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REVIEW

# Rheumatoid Factor Beyond Rheumatoid Arthritis: A Potential Marker of Cardiometabolic and Hepatic Risk

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**Abstract:** Rheumatoid factor (RF), which is an autoantibody that is predominantly targeted at the Fc region in IgG, has been a key point of diagnosis and prognostication of rheumatoid arthritis (RA). There is, however, an emergent body of evidence that RF positivity, including in persons with preexisting autoimmune disease as well as asymptomatic seropositive persons, can indicate more global immune dysregulation with consequences of cardiometabolic and hepatic health. RF is involved in the development of circulating immune complexes, which increases inflammation through complement activation, Fc receptor interaction and cytokine release. These routes are becoming well-known mechanistic causes of cardiometabolic diseases, such as atherosclerosis, insulin resistance, metabolic syndrome, and heart failure. Similarly, the immune-complex deposition and chronic inflammatory signaling also play a role in hepatic injury, metabolic dysfunction-associated fatty liver disease (MAFLD) and fibrosis. The present review summarizes the existing information about the role of RF as a predictor and a possible mediator of cardiometabolic and hepatic dysfunction in chronic diseases. We searched scientific databases for epidemiologic relationships, possible biological pathways, and clinical implications for risk stratification and integrated care. RF could serve as an accessible biomarker of systemic inflammatory risk, complementing its traditional role in rheumatology and, within the framework of precision medicine, helping to guide early detection and preventive strategies across diverse clinical populations.

**Keywords:** rheumatoid factor, cardiometabolic disease, atherosclerosis, hepatic injury, immune complexes

## Introduction

Rheumatoid factor (RF) is one of the first autoantibodies to be discovered in the field of clinical immunology and has been one of the most common serologic markers used in medical practice. Historically, the first time that RF was recognized in the context of rheumatoid arthritis (RA) became established as a traditional diagnostic and prognostic marker, as it was associated with the severity of the disease, extra-articular manifestations and also with immune complex formation.[1,2] Classically, RF denotes a group of autoantibodies against the Fc portion of immunoglobulin G (IgG), a number of isotypes or subtypes of which have been recognised, such as IgM-RF, IgA-RF and IgG-RF.[1] Among these, IgM-RF is the most commonly measured in a clinic and has long been the type of laboratory subtype in conventional laboratories used in the evaluation of RA, whereas IgA-RF and IgG-RF have also been linked to a more aggressive or systemic disease phenotype.[1] Although traditionally associated with RA, RF is not specific to RA and has also been found in other autoimmune conditions such as Sjogren's syndrome, systemic lupus erythematosus, mixed connective tissue disease and systemic sclerosis, as well as chronic infections and inflammatory diseases.[3] Outside rheumatologic disease, RF has been seen in a spectrum of chronic inflammatory, infectious and metabolic disorders. Its finding in around 5–10% of the general population highlights further that the presence of RF may be indicative of a broader humoral immune activation in opposition to RA.[4] This widespread distribution contradicts the opinion of RF as solely a marker

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linked to RA and may rather point to the interpretation of RF as a potential biomarker of systemic immuno-dysregulation. Over the past decades, therefore, the clinical meaning of RF has broadened from a diagnostic tool in rheumatology to be an even broader lens through which systemic pathophysiologic processes may be examined.[5] Mechanistically, RF is directly involved in the formation of immune complexes as it is able to bind the Fc region of IgG antigen, forming massive complication binding complexes. These immune complexes, along with this latter ability of RF to engage Fc receptors, amplify proinflammatory cytokine release, endothelial activation, and complement-mediated tissue injury.[6,] Importantly, the mechanisms are not limited to synovial tissues, but may also affect vascular, metabolic, and hepatic mechanisms of chronic disease development. Literature has pointed to low-grade, chronic inflammation as a driving factor in both cardiometabolic disease and metabolic dysfunction-associated fatty liver disease.[7] In this context, RF can represent a measurable signature of latent immune disturbance going before or promoting dysfunction of end-organ. Elevation of RF levels has been linked to increased inflammatory burden, dyslipidemia, endothelial dysfunction and insulin resistance, which directly cause or contribute to atherosclerosis, metabolic syndrome, and hepatic injury.[8] The biological plausibility of RF as both a mechanistic and predictive marker is further supported by the fact that RF is involved in the complement activation mechanism, macrophage polarization, oxidative stress generation, as well as its propagation of chronic cytokine signal.[9] These associations suggest that the utility of RF may be far reaching beyond the traditional role it continues to play in rheumatology. It may also be an indicator of cardiometabolic and hepatic risk, especially in individuals with chronic inflammatory disorders, metabolic abnormalities or subclinical autoimmune activation.[10]

Despite this emerging view, RF continues to be under-utilized as a biomarker in cardiometabolic and hepatologist practice. Many clinicians continue to interpret RF mostly within the framework of autoimmune evaluation without any consideration for its potential relevance for broader systemic performance risk stratification.[11] This review gives a synthesis of the current evidence of RF as a prognostic marker of cardiometabolic and hepatic risk in chronic disease. It incorporates information on mechanistic immunologic concepts, epidemiologic patterns based on population-based studies and clinical implications for prevention and treatment of diseases at an early stage. By taking a systemic approach to the consideration of RF, the purpose of this review is to underscore the potential role of RF in improving the prediction of risk, in the reasoning behind diagnoses, and in therapeutic decision-making. Continued research into the biological and clinical implications of RF may ultimately enhance the value of RF as an accessible biomarker of association between immune dysregulation and metabolic and hepatic pathology.

# Methodology

## Objectives of the Review

This comprehensive review aims to:

1. Critically review current epidemiological data on rheumatoid factor positivity in cardiometabolic diseases, atherosclerosis, metabolic syndrome, insulin resistance, cardiovascular disease, hepatic diseases, MAFLD, and fibrosis.
2. Concisely describe and combine mechanistic pathways by which RF and RF-bearing immune complexes both play a role in systemic inflammation, endothelial dysfunction, metabolic dysregulation, and hepatic injury.
3. Determine the predictive and prognostic capacity of RF in addition to its classical application in rheumatoid arthritis, as a biomarker of cardiometabolic and hepatic risk in chronic inflammatory and metabolic illnesses.
4. Discover how RF measurements can be used in clinical practice to identify and manage risks, detect conditions at an earlier stage, and incorporate risk management as part of the precision and preventive medicine approach.

### Inclusion Criteria

Studies were considered eligible for inclusion in this review if they met one or more of the following criteria:

Original research articles, systematic reviews, meta-analyses, and high-quality narrative reviews.

Human studies involving adults (≥18 years).

Studies reporting associations between RF (qualitative or quantitative) and cardiometabolic outcomes (eg., cardiovascular disease, atherosclerosis, diabetes, metabolic syndrome) and/or hepatic outcomes (eg., MAFLD, liver inflammation, fibrosis).

Studies conducted in populations with rheumatoid arthritis, other autoimmune or chronic inflammatory diseases, metabolic disorders, or asymptomatic RF-positive individuals.

Articles published in peer-reviewed journals and written in English.

Studies published between January 2010 and April 2025.

### Exclusion Criteria

The following were excluded from the review:

Case reports, editorials, conference abstracts, letters to the editor, and expert opinions without primary data.

Studies are limited solely to the diagnostic performance of RF in rheumatoid arthritis without evaluation of systemic, cardiometabolic, or hepatic outcomes.

Animal or in vitro studies not directly linked to clinical or translational relevance.

Articles lacking sufficient methodological detail or outcome data relevant to cardiometabolic or hepatic risk.

Studies published outside the selected range.

### Information Sources and Search Strategy

#### Information Sources

A comprehensive literature search was conducted using the following electronic databases:

PubMed/MEDLINE, Scopus, Web of Science, Embase and Google Scholar

To ensure completeness, reference lists of eligible articles and relevant review papers were manually screened for additional studies. Grey literature was minimised, and only peer-reviewed journal articles were considered. The search covered publications from January 2010 to April 2025, in accordance with the predefined inclusion criteria.

#### Search Strategy

The search strategy combined Medical Subject Headings (MeSH) terms and free-text keywords related to rheumatoid factor, cardiometabolic disease, and hepatic outcomes. Boolean operators (AND, OR) were used to refine the search.

## Epidemiologic Data on RF as the Cause of Cardiometabolic Disease

A body of epidemiologic studies in the last two decades is increasingly pointing to the rheumatoid factor as a clinically significant predictor of cardiometabolic disease, even though it has long been traditionally considered a marker of RA diagnosis.[1] Massive cohorts of the population, community-based ageing research, insurance, and modern biobanks all continue to indicate that RF positivity is associated with increased cardiovascular and metabolic risk in RA and non-RA groups.[12] These results have redefined the clinical paradigm of RF. Instead of being a disease-specific autoantibody, RF seems to represent a more limited inflammatory profile of chronic immune-triggered and immune-complex-mediated vascular damage and metabolic imbalances.[13] Notably, these relationships remain when these published risk factors are controlled for age, sex, body mass index, smoking, hypertension, and lipid abnormalities; therefore, RF could be a free, inflammatory biomarker that reduces the overall cardiometabolic load.[14] The increasing popularity of RF as a population-level risk marker can also be explained by evidence that RF titers predict subclinical atherosclerosis, endothelial dysfunction, and population-level biomarkers of systemic inflammatory processes, including C-reactive protein (CRP) and interleukin-6 (IL-6), which, in turn, cause cardiometabolic pathology.[15] Although RF has not yet been incorporated into formal cardiovascular risk scoring systems, converging epidemiologic evidence suggests it may be useful for improving risk stratification in specific patient groups, especially those with chronic inflammatory or metabolic comorbidities. Figure 1 illustrates this point.

### RF and Atherosclerotic Cardiovascular Disease (ASCVD)

There is substantial evidence of RF positivity and its association with a higher incidence of atherosclerotic cardiovascular disease.[16] In several longitudinal community samples, the risk of myocardial infarction, ischemic stroke, and coronary artery disease was much elevated in persons with testable RF, despite no documented RA.[17] The presence of high RF titers is associated with a dose-related increase in the incidence of atherosclerotic atherosclerotic cardiovascular disease, suggesting that the extent of autoantibody production reflects underlying inflammatory load or active immune complexes.[18] These associations were strong even after considerable modification for diabetes status, high blood pressure, lipids, smoking, exercise, socioeconomic factors,

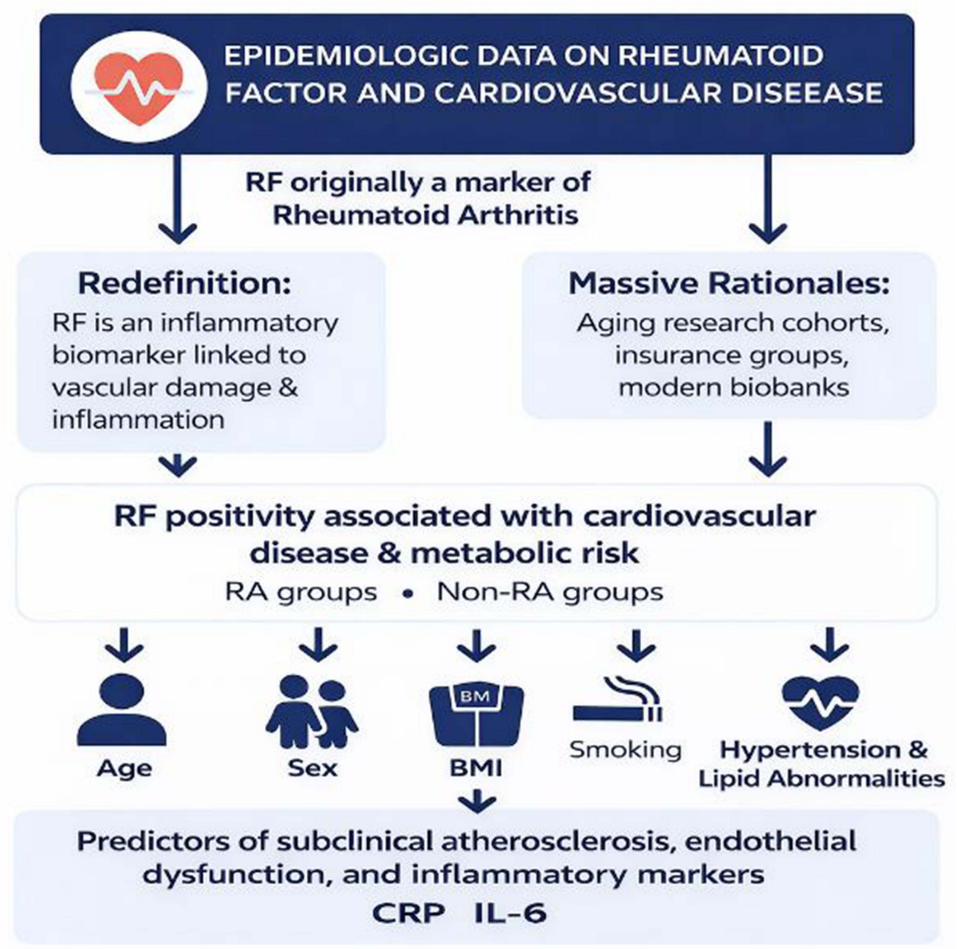


**Figure 1** Rheumatoid Factor as an Emerging Biomarker Linking Inflammation to Cardiovascular and Metabolic Risk: It summarizes epidemiologic evidence linking rheumatoid factor (RF), originally a marker of rheumatoid arthritis, to cardiovascular disease and metabolic risk. It highlights the redefinition of RF as an inflammatory biomarker associated with vascular damage across rheumatoid arthritis (RA) and non-RA populations, influenced by traditional risk factors (age, sex, BMI, smoking, hypertension, lipid abnormalities) and linked to subclinical atherosclerosis, endothelial dysfunction, and inflammatory markers such as c-reactive protein (CRP) and Interleukin-6 (IL-6).

and body composition, a fact that RF adds extra prognostic details to conventional cardiometabolic risk programs.[19,20] It is even more dramatic when it comes to the relationship among RA patients. Seropositive RA is always found to have a higher ASCVD risk than seronegative RA. High-titer RF patients demonstrate a faster rate of carotid intima-media thickness increase and coronary artery calcification earlier and more often with unstable or vulnerable atherosclerotic plaques.[21] Such an increased susceptibility indicates the interaction of synovial chronic inflammation, the presence of immune complexes in the blood, complement activation, and endothelial cell injury throughout the body.[19] Remarkably, the increased cardiovascular risk may be a preclinical event for the joint disease, and preclinical seropositivity may even be an early inflammatory condition that could initiate vascular pathology prior to the clinical emergence of rheumatic symptoms.[22]

## RF and Metabolic Dysregulation (Obesity, Diabetes, and Metabolic Syndrome)

In addition to vascular disease, RF has been epidemiologically associated with critical metabolic conditions such as obesity, insulin resistance, type 2 diabetes, and metabolic syndrome.[23] According to some population surveys, RF is more prevalent in persons with central obesity, high fasting glucose, or features of metabolic syndrome, indicating that RF can be associated with inflammation mediated by adipose tissue.[24] Adipose tissue also secretes pro-inflammatory cytokines, including TNF-α and IL-6, which induce B-cell activity and the production of immunoglobulins, which might stimulate RF production.[25] On the other hand, persistent immune stimulation by RFs can, in itself, malfunction insulin signalling

through macrophage stimulation and metabolic interference by cytokines.[26] Various cohort studies indicate a higher frequency of incident type 2 diabetes among RF-positive individuals of up to 4.75, despite eliminating those with RA and accounting for body mass index and glucose-linked biomarkers. This observation demonstrates a possible two-way relationship, that is, metabolic dysfunction promotes systemic inflammation and RF-related immune complexes enhance cytokine production, oxidative stress, and endothelial activation, all of which impair insulin sensitivity.[27] RF positivity has also been linked to increased levels of circulating CRP, fibrinogen, and IL-6, which combine in a synergistic network to enhance metabolic risk.[28]

### RF as Multisystem and Multisite Marker of Chronic Inflammation and Multisystem Risk

Collectively, epidemiologic evidence places RF in a vantage as a composite biomarker of multisystem chronic, low-grade systemic inflammation.[29] RF records immunologic processes that are not limited to autoimmunity, such as immune-complex deposition, complement activation, endothelial dysfunction, and cytokine-mediated metabolic impairment.[30] The connections between it and ASCVD and metabolic disorders are alike in various populations, age groups, and study designs. These results indicate that RF can be considered as a risk-increasing factor, especially when other inflammatory or metabolic comorbidities are present, and that further longitudinal research should help clarify the pathology and efficacy of RF as a predictive variable in clinical risk assessment tools.[9]

### RF and Heart Failure

Epidemiologic investigations also suggest a strong association between RF positivity and increased risk of heart failure, which contributes a significant aspect of cardiometabolic consequences of long-term autoantibody production.[30,31] Heart failure with preserved ejection fraction (HFpEF) is reported to have the greatest association and is a widely known phenotype that is inflammation-mediated and gaining more prevalence with age.[32] HFpEF is defined by diastolic dysfunction, dysfunctional ventricular relaxation, myocardial fibrosis and systemic vascular hardening, and all these processes may be aggravated by the persistent immune activation.[33] RF-positive individuals in population-based cohorts exhibit greater diastolic dysfunction, left ventricular stiffness, and minor reductions in myocardial strain parameters.[34] Even when there is no preexisting coronary artery disease, these abnormalities appear, and the mechanisms they involve are different from traditional ischemic injury. Endothelial dysfunction via immune complexes is probably key. The circulating RF-IgG immune complexes may activate complement pathways, elevate vascular permeability, and disrupt nitric oxide bioavailability.[35] This eventually leads to microvascular rarefaction and myocardial hypoperfusion established pathological characteristics of HFpEF. The correlation is even stronger among patients with rheumatoid arthritis. RF-positive RA is linked to earlier development of heart failure, more pronounced symptoms, higher hospitalization and worse long-term cardiac outcomes than seronegative RA.[36] These results represent the burden of systemic inflammation, persistent cytokine exposure and accelerated myocardial remodelling. Interestingly, certain researches denote that high RF titers are the most significant predictors of the development of heart failure several years preceding the clinical cardiac events or the emergence of cardiac symptoms, which is corroborated by its excellent preclinical risk prediction.[37]

### RF as Predictor in Non-Autoimmune Populations

One of the most important findings of modern epidemiologic studies is that RF is still predictive enough in people who do not already have any autoimmune disease or other recognizable inflammatory symptoms.[37] Consistent results of large community cohort studies such as aging studies and cardiovascular risk surveys indicate that RF-positive but otherwise healthy adults are at greater risk in the long-term metabolic syndrome, diabetes mellitus type 2, ASCVD events, and cardiovascular mortality.[38] These correlations remain even after age, body mass index, smoking, and lipid profiles have been considered, pointing to the fact that RF represents a sub-inflammatory environment that is not reflected in the conventional biomarkers. The predictive ability of RF in non-autoimmune cohorts informs the idea of silent seropositivity, in which low-grade immune activation in the chrono seems to drive vascular pathology dysregulation and metabolic pathology and cardiac remodelling in the years preceding the onset of a clinical illness.[38,39] The RF can thus be a convenient, and low-cost risk stratification instrument to target groups of individuals who would otherwise not have been picked up in conventional screening methods – especially in the elderly, obese or those with slightly elevated inflammatory indices.

## Pathophysiological Processes That Strictly Interconnect RF and Cardiometabolic Risk

Biological pathways by which the RF causes cardiometabolic dysfunction go far beyond its conventional contribution to autoimmune joint disease.[40] RF is involved in the direct production and maintenance of an internal environment rich in proinflammatory conditions and proatherogenic conditions via the formation of immune-complexes, amplification of cytokines, endothelial damage as well as impaired lipid metabolism.[41] These mechanisms lead to the formation and evolution of cardiovascular and metabolic disease, even in those who do not have clinically active autoimmune disease. It is crucial to understand these mechanisms to value RF as a systemic biomarker which will capture more profound pathophysiological perturbations.

### Chronic Low Grade Inflammation

Most of the significant cardiometabolic diseases, such as atherosclerosis, type 2 diabetes mellitus, obesity, hypertension and metabolic syndrome, are based on chronic, subclinical inflammation.[42] The active contributors to this inflammatory milieu are rheumatoid factor created through its ability to form large IgM-IgG immune complexes.[43] When these immune complexes enter the circulation, they will easily interact with Fcg receptors in the macrophages, dendritic cells, and endothelial cells. They also strongly stimulate the classical pathway of complement with downstream products of anaphylatoxins C3a and C5a-molecules that enhance leukocytes activation and cytokine release.[44] This preconditions a vicious circle of inflammation. One of the characteristic features of RF-driven inflammation is the enhancement of the cytokine release of tumor necrosis factor-alpha, interleukin-1b and interleukin-6. These cytokines interfere with the metabolic homeostasis in a couple of ways.[45,46] TNF-a disrupts the insulin receptor substrate (IRS)-mediated signaling in liver and skeletal muscle, limiting the glucose uptake and maximizing the hepatic gluconeogenesis.[47] B-cell dysfunction is aided by IL-1b which reduces insulin production with time, and hepatic very-low-density lipoprotein (VLDL) production is facilitated by IL-6 which also causes hypertriglyceridemia.[48] The infiltration and polarization of macrophages to a proinflammatory M1-like phenotype in adipose tissue is mediated by chronic cytokine signaling.[49] These macrophages release other cytokines and reactive oxygen species (ROS), which increase lipolysis and free the fatty acids into the circulation.[50] High concentrations of free fatty acids increase the insulin resistance in the liver and promote the synthesis of hepatic triglyceride and VLDL.[51] In the meantime, oxidative stress mediated by the immune activation and metabolic dysregulation - further worsens the endothelial functioning and aggravates insulin sensitivity.[52] The combination of damaged insulin signaling, chronic exposure to cytokines, inflammation of the adipose tissue, and oxidative stress over time provides a metabolic environment conducive to hypertension, dyslipidemia, and diabetes.[53] RF therefore does not simply serve as an indicator of autoimmune activation but rather serves as an active contributor to the idea of low-grade chronic inflammation which primates individuals to the entire repertoire of cardiometabolic disease.[54]

### Dyslipidemia and Abnormal Lipid Processing

RF-mediated inflammation is a serious interference with lipid homeostasis in such a way that it increases cardiovascular risk to a significant degree. The decreased number and the functional capacity of high-density lipoprotein (HDL) is one of the earliest metabolic effects of chronic inflammation.[55] Inflammatory cytokines and oxidative stress neutralize the HDL role to facilitate reverse cholesterol transport, and this reduces its ability to transport cholesterol in peripheral tissues and arterial macrophages to the liver.[56] HDL also loses its dysfunctional-less antioxidant, anti-inflammatory, and endothelium protecting ability.[54] Simultaneously, the oxidative conditions related to RF favor native LDL transformation into oxidized LDL (oxLDL) which is one of the most atherogenic lipoprotein varieties.[57] OxLDL is easily absorbed by macrophage through scavenger receptors, which hastens the process of foam-cells, growth of plaque and expansion of the necrotic core.[58] Immune complexes containing RF can also bind lipoproteins directly, which further alters the atherogenicity of the lipoproteins.[59]

Liver is the key organ in charge of lipid metabolism in the body, thereby being greatly affected. A persistent inflammatory signaling increases the secretion of VLDL and retards the clearance of triglyceride-rich lipoproteins.[60] Remnant lipoprotein-highly proatherogenic intermediate-induced accumulation can be added as a causal factor of vulnerability to the plaque and increased ASCVD risk.[61] Together, these mechanisms alter the lipid profile to a further distinctive inflammatory dyslipidemia with low levels of HDL, high levels of remnant particles, high levels of triglycerides, and high LDL oxidation.[62] This phenomenon is closely predictive of cardiovascular events and is commonly prominent in RF-positive individuals, even without their evident autoimmune disease.

### Endothelial Activation and Vascular Remodelling

Mediator of the interface between RF-related immune activity and vascular pathology relies to a large extent on the activation of the endothelial. The RF leads to the development of immune complexes in the presence of RF that easily adhere on or interact with endothelial surfaces, causing intracellular pathways, which result in upregulation of adhesion molecules, including vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1).[63] These molecules help to adhere and migrate into the vascular intima of the monocytes and T cells, which in turn trigger the initial stages of atherogenesis. Increased amounts of reactive oxygen species (ROS) are also produced by endothelial cells subjected to chronic inflammation and actin stimulation by immune-complexes.[64] Increasing ROS excess lowers the bioavailability of nitric oxide (NO) and hinders vasodilation, facilitates vasoconstriction, and raises the vascular tone.[62] Structural alterations such as intimal thickening, degradation of elastic fibers and greater arterial rigidity are the result of sustained endothelial dysfunction over years.[65]

Microvascular implications are also very important. Prolonged activation causes microvascular rarefaction – a decrease in capillary density which impairs tissue perfusion and causes the pathogenesis of heart failure with preserved ejection fraction (HFpEF), renal dysfunction and abnormal skeletal muscle metabolism.[66] The net outcome of this activation of endothelium and structural vascular is the creation of a primed vasculature in terms of plaque development, progression and instability. RF-positive people consequently tend to have a lower age of onset of and more rapid development of vascular dysfunction than RF-negative individuals.[67]

### Prothrombotic Tendencies

Inflammation by RF also facilitates atherogenesis, increases thrombogenesis and a hypercoagulable state which increases the risk of acute cardiovascular events.[68] High levels of fibrinogen-typical of RF-positive individuals-play a role in raising the viscosity of the blood and the clotting of the blood. One of the main fibrinolysis inhibitors, plasminogen activator inhibitor-1 (PAI-1) is also increased in chronic inflammatory conditions and prevents the body from dissolving the formed clots.[69] The platelet aggregation can be stimulated directly by the circulating immune complexes, stimulated by platelet aggregation, or indirectly by endothelial cells that have been stimulated by endogenously generated tissue factor and other procoagulant molecules.[70] Collectively, these processes increase exposure to myocardial infarction, ischemic stroke and venous thromboembolism.[71] This prothrombotic environment in those who already have the atherosclerotic plaque predisposes them to the occurrence of plaque rupture and acute ischemic events.[72] Therefore, RF is not only one of the factors of vascular disease development but also one of the most harmful complications.

## RF as a Hepatic Injury and Metabolic Liver Disease Marker

Whereas rheumatoid factor is believed to be a risk factor in extrahepatic autoimmune diseases, recent studies have shown RF can also be used as a marker into – and possibly a mediator – of hepatic damage and metabolic liver disease.[2] The liver is where immune regulation, the removal of toxins, lipids, and the maintenance of glucose levels can be found. It is thus very sensitive of systemic inflammation and circulatory immune complexes.[73] RF positivity is associated with greater liver enzyme elevations, a greater prevalence of nonalcoholic fatty liver disease and more severe fibrosis in subjects at risk of metabolic disease.[74] RF-induced chronic inflammation is a cause of stress in hepatocytes through mitochondrial dysfunction, insulin signaling disruption and hepatic lipid accumulation.[75] RF–RF immune complexes can also be deposited in hepatic tissue, and complement activation is locally activated and fibrotic remodeling promoted. In turn, RF is already being considered to be more than a rheumatologic biomarker: in metabolic contexts, it can be indicative of more profound disruptions in the state of hepatic health, a surrogate endpoint of the fibrosis process, systemic metabolic imbalance, and an increased predisposition to cardiovascular disease.[8]

### RF and Nonalcoholic Fatty Liver Disease (NAFLD)

Now increasingly referred to as metabolic dysfunction-associated steatotic liver disease (MASLD), nonalcoholic fatty liver disease is a continuum of simple steatosis to nonalcoholic steatohepatitis (NASH), fibrosis, cirrhosis and hepatocellular carcinoma. It has an insulin-resistance-induced, oxidative-stress, lipotoxicity-induced, mitochondrial-dysfunction, and chronic-low-grade-inflammation-factor pathogenesis, which largely overlap the biology of RF.[76,77]

## RF Linked-Inflammation Causes NAFLD in a Number of Mechanistic Ways

### *Stimulation of Oxidative Stress in the Hepatocellular*

RF-caused immune activation increases systemic reactive oxygen species (ROS) and inflammatory cytokine. These molecules get to the liver via portal and systemic circulation, overloading the mitochondrial antioxidant processes and inducing hepatocyte damage.[78,79]

### *Activation of the Kupffer Cell and Cytokines Amplification*

Strong activation of Kupffer cells is caused by complement activation that results because of RF-IgG immune complexes. The TNF-a, IL-1b and IL-6-key cytokines released by activated Kupffer cells are involved in the progression of benign steatosis to inflammatory NASH.[80]

### *Improvement of Metabolic Impairment*

RF-induced inflammation enhances insulin resistance to hepatic lipogenesis and antagonizes b-oxidation and deposition of toxic lipid intermediates. These cellular metabolic processes increase stress and fibrotic changes in cells.[81,82]

### *Metabolic Risk Factors Synergy*

Increasingly, clinical trials indicate that RF-positive persons have elevated NAFLD fibrosis scores, liver stiffness on elastography and metabolically induced cirrhosis.[83] RF positivity in non-RA populations is associated with worse metabolic phenotypes, such as high triglycerides, central obesity, and systemic inflammation – all contributors to NAFLD disease progressors.[74,84] Combined, these results imply that RF is not only the predictor of increased inflammatory burden but directly overlaps the pathophysiologic processes of NAFLD severity and progression.

## Immune-Complex Deposition and Chronic Stress of the Hepatic Tissue

The liver is involved in the primary role of clearance and filtration of circulating immune complexes including the large IgM-IgG complexes which characterize RF-positive conditions.[85] This function regulates immunologic balance under physiological conditions and prevents immune-mediated injury of peripheral tissues (Figure 2). However, in conditions of permanent increase in the production of immune complexes, as in persistent RF positivity, the hepatic reticuloendothelial system – in this case, especially of the Kupffer cells – is subjected to chronic immunologic load.[86] This

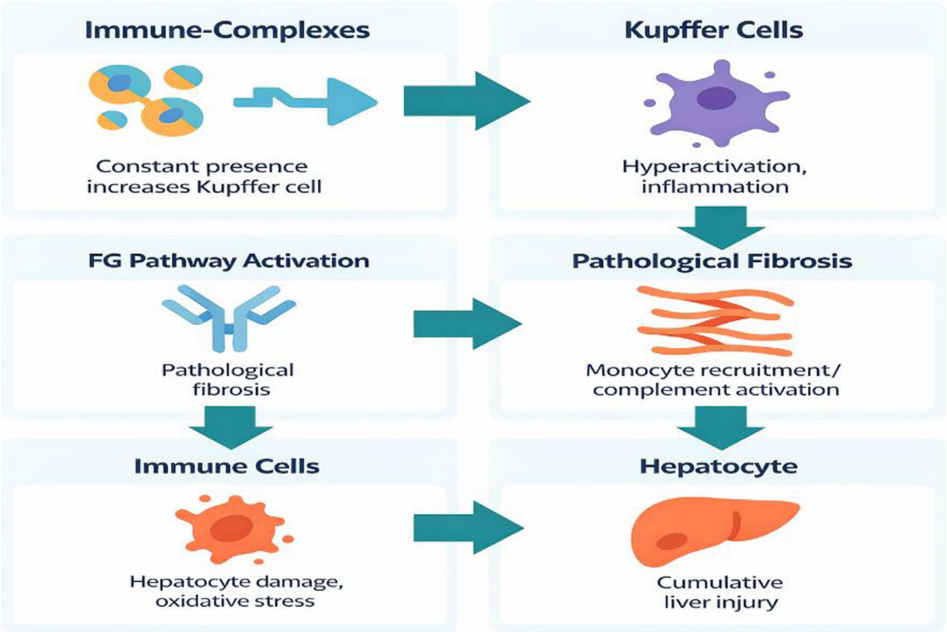


**Figure 2** Immune-Complex Deposition and Chronic Stress of the Hepatic Tissue: Figure depicts a proposed pathway linking immune complex persistence to progressive liver injury, beginning with Kupffer cell hyperactivation and sustained hepatic inflammation. Subsequent complement activation, monocyte recruitment, immune cell–mediated oxidative stress, and hepatocyte damage contribute to pathological fibrosis and cumulative liver injury.

eventually results in a typical pattern of chronic hepatic stress which could predispose them to progressive parenchymal injury, fibrotic remodeling and metabolic dysfunction.[87] One of them is dysregulation of the Kupffer cell activity. Constant absorption of immune complex may result in functional exhaustion, which decreases the ability of the liver to clear the circulating complexes effectively and permit their accumulation in the bloodstream.[88] Other people, on the other hand, find themselves in a state of chronic Kupffer cell hyperactivation whereby repeated stimulation of the Fc receptors leads to the continued release of pro-inflammatory, pro-fibrogenic and immunomodulatory cytokines.[89,90] This excessive activity disturbs hepatic immune homeostasis and facilitates an environment that supports chronic inflammation. Another important outcome is the activation of fibrogenic pathways. Hyperstimulated Kupffer cells release transforming growth factor (beta), tumor necrosis factor (alpha), and platelet-derived growth factor. These signaling molecules directly cause hepatic stellate cell differentiation of quiescent vitamin A – storing cell into proliferative, collagen-producing myofibroblasts.[91] Hepatic fibrosis is structurally based on the accumulation of extracellular matrix proteins that are generated by activated stellate cells and forms the basis of the transition of inflammatory injury to chronic architectural distortion.[92] Recruitment of CCR2-positive inflammatory monocytes into circulation is also facilitated further by immune-complex-mediated chemotactic signaling. Once in the liver, these monocytes develop into macrophages which enhance local inflammation and complement the fibrogenic process. Their prolonged existence increases the inflammatory environment and develops the feed-forward loop of liver damage. There is an added pathogenicity of complement activation.[93] The immune complexes effectively trigger the complement pathways resulting in the deposition of complement fragments on the hepatocyte membranes and inside the sinusoidal structures. This facilitates the subclinical hepatocellular trauma, augments oxidative stress and sustains inflammatory signaling.[94] Taken together, these processes reveal the cumulative effect of chronic exposure to RF-containing immune complex on the hepatic immune and structural cells. Such processes could cause slow remodeling of the hepatic architecture and play a role in metabolic and fibrotic liver pathology in the long term, even in a classical form of autoimmune liver disease.

## RF in Autoimmune Hepatitis and Overlap Syndromes

Rheumatoid factor is not a pivotal diagnostic tool in autoimmune hepatitis (AIH) or other cholestatic autoimmune liver diseases, including primary biliary cholangitis (PBC), although a subset of patients develops RF which is gradually being observed as clinically significant. RF positivity in such states is typically indicative of a broadened B-cell activity and autoantibody production in the body in general, and these findings suggest that immune dysfunction is not limited to the liver.[95] Instead of playing a direct role in hepatic autoimmunity, RF is used as an indicator of a larger immunological derangement, and tends to be found in company with other autoantibodies that are typical of autoimmune liver disease.[2,96]

### Increased Inflammatory Load

Different studies indicate that RF-positive patients of AIH or PBC have greater levels of biochemical and histologic inflammation. High levels of aminotransferases, high serum immunoglobulins, and heightened portal and periportal inflammatory infiltrates are usually characterized. The results indicate that RF positivity could indicate a more passive or severe immunopathologic process, which might be mediated by increased cytokine activity and the formation of immune-complexes.[97,98]

### More Violent Histologic Characteristics

There are also increased histologic disease markers among RF-positive individuals. Some cohorts have demonstrated increased rates of interface hepatitis, dense plasma-cell infiltration, as well as early fibrotic remodeling. These trends suggest that RF might be an indicator of a phenotype with rapid transformation of inflammation to fibrogenesis. Even though it is not universal, the association shows the possibility of RF as an indicator of patients who may develop faster structural liver degradation.[99]

### Possible Ineffective Response to Treatment

The initial clinical experiences indicate that RF positivity can be an omen of a less successful treatment course. There are RF-positive patients who have slower normalisation of the aminotransferases or do not have biochemical remission

despite conventional immunosuppressive therapy.[100] Although the evidence is still sparse, this tendency makes it possible to assume that RF detects those with more refractory or complex immune-mediated liver damage.[101] In general, RF aids in showing the immunologic heterogeneity in autoimmune hepatitis, primary biliary cholangitis, and overlap syndromes.[99] Its existence can represent a group of patients with enhanced systemic autoimmunity, increased inflammatory process, and possibly different clinical courses, and the importance of RF as an additional marker in the evaluation of autoimmune liver disease is significant.[102,103]

### Hepatocardiometabolic Axis

Hepatocardiometabolic axis provides the importance of liver activity, metabolism, and cardiovascular well-being interaction. Liver is an important centre of glucose homeostasis, lipoproteins, bile acids and systemic inflammation regulation. When hepatic damage or metabolic pathology happens in the RF-positive situation, the imbalance does not only affect the liver but it systematically impacts the metabolism and vascularization of the body.[104] Persistent RF-related immune response and inflammation may hence trigger a cascade of interrelated metabolic and cardiovascular dysfunction.[105]

#### Impact on Lipid Metabolism

RF-related hepatic inflammation has significant disruptions on lipids regulation. Inflammatory signaling changes the hepatic very-low-density lipoprotein secretion, decreases the ability of high-density lipoprotein remodeling, and diminishes the cholesterol efflux capacity.[106] All of these changes lead to a proatherogenic lipid profile that is typified by high levels of triglyceride-rich lipoproteins, oxidized LDL deposition, and malfunctioning HDL. This type of phenotype does not only speed up the mechanism of atherosclerosis but also predisposes the RF-positive person to cardiovascular events.[107]

#### Stimulation of Insulin Resistance

The cytokines produced by inflamed hepatic and adipose tissues, in particular interleukin-6 and tumor necrosis factor (alpha), inhibit insulin receptor signaling in hepatocytes and skeletal muscle. This interference systemically causes reduced uptake of glucose, enhanced production of glucose in the liver, and insulin resistance that is long term. Such metabolic imbalances intensify the threat of diabetes type 2 and the continuous deposition of hepatic lipids, which further enhances the loop of metabolic imbalance.[108]

#### Enhancement of Vascular Inflammation

Released by a stressed liver, inflammatory and oxidized lipids get into the blood supply and induce endothelial activation. This is followed by an endothelial dysfunction, leukocyte adhesion and vascular remodeling, which provide a pro-inflammatory and pro-atherogenic vascular environment. These modifications connect hepatic inflammation directly to the cardiovascular risk that is systemic in the case of the absence of an evident autoimmune disease.[109,110]

#### Bile Acid Signaling Disruption

The changes in bile acid composition in relation to RF-positive hepatic dysfunction disrupt the farnesoid x-receptor (FXR), Takeda G-protein coupled receptor-5 (TGR5), liver-to-peripheral tissue signaling pathways, regulating lipid oxidation, glucose homeostasis, and inflammatory reactions. This interruption strengthens systemic metabolic dysregulation and may increase the rate of hepatic and cardiometabolic damage.[111] Cumulatively, RF-related hepatic injury triggers a vicious cycle whereby hepatopathy increases systemic metabolic and vascular upheaval, which subsequently increases hepatic stress. RF is a clinically significant biomarker on the hepatocardiometabolic continuum and an indicator of direct hepatic injury and the overall systemic impact of chronic inflammation.[112]

## RF Clinical Utility as a Predictor and Risk Stratification Tool

Rheumatoid factor is one of the most commonly availed immunologic assays in clinical medicine, and its possible ability to serve as a biomarker is not limited to the classic area of autoimmune diagnosis.[113] Its most significant strength is accessibility: RF testing is cheap, has minimal technical skills, and has already become a part of almost every laboratory system on the planet. This places RF as a viable instrument to further applications in cardiometabolic and hepatic risk stratification, especially in the areas where the prevalence of chronic diseases is on the rise, but access to advanced

biomarker platforms is scarce. The routine nature of RF testing, compared to emerging molecular tests which can only be applied with specialized equipment or an analytical pipeline, enables the application of the technique without needing a change in infrastructure or the cost burden.[114]

The growing body of evidence is in line with the fact that RF can have greater pathophysiological implications, particularly in patients with chronic inflammatory diseases.[115] RF positivity could be used as a prognosticator of increased systemic inflammation and metabolic stress in such conditions as rheumatoid arthritis, psoriasis, chronic obstructive pulmonary disease (COPD), chronic viral infections, obesity, and metabolic syndrome.[1,8] The integration of RF into the current risk assessment models can assist clinicians in determining persons that may require closer surveillance and prompted intervention. Indicatively, a patient with metabolic syndrome and positive RF could have an early coronary artery calcium scoring done or carotid ultrasound so that subclinical atherosclerosis could be noted before symptomatic disease occurred.[116] In the same manner, RF-positive patients might be put under increased observation of fasting glucose, hemoglobin A1c, triglycerides, HDL functionality, and hepatocellular injury or fibrosis markers. This might be useful in clinical decision-making, such as the prompt commencement of preventive pharmacotherapy, such as statins, glucagon-like peptide-1 (GLP-1) receptor agonists, or sodium glucose co-transporter (SGLT2) inhibitors, and prompt referral to hepatology to evaluate fibrosis.[117]

In the framework of rheumatoid arthritis, the usefulness of RF concerning clinical prediction is already known. High-titer RF can detect those patients, who have an increased risk of developing severe joint disease, extra-articular involvement, and accelerated atherosclerosis.[115] Cardiovascular disease frequently manifests and develops at a faster rate in such individuals compared to the general population. RF, especially in combination with anti-citrullinated protein antibodies, indicates a more aggressive immunologic phenotype with chronic vascular inflammation, microvascular dysfunction and a high risk of thrombosis. This indicates that RF-positive persons with the autoimmune disease might need a more intense cardiovascular screening and risk adjustment even at a young age which emphasizes the significance of the biomarker in the preventive approach long term.[118] High RF is also a feature of a variety of other autoimmune diseases such as Sjogrens syndrome and cryoglobulinemic vasculitis, but in these cases, it tends to correlate with systemic inflammation and can manifest more generalized immune dysregulation that borders on cardiometabolic health.[119] The RF has not been interpreted with caution, although it has these benefits, in cardiometabolic and hepatic risk prediction. RF is not a disease-specific marker, and there are various confounding factors that have to be taken into consideration.[120] With age, RF levels increase as a result of immune system remodelling in immunosenescence. The presence of chronic infection like hepatitis B, hepatitis C, tuberculosis and endocarditis may result in polyclonal B-cell stimulation and subsequent elevation of RF levels which are not indicative of an autoimmune pathology.[2] There is also the complication of RF interpretation by chronic liver disease since the artificial increase of RF titers can be caused by impaired clearance of immune complexes and the presence of portal inflammation.[121] In addition, cigarette smoking is also a potent environmental determinant which increases mucosal immune activation and RF production without incurring metabolic illness in the body. These variables imply the necessity of contextual interpretation, preferably along with the data on inflammatory biomarkers, including hs-CRP, IL-6, ferritin, or fibrinogen, for imaging and clinical evaluation.[122,123] Combined, RF cannot be considered a single predictor. However, when considered in the framework of the greater clinical picture, it has a significant potential to serve as an effective marker that can be used to bring together the association of chronic inflammation with cardiometabolic and hepatic risk, which can be used to support more personalized and proactive approaches to disease prevention[120] (Figure 3).

## Future Implications and Research Recommendations

Although there is increasing appreciation of the potential role of rheumatoid factor as a predictor of systemic inflammatory burden, there are still many questions regarding the actual predictive capacity of the factor in cardiometabolic and hepatic disease. The emerging data is convincing yet not complete, and further studies should combine epidemiologic, mechanistic, and clinical trial studies to determine the role of RF in the risk of chronic disease (Figure 4). Such an understanding will dictate whether RF will be incorporated into a routine part of risk stratification or only in certain groups of people.

### Longitudinal Non-Autoimmune Population Studies

High-quality non-autoimmune cohort longitudinal data of large, diverse, non-autoimmune cohort is one of the most immediate needs. The existing evidence is largely informed by the research done on patients with rheumatoid arthritis or

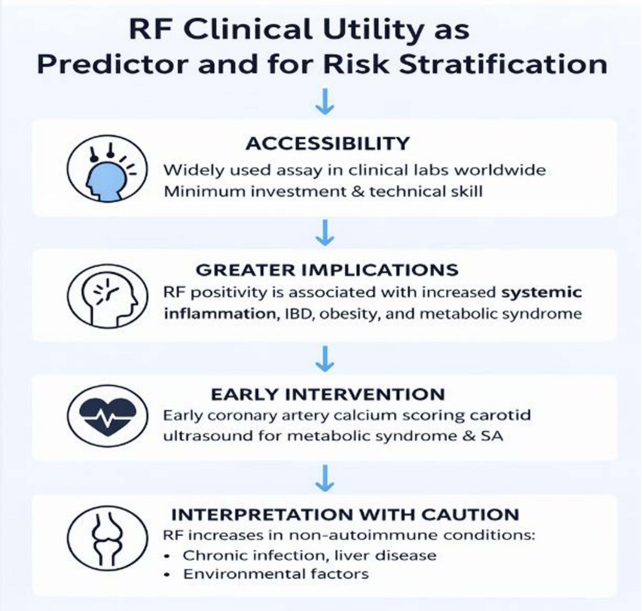


**Figure 3** Clinical Utility of Rheumatoid Factor for Risk Prediction and Stratification: It illustrates the clinical utility of rheumatoid factor (RF) as a predictor and tool for risk stratification, emphasizing its accessibility as a widely available and low-cost laboratory assay. It highlights its broader implications in systemic inflammation and cardiometabolic risk, the potential for early intervention strategies (such as coronary calcium scoring and carotid ultrasound), and the need for cautious interpretation due to elevations in non-autoimmune conditions like chronic infections and liver disease.

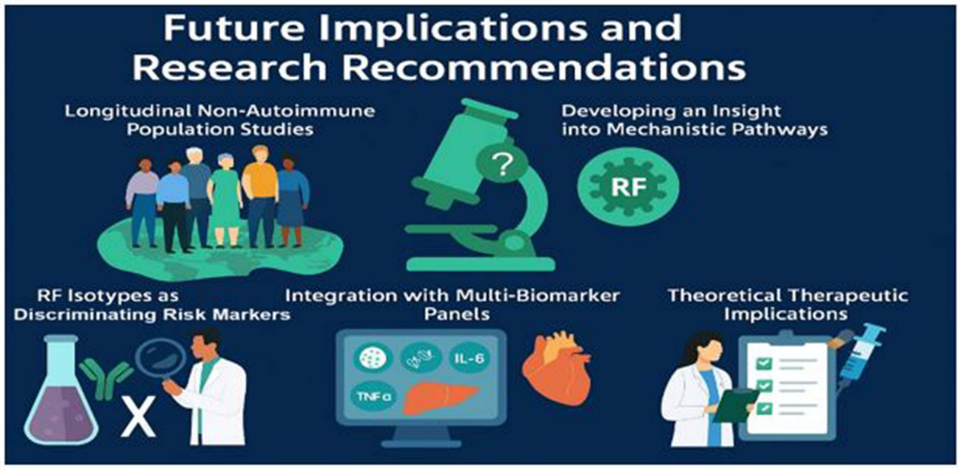


**Figure 4** Proposed Future Directions and Research Priorities for Rheumatoid Factor in Cardiometabolic and Inflammatory Disease: Figure outlines future implications and research recommendations regarding rheumatoid factor (RF), emphasizing the need for longitudinal studies in non-autoimmune populations and deeper exploration of underlying mechanistic pathways. It also highlights the potential of RF isotypes as discriminating risk markers, integration with multi-biomarker panels (e.g., IL-6, TNF-α), and consideration of theoretical therapeutic implications for improved clinical decision-making.

other inflammatory diseases of a chronic nature.[124] To understand whether RF is an independent predictor of RF-positive individuals in the absence of an overt autoimmune disease and followed prospectively, the development of atherosclerosis, diabetes, MAFLD, and major cardiovascular events should be evaluated. Some of the confounders that should be avoided in such studies include age, smoking and chronic infections, which are known to enhance the RF levels. It is only under such data that RF can be verified as a general population biomarker.[125]

## Developing an Insight Into Mechanistic Pathways

It is also necessary that mechanistic exploration takes place. Though the chronical presence of immune-complex activity is an effective biological hypothesis, the underlying pathways should be characterized in depth. Future studies are needed

to investigate the associations with some immune-complex signature or complement activation patterns even more closely with metabolic malfunction. Research into the interaction of RF and adipose tissue macrophages can provide insight into the mechanism by which systemic immune dysregulation is converted to insulin resistance. Likewise, the role of RF in hepatic lipid metabolism, the activation of stellate cells, and bile acid regulation might be investigated, and these mechanisms may be used to understand the RF effects on the development of progressive liver disease.

### RF Isotypes as Discriminating Risk Markers

One of the areas of potential advancement in RF research is the de-facto analysis of the prognostic value of single RF isotypes.[126] Although IgM-RF has been the most widely measured and traditionally focused subtype, increasing observations indicate that it is possible that IgA-RF is better associated with systemic inflammatory burden and chronic mucosal immune activation.[127] IgA-RF is overloaded in those individuals with smoking-related immune dysregulation, periodontal disease, and subclinical airway inflammation, which in its turn are linked to the heightened cardiometabolic risk.[128] Some of the cohort studies have shown that patients who produce high levels of IgA-RF have more common frequencies of endothelial dysfunction, insulin resistance, and subclinical atherosclerosis than those who only produce IgM-RF.[129] These results confirm the hypothesis that the RF isotypes cannot be interchangeable but rather have different immunological pathways with different effects on metabolic and vascular physiology. Additional clarification of the additive or synergistic risk, on the basis of single- or multi-isotype positivity, would offer the much-needed granularity of precision risk stratification, particularly in early or preclinical conditions of disease.

### Multi-Biomarker Panels Two Approaches Can Be Integrated with Multi-Biomarker Panels

There are two ways of integrating with Multi-Biomarker Panels: Integration where the Multi-Biomarker Panel is considered as an extension of the underlying model; Integration where both models are developed initially and subsequently integrated.[130] In addition to the assessment of RF alone, future studies are encouraged to adopt RF within unified multi-biomarker models with the potential to represent a complex cardiometabolic disease pathogenesis. RF, in combination with circulating cytokines (eg., IL-6, TNF-a), oxidative stress markers, lipoprotein particle profiles, adipokines, and fibrosis-related proteins (eg., galactin-3, PRO-C3), could be beneficial in increasing sensitivity and specificity of predictive models.[131,132] Together with more powerful imaging modalities – like cardiac MRI to identify early signs of myocardial fibrosis, coronary calcium scoring and hepatic stiffness – the composite panels would be able to identify the subtle change between minimal inflammation and structural damage in organs long before clinical syndromes develop.[133] These formulations of integration are consistent with new paradigms of precision-medicine and, potentially, enable clinicians to recognize high-risk phenotypes in a wide range of populations, including individuals who have not received overt autoimmune diagnoses.

### Theoretical Therapeutic Implications

The therapeutic implications associated with the choice of knowledge regarding the RF being a biomarker or causally related to tissue injury are immense. In case pathogenic functions are validated-by mechanisms like complement activation, Fc receptors, or direct enhancement of immune-complex-induced inflammation-mediated damage may be used to reduce downstream cardiometabolic and hepatic damage. It is possible to repurpose or even optimize therapies that deplete B-cells, inhibit complement, or decrease the number of immune-complexes in patients with high-risk RF signatures. Furthermore, RF stratification may be added to the clinical trial designs, which would demonstrate differences in treatment responses and allow tailoring the treatment pathways to patients. Finally, elucidating the mechanistic role of RF will inform preventive measures and can possibly expand the preventive use of RF beyond diagnosis to active risk prevention.

## Conclusion

Long regarded as an inflammatory indicator of rheumatologic biomarker, rheumatoid factor is starting to be seen as a systemic signifier with effects far beyond the joint pathology. Its involvement in immune complex, complement activation, endothelial injury, and chronic inflammatory signaling provides a biologically viable connection to cardio-metabolic and hepatic dysfunction. The epidemiologic data indicate that RF positivity – that is, in RA or in patients without apparent autoimmune disease – is linked to the higher risk of atherosclerosis, metabolic syndrome, heart failure,

MAFLD and hepatic fibrosis. These associations put RF as a potentially useful and broadly available biomarker of early risk detection and combined control. It could be a potential biomarker for cardiometabolic and hepatic risk monitoring, its inclusion in routine diagnosis is advocated. With the development of precision medicine, one of the roles RF may fulfill is a more finely tuned system for detecting systemic inflammation and preventing the advancement of chronic diseases in a wide variety of clinical patients.

## Abbreviations

IL-6, Interleukin-6; TNF-α, Tumour necrosis factor-alpha; BPD, Bronchopulmonary dysplasia; SA, sleep apnea; IBD, inflammatory bowel disease; BMI, body mass index.

## Disclosure

The authors report no conflicts of interest in this work.

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