) and non-ischaemic myocardial injury (i.e., regional or global increase of native T1 or extracellular volume (EVC), or presence of LGE) must be present. The coexistence of pericardial involvement and/or LV systolic—global or regional—dysfunction further support the diagnosis.

2.2.1 Edema and hyperemia

Immune dysregulation in SSc leads to the upregulation of endothelial adhesion molecules, leukocytes diapedesis and release of cytokines, with consequent increase in tissue free water content. On CMR analysis, edema prolongs both T1 and, particularly, T2 relaxation times. In T2-weighted short-tau inversion recovery (STIR) images, edema appears as regional or global signal hyperintensity. However, poor image quality and limited sensitivity can hinder the detection of diffuse and subtle edema, which is typical of SSc, especially when muscle signal intensity cannot be used as reference due to coexistent skeletal myositis. The introduction of cardiac T1 and T2 mapping has helped overcome the limitations of conventional CMR. Compared to T2-wheighted imaging, both T1 and T2 mapping techniques have shown greater sensitivity for the detection of MI. In particular, T2 mapping can directly measure the prolongation of myocardial T2 relaxation time, identifying free water related to MI or acute ischemia with more accuracy than traditional T2-weighted imaging (20, 21). Myocardial T1 is also influenced by edema, even though the increase in native T1 is less specific, since it reflects both the intracellular and extracellular space, and is also influenced by fibrosis and capillary leak (19). The addition of T1 and T2 mapping improves the diagnostic yield of CMR in detecting MI, increasing sensitivity from 52 to 89%, compared to traditional CMR (22). Furthermore, hyperemia and increased vascular permeability can be detected using early gadolinium enhancement, which manifests as an increased signal in T1-weighted post-contrast images due to the interstitial uptake of the contrast agent. Elevated native T1 and/or T2 has been found in over 62% of SSc patients with normal conventional CMR (i.e., negative LGE and T2-weighted images), highlighting that subclinical myocardial damage is common, even in patients without overt heart disease (23). The detection of an early myocardial inflammatory stage provides the opportunity for anti-inflammatory therapies, preventing the progression towards irreversible fibrosis (24).

2.2.2 Fibrosis

Myocardial fibrosis is the pathogenic hallmark of cardiac involvement in SSc, and has been reported in over 80% of cases in autoptic studies (3, 25). CMR enables non-invasive detection of myocytes loss and myocardial fibrosis, and is now considered the gold standard for this purpose. The presence of LGE significantly influences overall outcome, so its systematic research is mandatory (10, 26). Various CMR studies have reported a wide range of LGE prevalence in SSc, from 15 to over 60% (27). Several distinct patterns of LGE have been described (Figure 1): mid wall linear distribution is the most frequent, typically affecting the septal, infero-lateral, lateral or inferior mid/basal segments, following a non-coronary distribution (27, 28). Patchy and insertional LGE have also been reported, with the latter likely reflecting RV overload due to PAH; ultimately, mixed pattern

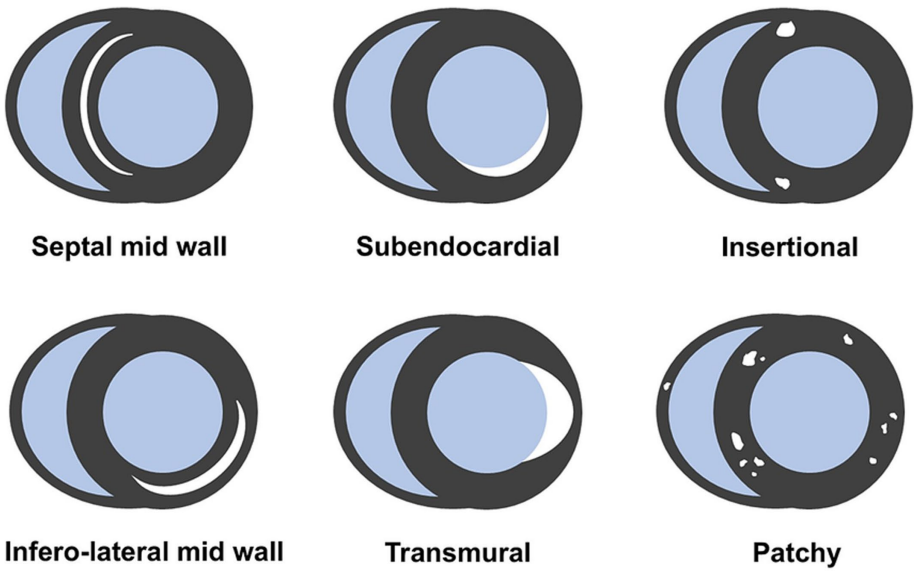

FIGURE 1
Different patterns of late gadolinium enhancement in systemic sclerosis.

and subendocardial to transmural LGE have been observed (Figure 2) (29, 30). The RV free wall is also affected by replacement fibrosis; however, its detection is challenging and may be underestimated due to the peculiar characteristics of the RV wall (thin and trabeculated). The presence of myocardial fibrosis is associated with a lower LV ejection fraction, and a relevant amount of LGE has been found in patients with ventricular arrhythmias (27, 29, 30). Prognosis is significantly worsened by the presence of LGE, with an event-free 5-year survival rate of less than 50% in such cases (26). While LGE can identify replacement fibrosis, interstitial fibrosis is more diffuse and nuanced, and may be missed by traditional post-contrast imaging. More recent parametric mapping techniques, particularly native T1 and extracellular volume (ECV), provide an accurate assessment of tissue relaxation times, enhancing diagnostic sensitivity for detecting diffuse fibrosis rather than focal scarring. Native (pre-contrast) T1 relaxation time is influenced by changes in both extracellular and intracellular spaces, occurring in conditions where free water is present, such as edema, as well as in fibrosis or amyloidosis, where water is bound to large molecules like collagen (31, 32). Elevated native T1 is detectable in more than half of SSc patients, representing the only abnormal parameter in approximately one-third of cases (33). Myocardial ECV is indirectly measured from the ratio of T1 changes before and after contrast administration. ECV is a precise indicator of the myocardial extracellular space, and proves particularly useful in infiltrative diseases like cardiac amyloidosis, where the interstitial space is abnormally high. Accordingly, native T1 and ECV are sensitive surrogates of diffuse, interstitial fibrosis, and appear to be significantly elevated in SSc patients compared to healthy controls. Both T1 and ECV correlate with N-Terminal-pro-Brain Natriuretic Peptide levels, disease severity and activity, and predict adverse outcomes in SSc patients (18, 34). Gotschy et al. found no significant differences in LV function, volume, or LGE in early stage SSc patients with high and low native T1, suggesting that that conventional CMR may not effectively identify patients at increased risk (18). Bordonaro et al. reported that elevated T1 and ECV are independent predictors of adverse events (including cardiac death, haemodynamically significant arrhythmia, or heart failure) in SSc patients (34). These findings highlight the additional contribution of CMR mapping to risk stratification compared to standard LGE, and suggest that it should be systematically evaluated in patients with SSc.

2.3 Deformation imaging

Traditional echocardiographic parameters are often ineffective for detecting subclinical systolic impairment. However, reduced LV and RV global longitudinal strain (GLS) is common among patients with SSc and has been associated with an increased risk of all-causes mortality and hospitalization (35–37). A basal–apical gradient has also been observed, with basal segments being more affected than the apex in both ventricles (35, 38). More recently, feature-tracking CMR analysis has emerged as a novel method for studying biventricular deformation and, accordingly, myocardial performance. Several studies have evaluated LV deformation in SSc using future-tracking analysis, showing that LV and RV strains are often impaired despite preserved LV ejection fraction (39, 40). Gotschy et al. reported the

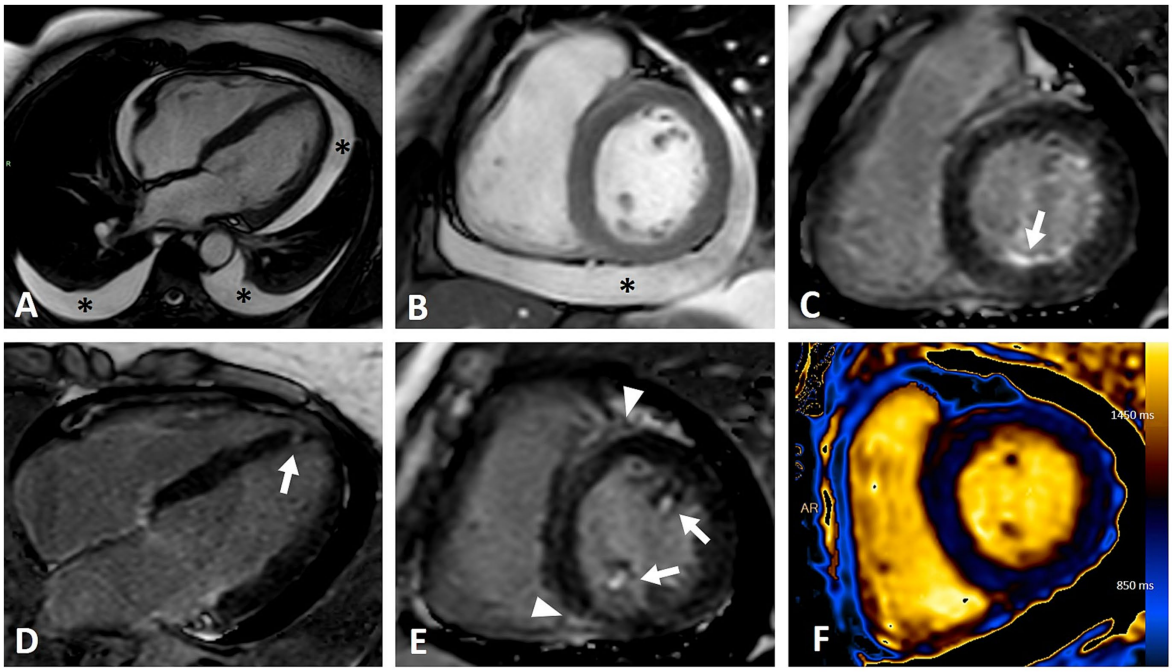

FIGURE 2
CMR imaging of a female patient with diffuse cutaneous systemic sclerosis and heterogeneous cardiac involvement. **(A,B)** Moderate pericardial and bilateral pleural effusion (asterisks) in four-chambers **(A)** and short axis **(B)** steady-state free precession (SSFP) sequences. **(C–E)** Inversion recovery sequences demonstrating various patterns of LGE: infero-basal subendocardial (**C**, arrow), focal septal apical (**D**, arrow), papillary muscles involvement (**E**, arrows), insertional (**E**, arrowhead). **(F)** T1 mapping showing abnormal elevated values (mean value of 1,100 ms) due to myocardial fibrosis and edema.

potential prognostic utility of deformation analysis, demonstrating that reduced GLS and elevated T1 can identify subjects at increased risk of death for any cause (18). Faher et al. demonstrated that GLS assessed by feature-tracking predicts overall survival regardless of cardiac output, reduced LVEF, and LGE (41). Moreover, some studies have reported significant improvement in LV and RV strain after the initiation of specific therapies for PAH, suggesting the potential utility of strain imaging for monitoring the response to therapies (42). However, data are still scarce, and further evidence is warranted.

2.4 Pulmonary arterial hypertension

PAH is common in SSc, with an estimated prevalence of 7–12% (43). Compared to idiopathic one, prognosis in PAH related to SSc is worse. One potential explanation seems to be a more impaired RV pump function, likely due to intrinsic abnormal collagen deposition. Additionally, microvascular disease and resulting chronic ischaemic damage have been postulated as contributing factors (44). Although CMR cannot directly measure pulmonary pressures, it provides valuable information on RV wall thickness, volumes and function, complementing echocardiographic assessment. Furthermore, assessment of fibrosis, measurement of myocardial strain and precise quantification of pulmonary and tricuspid regurgitant volumes are other potential applications. Patients with SSc-associated PAH have higher native myocardial, T2 and ECV, compared with patients without, and have more frequently pericardial effusion (9). Insertional myocardial scar, detected by LGE or native T1 elevation, is indicative of RV pressure overload, and correlates with disease severity (45). More recently, Knight et coll. Demonstrated that native T1 and indexed RV end-systolic volume are independent predictors of all-cause mortality in SSc-associated PAH, providing also potential thresholds to identify patients with a poorer prognosis (46). Given the growing body of evidence, CMR has become an integral part for comprehensive risk assessment in PAH together with the traditional prognostic predictors, offering the advantage of being non-invasive and reproducible over time.

2.5 Pericardial involvement

The pericardium is frequently affected, with involvement ranging from 33 to 72% (47). Asymptomatic mild pericardial effusion is the most common finding, whereas clinically symptomatic pericardial disease is less frequent. Some patients may present with typical acute pericarditis, characterized by elevated serum inflammatory biomarkers, chest pain and pericardial rubs. Constrictive pericarditis and pericardial tamponade, although possible, occur infrequently. CMR is typically considered a second-line imaging modality for diagnosing acute pericarditis; however, its high resolution and ability to perform tissue characterization make CMR the gold standard for non-invasive evaluation. A thickened pericardium of $\geq$ 3 mm can be seen in both acute and chronic pericarditis. Cine imaging offers a comprehensive functional assessment of the cardiac chambers and pericardial space, revealing pericardial effusion and its potential effects on cardiac functions, such as right chambers collapse in cardiac tamponade, or septal bounce in constrictive pericarditis at real-time cine images.

2.6 Valvular heart diseases

Heart valves are also affected by the immune dysregulation of SSc. Nodular thickening of the tricuspid, aortic and especially mitral valves (in approximately 38% in autoptic studies), along with retraction of the chordae tendineae and consequent valvular regurgitation, are the most common valvular alteration observed (48, 49). Also anecdotical cases of non-bacterial thrombotic endocarditis have been reported (50). Due to its superior temporal resolution and widespread availability, echocardiography remains the first approach for evaluating heart valves. However, CMR, using phase contrast imaging, can be a valuable alternative for approaching valvular disorders, especially in cases with poor acoustic windows, or when results are inconclusive, providing a more precise quantification of valvular regurgitation.

2.7 Microvascular dysfunction

Myocardial damage in SSc is also caused by repeated chronic ischaemic injury, resulting from structural microvascular impairment and abnormal vasoreactivity, rather than epicardial coronary arteries disease. Advances in myocardial perfusion imaging have spurred growing interest in the evaluation of microvascular dysfunction in SSc. The first demonstration of cold-induced coronary vasospasm in SSc was documented in several nuclear medicine studies, who found reversible myocardial perfusion defects after cold exposure, that seem to predict cardiac events and mortality in SSc (51–53). More recently, even CMR has found application in this context. Inducible subendocardial perfusion defects have been reported in about 79% of the patients assessed by stress CMR with adenosine, and resulted to be associated with higher plasmatic levels of ultrasensitive C reactive protein, suggesting a potential link between chronic MI and microvascular dysfunction (30). Gyllenhammar et al. demonstrated that patients with SSc exhibit decreased myocardial perfusion during adenosine stress, but not at rest, compared to healthy controls (54). Furthermore, Galea et coll. Reported a reduced vasodilatory response to the cold pressure test in SSc patients without cardiac symptoms, indicating a potential early role of endothelial microvascular dysfunction in the pathogenesis of cardiac damage (55). However, evidences regarding the potential prognostic implications of microvascular impairment remain limited and warrants further investigation.

3 Conclusion

Cardiac involvement in SSc is frequent, often subclinical, and carries an ominous prognosis. Given its relevant prognostic implications, early detection is mandatory, in order to timely start specific therapies and potentially prevent irreversible damage. Growing evidence underscores the central role of CMR in identifying subclinical cardiac involvement in SSc. CMR provides a non-invasive, multiparametric assessment through precise morphological and functional evaluation. Tissue characterization enables preclinical detection, even without the use of contrast agent, especially with recent advancements in mapping techniques. This capability can help clinicians to better understand the complex pathogenesis of cardiac damage. Furthermore, thanks to its non-radiating nature, CMR

permits to safely monitor SSc patients at follow-up. Unfortunately, the well acknowledged utility of CMR is limited in real-world practice due to its elevated costs, scarce availability, and the prolonged time for both acquisition and analysis process. Further evidences are still need to elucidate the potential role of CMR in predicting outcomes and monitoring therapy response.

Author contributions

GV: Writing – review & editing, Writing – original draft, Conceptualization. MC: Writing – review & editing, Supervision, Writing – original draft, Conceptualization. DA: Writing – original draft. FN: Writing – original draft. PO: Writing – review & editing, Writing – original draft.

Funding

The author(s) declare that no financial support was received for the research and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no Gen AI was used in the creation of this manuscript.

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TYPE Review
PUBLISHED 15 October 2025
DOI 10.3389/fmed.2025.1557312

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RECEIVED 08 January 2025
ACCEPTED 28 July 2025
PUBLISHED 15 October 2025

CITATION
Gremese E, Bruno D, Perniola S, Ceolan J and Ferraccioli G (2025) Autoimmune inflammation as a key risk factor for heart failure with preserved ejection fraction: the different types of inflammation driving to HFpEF.
Front. Med. 12:1557312.
doi: 10.3389/fmed.2025.1557312

Autoimmune inflammation as a key risk factor for heart failure with preserved ejection fraction: the different types of inflammation driving to HFpEF

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Importance: Heart failure with preserved ejection fraction (HFpEF), defined by an ejection fraction >50%, has emerged as the most prevalent form of heart failure at the community level. Multiple comorbidities, including diabetes, hypertension, obesity, atrial fibrillation, renal diseases, and autoimmune conditions, have been linked to its development. These conditions share common pathways involving oxidative stress, metabolic dysregulation, ischemia, and a chronic inflammatory milieu.

Observations: Patients with autoimmune diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and systemic sclerosis (SSc) exhibit an increased risk of developing HFpEF, often through mechanisms involving chronic inflammation and endothelial dysfunction, which precede the clinical manifestation of HFpEF. Clinical studies have demonstrated that the risk of developing HFpEF exists independently of traditional cardiovascular risk factors, underscoring the pivotal role of chronic inflammation and autoimmunity as key contributors to its pathogenesis.

Conclusions and relevance: The translational implication is that the distinct inflammatory pathways driving these autoimmune diseases (e.g., myeloid-T cells and T-B cell-mediated inflammation in RA, and B cell-driven inflammation in SLE and SSc) should become personalized therapeutic targets to prevent HFpEF progression. Early intervention with novel therapies, such as sodium-glucose cotransporter type 2 (SGLT2) inhibitors, could be crucial in managing these patients during the early disease stages. Additionally, the H2FPEF score should be routinely employed to facilitate early diagnosis and risk stratification, providing a robust framework for personalized management strategies.

KEYWORDS

inflammation, autoimmunity, endothelial dysfunction, diastolic dysfunction, heart failure with preserved ejection fraction

Introduction

Heart failure with preserved ejection fraction (HFpEF) has emerged as a leading cause of mortality among heart failure patients (1). According to the current guidelines of the American Heart Association/American College of Cardiology and the European Society of Cardiology, the diagnosis of HFpEF is based on three primary criteria: 1. the presence of signs and symptoms consistent with heart failure; 2. a preserved left ventricular ejection fraction (LVEF ≥50%); and 3. objective evidence of impaired left ventricular (LV) diastolic function (2). Estimates suggest that at least 50% (range 44–72%) of all heart failure cases occur with preserved ejection fraction (3).

Community-based data from Olmsted County indicate that only 16% of HFpEF patients had a prior myocardial infarction, compared to 28% of those with heart failure with reduced ejection fraction (HFrEF). Additionally, coronary heart disease accounted for 29% of deaths in HFpEF patients compared to 43% in HFrEF patients (4). These findings suggest that coronary artery disease plays a less dominant role in HFpEF, while myocardial disease appears to be more prevalent. Between 2000 and 2010, the proportion of HFpEF among new heart failure cases in Olmsted County increased from 48 to 52%, with women being affected twice as often as men. Furthermore, over this decade, the incidence of HFpEF showed a smaller decline compared to HFrEF (−27 versus −61%, respectively) (5).

HFpEF is generally characterized by older age, female predominance, and a higher prevalence of atrial fibrillation, with lower rates of stroke and coronary artery disease (1). Its global prevalence is rising, driven by both traditional risk factors (i.e., obesity, diabetes, hypertension, smoking, metabolic syndrome, renal failure, anemia), and emerging pathophysiological mechanisms, including diastolic dysfunction, endothelial dysfunction, microvascular damage, and systemic low-grade inflammation that promotes myocardial remodeling (3, 6). Oxidative stress and fibrosis are also recognized as critical contributors to the disease's pathogenesis (7).

Inflammation plays a pivotal role in the development of heart failure, potentially contributing differently to its various subtypes, with evidence highlighting a specific association between the interleukin-6 (IL-6)/C-reactive protein (CRP) pathway and the pathogenesis of HFpEF (8). In inflammatory and autoimmune rheumatologic diseases, HFpEF remains underrecognized, despite evidence suggesting that its development may be driven by distinct autoimmune and inflammatory mechanisms specific to each condition.

Therefore, in this review, we focus on evidence from the past two decades (2004–2024) exploring the intersection of HFpEF and three autoimmune diseases: rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and systemic sclerosis (SSc). Specifically, we conducted a literature search using PubMed and Scopus, covering the years 2004–2024. Search terms included "HFpEF," "diastolic dysfunction," "autoimmune," "rheumatoid arthritis," "SLE," and "systemic sclerosis." We included english-language studies focusing specifically on HFpEF in the context of autoimmune diseases, ultimately identifying five studies in RA, seven prospective studies overall, and one observational study with relevant clinical data. We excluded studies that did not clearly distinguish between HFpEF and HFrEF, or that lacked primary data on cardiovascular outcomes.

Endothelial dysfunction, chronic inflammation, diastolic dysfunction, and HFpEF: experimental models

While not all diastolic dysfunctions (DD) progress to HFpEF, all HFpEF cases exhibit DD (9). Understanding the pathophysiology of DD is therefore crucial to elucidate its progression to heart failure. An ideal murine model of HFpEF should present specific characteristics, such as exercise intolerance, pulmonary edema, concentric cardiac hypertrophy, and a preserved EF > 50% (10). Among the proposed models, three particularly emphasize the link between DD and inflammation.

In Goto-Kakizaki (GK) rats, a prediabetic model with insulin deficiency, DD originates in the myofilaments. Synchrotron radiation small-angle X-ray scattering (SAXS) on beating hearts revealed displacement of myosin heads from actin filaments during diastole, along with impaired relaxation and cross-bridge dynamics (11, 12). Mitochondrial oxidative stress and elevated activity of protein kinase C (PKC) and Rho kinase (ROCK) increase cardiomyocyte stiffness and passive tension, ultimately promoting DD (13). Oxidative stress acts as a secondary messenger, activating PKC (14) and the Rho/ROCK pathway (15), which in turn trigger NF-κB and AP-1 activation. These pathways promote cytokine and growth factor transcription, extracellular matrix (ECM) remodeling, vasospasm, hypertension, and myocardial remodeling (16, 17) (Figure 1).

Notably, GK rats showed elevated myocardial IL-6, TGF-β1, and Nox2 (a ROS-producing enzyme). Despite these changes, eNOS and NO-mediated vasodilation were preserved. These findings establish oxidative stress and inflammation as central mechanisms driving DD and endothelial dysfunction (13, 17). Likewise, in women with ischemia but no coronary artery disease, oxidative stress has been linked to DD (18).

Diabetes further contributes to DD via chronic low-grade inflammation, termed "metabolic inflammation" (19). Once DD develops, its association with ED becomes evident (20, 21), and ED has emerged as a promising therapeutic target in heart failure (22).

Additional validated models of DD include the SAUNA model (salty water, unilateral nephrectomy, aldosterone) and an aging murine model. In both, increased hematopoiesis correlates with macrophage recruitment and elevated ROS production. These macrophages secrete TGF-β and IL-10, promoting fibroblast activation and ECM synthesis (e.g., type I collagen, α-SMA) (23, 24).

Resident cardiac macrophages (RCMs), classified as CCR2 + or CCR2-, play differential roles. CCR2- macrophages aid repair and angiogenesis (25), while CCR2 + macrophages fuel inflammation through IL-1β and Nlrp3 activation, contributing to adverse remodeling (26). In failing human hearts, CCR2 + cells dominate, enriched in NF-κB, IL-6, and STAT3 pathways (27, 28). These cells also express oncostatin M (OSM), known to inhibit myoblast differentiation, especially after ischemic injury (27). Single-cell RNA-seq studies confirmed their pro-inflammatory role (28).

Thus, even conditions like hypertension and aging contribute to cardiac injury and DD, largely through inflammation-driven mechanisms.

In conclusion, the pathophysiology of HFpEF encompasses cardiomyocyte stiffness, fibrosis, microvascular dysfunction, oxidative stress, and chronic inflammation. As stated by Paulus and Tschope (29), all comorbidities associated with HFpEF appear to converge on

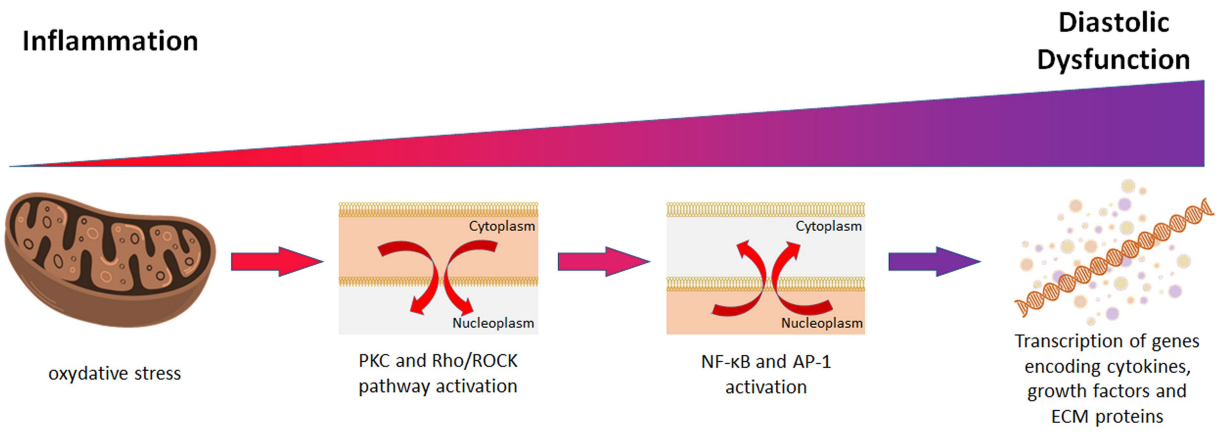

FIGURE 1
During inflammatory response, in the mytochondrial environment, oxidative stress activates PKC and Rho/ROCK pathway, subsequently triggering cellular NF-κB and AP-1, which drive inflammatory cascades. Thus, contributes to the development of coronary vasospasm, hypertension, and myocardial remodeling, ultimately resulting in diastolic dysfunction. PKC, protein kinase C; NF-κB, nuclear factor kappa light chain of B cells; AP-1, activator protein-1; ECM, extracellular matrix.

a shared inflammatory axis that sustains myocardial dysfunction (Figure 2).

This section emphasizes that inflammation is a unifying mechanism across diverse HFpEF models and sets the stage for exploring human clinical phenotypes.

HFpEF human phenotypes

These experimental insights highlight how inflammation initiates and perpetuates the pathophysiology of HFpEF and justify exploration of clinical phenotypes linked to such mechanisms. The relationship between HFpEF and comorbidities is well-documented beyond aging (30, 31). Across cohorts, approximately 45% of HFpEF patients have diabetes (32), 80% in the US are obese (33), 40–60% present with atrial fibrillation/flutter (34, 35), 55% have hypertension (36–38), and 26–49% have renal disease (39, 40). These comorbidities collectively create a low-to-moderate inflammatory state. Combined with neurohormonal, metabolic, and ischemic factors, this milieu promotes myocardial stiffness via oxidative stress, ischemia, and inflammation (Table 1).

Understanding these phenotypes helps contextualize the relevance of inflammation in HFpEF and paves the way to analyze autoimmune conditions in the following sections.

Chronic inflammation, autoimmunity, and the heart

Understanding the role of systemic inflammatory burden across populations helps translate experimental evidence into clinical relevance.

Chronic heart inflammation, unlike acute myocarditis, is typically driven by autoimmune diseases, which vary in inflammatory load and vascular involvement. Analyzing cardiovascular comorbidities in these conditions provides valuable insights into how chronic inflammation contributes to HFpEF.

Several studies have shown that the risk of acute myocardial infarction (AMI) in rheumatoid arthritis (RA) rivals that of type 2 diabetes (41), and that heart failure (HF) risk is doubled in RA compared to the general population (42). The QRISK 3 algorithm now includes RA and systemic lupus erythematosus (SLE) in its 10-year cardiovascular risk estimation (43). Additionally, persistent inflammation—as measured by high-sensitivity CRP—has been shown to better predict cardiovascular events and mortality than LDL cholesterol in statin-treated patients (44).

Notably, the Reynolds score used in women also incorporates hsCRP, linking inflammation and cardiovascular risk. CRP is strongly associated with endothelial dysfunction (ED) in hyperlipidemic individuals (45), reinforcing the tight interplay among inflammation, lipids, and endothelial damage.

Together, these observations build a strong rationale for focusing on vascular inflammation as a shared pathway driving HFpEF in autoimmune diseases.

Autoimmunity, chronic inflammation, and diastolic dysfunction

Diastolic dysfunction (DD) affects approximately 28.1% of the general population (46), where it independently predicts mortality and heart failure (47, 48). In autoimmune diseases, DD is even more prevalent and strongly associated with disease features.

For example, in RA, DD was observed in 31% of patients and linked to disease duration and elevated IL-6 levels (49). Premenopausal RA patients showed an even higher prevalence (47%) compared to age-matched controls (26%), with CRP being the strongest independent predictor (50).

In PsA, DD prevalence reached 38%, associated with older age and hypertension (51). In SSc, DD affected 35% of patients, regardless of whether disease was limited or diffuse, and correlated with Raynaud's duration (52).

In SLE, 39% had DD independent of disease activity (SELENA-SLEDAI), with disease duration being the strongest determinant,

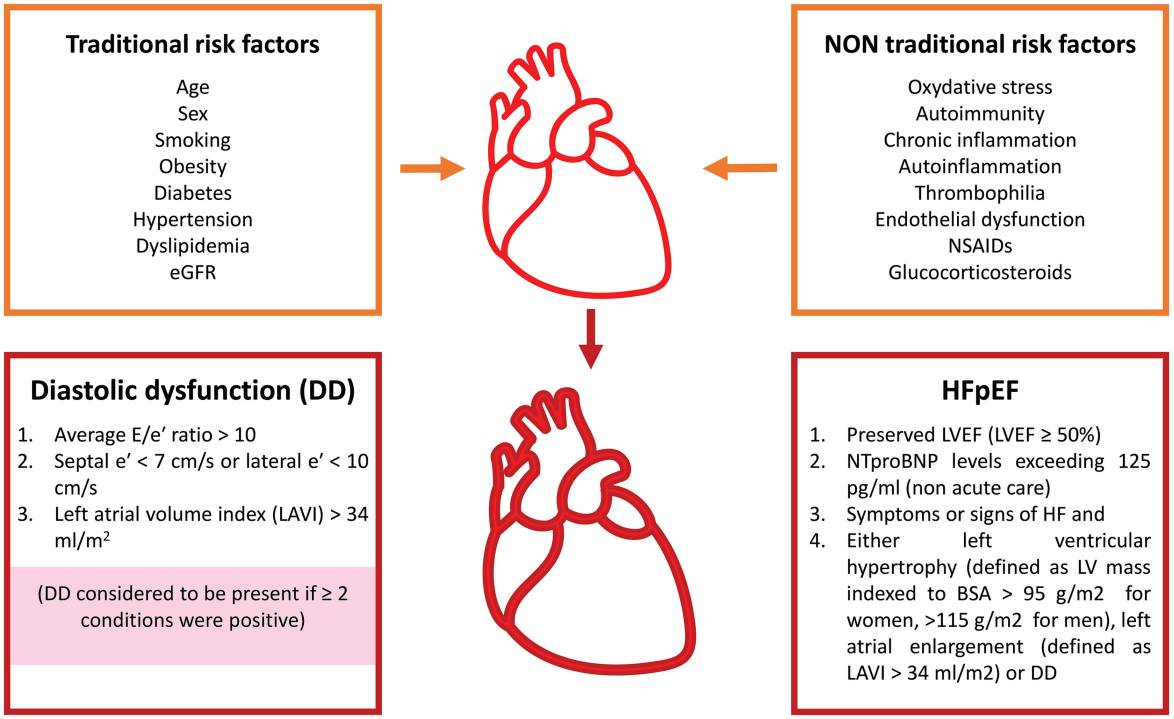

FIGURE 2
Traditional and non-traditional risk factors leading to diastolic dysfunction and to heart failure with preserved ejection fraction. eGFR, estimated glomerular filtration rate; NSAIDs, non-steroidal anti-inflammatory drugs; HFpEF, heart failure with preserved ejection fraction; LVEF, left ventricular ejection fraction; NTproBNP, N-terminal pro–B-type natriuretic peptide; BSA, body surface area.

while the Framingham score proved unreliable (53). Anti-cardiolipin antibodies, especially LAC, predicted worse DD progression (54).

Similarly, in IBD, DD was associated with reduced coronary flow reserve (CFR), an indicator of microvascular function (55), and cardiovascular risk has been recognized by expert panels (56).

These findings consistently show that autoimmune and chronic inflammatory diseases are strong contributors to DD, reinforcing the importance of cardiovascular monitoring in these patients.

Endothelial dysfunction in autoimmune-chronic inflammatory diseases: a screening of diastolic dysfunction?

The 2013 paradigm by Paulus and Tschöpe (29) proposed that cardiovascular risk factors induce systemic inflammation, which impairs endothelial and coronary microvascular function, ultimately leading to HFpEF. This is supported by histological evidence of microvascular rarefaction and NOX2 expression in macrophages from HFpEF patients (57), as well as high prevalence of vascular dysfunction in this condition (58). Accordingly, autoimmune diseases frequently exhibit ED. Specifically:

1. RA: impaired response to acetylcholine, reversible with TNF-α blockade; long-term improvement requires disease remission (59, 60).
2. SSc: ED reversible with endothelin A receptor antagonism, but not with nitroprusside (61).
3. SLE: reduced FMD, worsened by comorbidities (62, 63).
4. PMR: FMD remained low even after 6 months of treatment, inversely correlated with CRP (64).

Normal FMD is ~6.4%, with age-related decline (65); standardized protocols now enable its use as a biomarker (66). Moreover, prospective studies show that ED predicts DD progression (67), and DD precedes HFpEF (48). Hence, maintaining control of systemic inflammation (as in RA and SLE) is essential (60, 68).

All together, these data support the concept of ED as an early and actionable marker in the prevention of HFpEF among patients with chronic autoimmune inflammation.

HFpEF in rheumatoid arthritis, lupus and systemic sclerosis

While DD and ED are well-documented in autoimmune diseases, the clinical burden of HFpEF is only recently emerging as a distinct phenotype. Multiple studies from 2008 to 2024 have demonstrated that HFpEF is the dominant HF subtype in these populations (69–73) (Table 2). In RA, one-year mortality after HF diagnosis was 35%, compared to 19% in controls (69), and incidence ranged from 2.5 to 8.2% across cohorts (70–72). These risks remained stable over decades and were linked to disease activity.

TABLE 1 Experimental models and *in vivo* human phenotypes of endothelial and diastolic dysfunction ending up to HFpEF.

Experimental models	
GOTO-KAKIZAKI Diabetes rat model (Insulin deficient- increased PKC and ROCK activity- Cardiomyocyte stiffening) (11, 12)	Diastolic dysfunction precedes endothelium dysfunction
SAU-NA Hypertensive mouse model (unilateral nephrectomy, chronic exposure to aldosterone and accelerated mortality—hypertensive model—increased recruitment of macrophages CCR2+) (23)	Diastolic dysfunction followed by cardiomyopathy and accelerated mortality
AGING Mouse model (increase in left ventricular mass, interstitial fibrosis, with high expression of TGFb and IL10 and CCR2 + macrophages) (24)	Diastolic dysfunction, cardiomyocites hypertrophy and stiffness, microvascular dysfunction
Human phenotypes (age as the major risk factor)	
DIABETES (pathophysiologic mechanisms: alteration in sodium handling; increased volume overload; release of pro-inflammatory cytokines; endothelial and diastolic dysfunction) (32)	45% of HFpEF have diabetes
OBESITY (pathophysiologic mechanisms: volume overload; endothelial and diastolic dysfunction; biventricular remodeling; impaired pulmonary vasodilation; systemic inflammation) (33)	80% of HFpEF in US are obese
ATRIAL FIBRILLATION and FLUTTER (pathophysiologic mechanisms: widespread endothelial dysfunction; oxidative stress; microvascular inflammation with increased CRP levels; atrial and ventricular fibrosis) (35)	40–60% of HFpEF have atrial fibrillation or flutter
HYPERTENSION (pathophysiologic mechanisms: coronary microvascular endothelial dysfunction; increased afterload on left ventricle; ventricular hypertrophy; diastolic dysfunction; systemic inflammation) (37)	55% of patients with HFpEF have hypertension
CHRONIC RENAL DISEASES (pathophysiologic mechanisms: endothelial dysfunction, inflammation and systemic and renal fibrosis are mutual consequences of diabetes, hypertension and dyslipidaemia, which can also be drivers of cardiorenal syndrome) (40)	HFpEF patients: 26–49% have renal disease

Similarly, HF incidence was higher in RA (4.87/1,000 person-years vs. 3.96 in controls) (73). In other autoimmune diseases, HFpEF also emerged as the predominant phenotype. For instance, the Athero-APS study showed an increasing gradient of HFpEF prevalence from asymptomatic aPL carriers (6.3%) to full-blown SLE-APS (27.8%) (74). Large population studies confirmed that HF risk is markedly elevated in SSc, SLE, and RA (75), with worse in-hospital outcomes for SLE patients (76). In SSc, 27% met HFpEF criteria, and interstitial lung disease was a key predictor (77). Up to 70.5% of patients with autoimmune HF had the preserved EF phenotype (78).

Interestingly, RA patients on biologics were more likely to recover EF (78), but those with autoimmune comorbidities had a 3x higher risk of mortality or hospitalization (79). The underlying inflammatory drivers differ: RA involves myeloid–T and T–B cell inflammation (80, 81), SLE and SSc involve B-cell-mediated pathways (82–85).

Thus, therapies should reflect this heterogeneity: IL-6 blockers show promise in ischemic damage (86), T cell costimulation blockade prevents age-related dysfunction (87), and B-cell depletion has improved dilated cardiomyopathy (88).

This highlights the need for a personalized, inflammation-targeted approach in preventing and managing HFpEF in autoimmune disease.

Evidence and perspectives

Controlling inflammation has emerged as a crucial strategy for improving diastolic dysfunction and potentially preventing HFpEF. Animal studies have offered compelling evidence supporting this approach. In a model of HFpEF using DAHL/SS salt-sensitive hypertensive rats, the administration of colchicine significantly improved survival, reduced cardiac dysfunction, and diminished oxidative stress and inflammatory cell infiltrates (89). These findings suggest the potential efficacy of colchicine, with human trials expected to provide further clarification (90).

Among the most promising emerging therapies, sodium-glucose cotransporter 2 (SGLT2) inhibitors have demonstrated clinical benefits in HFpEF, particularly in patients with comorbid conditions such as type 2 diabetes and obesity. Results from large randomized trials, including EMPEROR-Preserved (91) and DELIVER (92), showed that treatment with empagliflozin or dapagliflozin significantly reduced the risk of heart failure hospitalization and cardiovascular death. These effects are thought to arise from improved myocardial energetics, decreased preload and afterload, and anti-inflammatory as well as antifibrotic properties. While data specifically addressing autoimmune populations are currently lacking, the potential of SGLT2 inhibitors to modulate endothelial dysfunction and low-grade systemic inflammation suggests they may also benefit patients with autoimmune-driven HFpEF. Nonetheless, clinicians should be cautious of adverse effects, including genital infections, volume depletion, and ketoacidosis, particularly in elderly or non-obese individuals (Figure 3). Further studies are needed to explore the safety and efficacy of these agents in this specific subgroup.

Plasma IL-6 has been a focal point of recent research, with its levels showing a strong predictive value for HFpEF but not for HFrEF in the PREVEND cohort—a prospective study of 961 participants. This association persisted even after adjusting for key risk factors, suggesting IL-6 as a potential target for novel therapeutic strategies (93). Supporting this, IL-6 was found to be an independent predictor of all-cause mortality in hospitalized HFpEF patients, even after accounting for B-type natriuretic peptide (BNP) levels (94). Furthermore, tocilizumab, an IL-6

TABLE 2 Clinical evidence of HFpEF in autoimmune diseases.

Study	Disease	Key findings	Notable observations
Davis et al. (69)	RA	35% 1-year mortality after HF vs. 19% in controls	High mortality burden in RA-related HF
Huang et al. (70)	RA	8.2% developed HF over 10.7 years	Long-term CV risk in RA
Mantel et al. (71)	RA	2.5% HF incidence over 5 years	Modest but relevant incidence
Myasoedova et al. (72)	RA	Stable HF prevalence over 30 years	Persistent CV burden despite treatment evolution
Ahlers et al. (73)	RA	HF incidence: 4.87 vs. 3.96 per 1,000 person-years	Higher chronic inflammatory load linked to HF
Athero-APS Study (74)	APS/SLE	HFpEF prevalence: 6.3% (carriers) to 27.8% (SLE-APS)	Severity-dependent CV risk escalation
Prasada et al. (75)	SSc, SLE, RA	HR for HF: 7.26 (SSc), 3.15 (SLE), 1.39 (RA)	Significant HF risk across diseases
Nomigolzar et al. (76)	SLE	0.61% of 10 M HF cases had SLE; higher in-hospital mortality	Increased pericardial complications
Oliveira et al. (77)	SSc	27% met HFpEF criteria	Age, AF, and ILD were key predictors
Rivera et al. (78)	ACIDs	70.5% with HF had HFpEF	Higher rate than general population
Tada et al. (79)	ACIDs	3x increased risk of death/hospitalization in HFpEF with ACID	Poorer prognosis vs. non-ACID patients

RA, rheumatoid arthritis; APS/SLE, antiphospholipid syndrome/systemic lupus erythematosus; SSc, systemic sclerosis; ACIDs, autoimmune and chronic inflammatory diseases; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; AF, atrial fibrillation; ILD, interstitial lung disease.

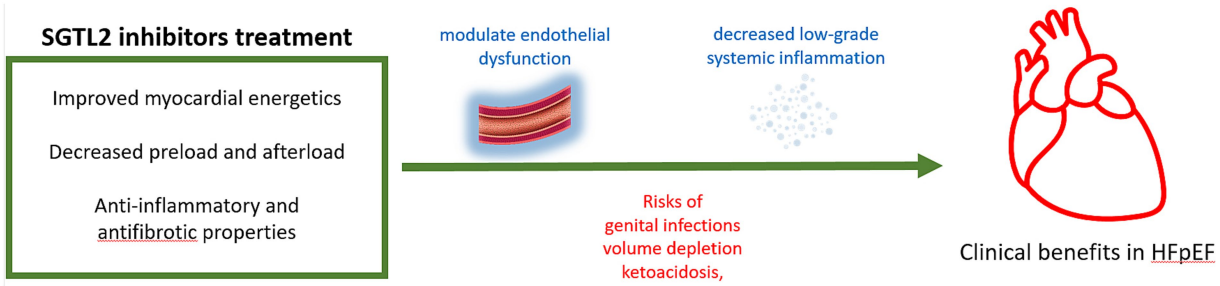

FIGURE 3
SGLT2 inhibitors have demonstrated clinical benefits in HFpEF, reducing the risk of heart failure hospitalization and cardiovascular death by modulating endothelial dysfunction and low-grade systemic inflammation, leading to improve myocardial energetics, decrease preload and afterload, and thought anti-inflammatory and antifibrotic properties. Nonetheless, adverse effects include genital infections, volume depletion, and ketoacidosis. SGLT2, sodium-glucose cotransporter 2; HFpEF, heart failure with preserved ejection fraction.

receptor antagonist, demonstrated improvements in left ventricular ejection fraction in rheumatoid arthritis patients without overt cardiac symptoms, reinforcing the potential benefits of targeting IL-6 (95).

However, the results of targeting inflammation in HFpEF have been mixed. Anakinra, an IL-1 receptor antagonist targeting IL1α/β, failed to improve cardiac function in obese HFpEF patients, despite successfully lowering CRP and NT-proBNP levels (96). Similarly, the CANTOS trial, which investigated canakinumab (an anti-IL1β therapy), found that higher IL-6 levels 3 months post-initiation were associated with a substantial increase in major adverse cardiovascular events (MACE) and all-cause mortality (97), complicating the role of IL-1β inhibition in this context.

The link between inflammation and NT-proBNP levels provides additional insight. Among participants in the MESA study, IL-6 levels were significantly correlated with NT-proBNP levels, although it remains unclear whether these increases directly reflect the risk of incident HFpEF (98).

Of particular interest is the emerging evidence regarding IL-17. A preliminary study indicated that secukinumab, an IL-17A inhibitor, improved inflammation and diastolic dysfunction, which was present in nearly 39% of patients (99). If confirmed, this finding is especially significant given the central role of IL-17 in autoimmune inflammatory diseases (100) and its established involvement in inducing ventricular arrhythmias in ischemic heart failure (101). In addition, both IL-17 and IL-6 were identified as independent predictors of DD progression in patients with normal left ventricular ejection fraction who underwent invasive hemodynamic assessment (102).

Conclusions and research agenda

Compelling evidence underscores the pivotal role of inflammation in the development of HFpEF. Endothelial dysfunction emerges as a critical early biomarker, signaling the onset of microvascular damage that can progress to diastolic dysfunction and ultimately HFpEF. Despite these insights, there is a notable absence of clinical trials focused on identifying the optimal diagnostic approach for early detection of DD and stratifying patients for targeted therapeutic protocols based on the type and intensity of underlying inflammation.

No long-term studies have yet evaluated whether tailored treatments can reduce HFpEF incidence in patients with autoimmune chronic inflammatory diseases such as RA, SLE, or SSc. Additionally,

TABLE 3 H2FPEF score to evaluate the possible presence of HFpEF in patients with symptomatic dyspnea.

Clinical variables	Points
Weight (BMI > 30)	2
Hypertension (antihypertensive medications)	1
Atrial fibrillation (history or presence)	3
Pulmonary hypertension (RVSP at rest >35 mmHg)	1
Age (age >60 yrs)	1
Filling pressure (Rest E/e' > 9)	1

Score 0–1	Score 2–5	Score 6–9
HFpEF ruled out	HFpEF possible: assess rest/ stress RHC or Echo stress	Very likely HFpEF

BMI, body mass index; RVSP, right ventricle systolic pressure; E/e', ratio of early diastolic mitral inflow blood velocity to mitral annular tissue velocity; RHC, right heart catheterization.

the field lacks consensus on key diagnostic thresholds, such as the cutoff values for assessing DD or levels of natriuretic peptides (e.g., NT-proBNP) indicative of imminent HFpEF (103). Research should prioritize defining whether NT-proBNP levels warrant routine annual evaluation, particularly in older patients. The importance of early biomarker evaluation is further highlighted by data from the U.S. National Inpatient Sample Database (2016–2020), which showed that SLE patients hospitalized with acute decompensated heart failure—whether HFpEF or HFrEF—had a mean age of 61 years, compared to 72 years for non-SLE patients. SLE patients also exhibited higher in-hospital mortality rates, emphasizing the need for timely identification of predictive biomarkers to guide early interventions (104).

This approach gains urgency in the context of ACIDs coexisting with metabolic comorbidities such as type 2 diabetes or obesity, particularly in aging populations, where the cumulative risk of HF increases significantly (103). These scenarios reflect the additive impact of metabolic dysfunction and chronic inflammation on cardiac damage. Addressing this, a cardio-immuno-rheumatologic framework should be integrated into clinical practice (105, 106), ensuring that patients with persistent active inflammation are systematically monitored for HFpEF risk.

For diagnostic precision, the H2FPEF score—a composite tool combining clinical and echocardiographic parameters—offers a valuable approach. This scoring system can predict HFpEF with up to 95% probability when the score exceeds 5/9 (Table 3). Implementing such algorithms could revolutionize screening and management strategies in ACIDs, ensuring timely intervention for patients at elevated cardiovascular risk.

Future research must focus on:

1. Longitudinal studies evaluating the impact of targeted anti-inflammatory therapies on HFpEF incidence across RA, SLE, and SSc.
2. Establishing evidence-based thresholds for biomarkers like NT-proBNP to guide routine screening.
3. Developing and validating diagnostic algorithms that integrate inflammatory markers, clinical parameters, and imaging data to improve early identification and risk stratification.

By addressing these gaps, we can move closer to a personalized, proactive approach in preventing HFpEF, particularly in high-risk populations.

Finally, considering the heterogeneity of the available studies, particularly regarding HFpEF definitions, patient populations, and outcome measures, as well as the scarcity of randomized controlled trials in autoimmune settings, our conclusions should be interpreted with caution. These limitations further underscore the urgent need for disease-specific, prospective investigations.

Author contributions

EG: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing. DB: Data curation, Resources, Visualization, Writing – original draft, Writing – review & editing. SP: Data curation, Resources, Visualization, Writing – original draft, Writing – review & editing. JC: Data curation, Validation, Writing– review & editing. GF: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The authors declare that no Gen AI was used in the creation of this manuscript.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2025.1557312/full#supplementary-material

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Glossary

HFpEF - Heart Failure with Preserved Ejection Fraction

HFrEF - Heart Failure with Reduced Ejection Fraction

LVEF - Left Ventricular Ejection Fraction

LV - Left Ventricle

DD - Diastolic Dysfunction

ED - Endothelial Dysfunction

IL-6 - Interleukin-6

CRP - C-reactive Protein

RA - Rheumatoid Arthritis

SLE - Systemic Lupus Erythematosus

SSc - Systemic Sclerosis

APS - Anti-Phospholipid Syndrome

FMD - Flow-Mediated Dilation

ECM - Extracellular Matrix

TGF-β - Transforming Growth Factor Beta

NF-κB - Nuclear Factor Kappa-light-chain-enhancer of activated B cells

AP-1 - Activator Protein 1

ROS - Reactive Oxygen Species

eNOS - Endothelial Nitric Oxide Synthase

NO - Nitric Oxide

α-SMA - Alpha Smooth Muscle Actin

CCR2 - C-C Chemokine Receptor Type 2

STAT3 - Signal Transducer and Activator of Transcription 3

AMI - Acute Myocardial Infarction

DM2 - Type 2 Diabetes Mellitus

hsCRP - High Sensitivity C-Reactive Protein

MACE - Major Adverse Cardiovascular Events

BNP - B-type Natriuretic Peptide

NT-proBNP - N-terminal pro B-type Natriuretic Peptide

TNF - Tumor Necrosis Factor

OSM - Oncostatin M

BITE - Bispecific T-cell Engager

FDR - False Discovery Rate

WHS - Women's Health Study

PMR - Polymyalgia Rheumatica

UC - Ulcerative Colitis

IBD - Inflammatory Bowel Disease

CFR - Coronary Flow Reserve

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