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EARLY IMMUNE SYSTEM CHANGES IN AT-RISK INDIVIDUALS PRIOR TO RHEUMATOID ARTHRITIS SYMPTOM ONSET: A SYSTEMATIC REVIEW

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ABSTRACT

Background: Rheumatoid arthritis (RA) develops through a prolonged preclinical phase characterized by progressive immune dysregulation before the onset of clinically apparent arthritis. Increasing evidence suggests that autoantibodies, cytokine abnormalities, cellular immune alterations, environmental exposures, and subclinical inflammation emerge years before diagnosis. Understanding these early immune changes may facilitate earlier prediction and preventive intervention in at-risk individuals.

Objective: To systematically review the evidence regarding early immune system alterations associated with progression to rheumatoid arthritis in at-risk individuals prior to symptom onset or clinical arthritis development.

Methods: A systematic review was conducted according to PRISMA 2020 guidelines. Electronic searches were performed in PubMed, Scopus, Web of Science, Embase, and Google Scholar for studies published between 2010 and 2025. Eligible studies included prospective cohort studies, observational studies, and nested case–control studies evaluating immunological, serological, imaging, genetic, or environmental predictors of RA development in at-risk populations. Ten studies met the inclusion criteria.

Results: Consistent evidence demonstrated that anti-citrullinated protein antibodies (ACPAs), rheumatoid factor (RF), and high anti-CCP titers strongly predicted progression to inflammatory arthritis and RA. Subclinical ultrasonographic abnormalities, including synovitis and power Doppler signals, were associated with future arthritis development. Altered lymphocyte subsets, elevated inflammatory cytokines such as IL-6, Epstein–Barr virus reactivation markers, anti-carbamylated protein antibodies, and environmental factors including smoking and dietary sodium intake also contributed to increased RA risk. Predictive models integrating serological, imaging, and clinical factors showed improved risk stratification accuracy.

Conclusion: Early immune dysregulation precedes the onset of rheumatoid arthritis by several years and involves complex interactions between autoimmunity, inflammation, genetic susceptibility, and environmental exposures. Identification of high-risk individuals through integrated predictive approaches may enable earlier intervention and support future RA prevention strategies.

KEYWORDS: Rheumatoid arthritis; preclinical rheumatoid arthritis; autoantibodies; anti-citrullinated protein antibodies; rheumatoid factor; immune dysregulation; inflammatory arthritis; prediction; arthralgia; biomarkers.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease characterized by persistent synovial inflammation, progressive joint destruction, disability, and increased cardiovascular morbidity. Current evidence indicates that the pathogenic processes leading to RA begin many years before the appearance of clinically apparent arthritis. During this preclinical phase, genetically susceptible individuals undergo a gradual transition from asymptomatic autoimmunity to systemic immune dysregulation and eventually inflammatory joint disease. This evolving concept has shifted the understanding of RA from a disease of established synovitis to a continuum of immunological and inflammatory events that occur long before diagnosis. Early identification of these changes

may allow the implementation of preventive strategies aimed at delaying or even preventing the onset of clinical RA (Tracy et al., 2017; O'Neil et al., 2024).

The prearthritis phase of RA is increasingly recognized as a dynamic process involving multiple sequential immunological events. Initially, environmental and genetic interactions promote the breakdown of immune tolerance, leading to the production of autoantibodies and activation of both innate and adaptive immune pathways. Over time, these abnormalities become amplified and are accompanied by systemic inflammation, mucosal immune activation, and subclinical synovitis before clinically detectable arthritis develops. Studies evaluating the chronological sequence of autoimmune events suggest that serological and cellular abnormalities may precede symptoms by several years, supporting the concept of a prolonged window of opportunity for early intervention and prevention (Heutz et al., 2025; Rantapää-Dahlqvist & Andrade, 2019).

One of the earliest detectable immune abnormalities in preclinical RA is the appearance of rheumatoid arthritis–related autoantibodies, particularly anti-citrullinated protein antibodies (ACPAs) and rheumatoid factor (RF). These antibodies can be detected years before symptom onset and are associated with increased risk of progression to inflammatory arthritis. The process of epitope spreading, whereby the immune response expands toward multiple citrullinated antigens over time, appears to reflect maturation of the autoimmune response and increasing disease imminence. Furthermore, changes in antibody glycosylation patterns and isotype switching have been associated with transition toward clinically manifest disease, suggesting progressive immune dysregulation during the preclinical phase (Sokolove et al., 2012; Kokkonen et al., 2011; Kissel et al., 2019).

Accumulating evidence also highlights the importance of mucosal inflammation and microbial dysbiosis in initiating RA-related autoimmunity. The oral, pulmonary, and gastrointestinal mucosae are believed to represent key sites where immune tolerance may first be disrupted. Periodontal pathogens, particularly Aggregatibacter actinomycetemcomitans and Porphyromonas gingivalis, have been implicated in promoting protein citrullination and triggering ACPA production. Exposure to these pathogens before symptom onset has been associated with increased risk of progression to RA, further supporting the hypothesis that mucosal immune activation plays a central role in disease initiation (Gomez-Bañuelos et al., 2020; Tracy et al., 2017).

In addition to humoral autoimmunity, significant alterations in cellular immune responses occur during the preclinical stages of RA. Abnormal T-cell activation, B-cell expansion, cytokine dysregulation, and altered natural killer (NK) cell function have all been described in at-risk individuals. These immunological changes contribute to a pro-inflammatory environment that may facilitate synovial infiltration and chronic inflammation. Elevated inflammatory mediators such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and chemokines have been detected prior to arthritis onset, suggesting that systemic inflammation develops well before overt joint manifestations appear (De Hair et al., 2014; O'Neil et al., 2024).

Advanced imaging studies have further demonstrated that subclinical joint inflammation can precede clinically detectable synovitis. Ultrasound and magnetic resonance imaging (MRI) frequently identify synovial hypertrophy, tenosynovitis, bone marrow edema, and power Doppler signal abnormalities in individuals at risk of RA who do not yet fulfill classification criteria for inflammatory arthritis. These findings support the notion that inflammatory changes are already active during the symptomatic prearthritis phase and may represent an intermediate stage between systemic autoimmunity and clinically evident disease (van Boheemen & van Schaardenburg, 2019; De Hair et al., 2014).

The identification of individuals at highest risk for RA progression has become a major focus of recent research. Risk stratification models incorporating serological markers, imaging findings, genetic predisposition, family history, smoking exposure, and clinical symptoms have demonstrated promising predictive accuracy. Such models may facilitate targeted surveillance and enable future implementation of preventive therapeutic strategies in selected high-risk populations. Importantly, several studies have emphasized that the risk of progression is not determined by a single factor, but rather by the cumulative interaction between genetic susceptibility, environmental exposures, and evolving immune abnormalities (Duquenne et al., 2023; Tanner et al., 2019).

Given the growing evidence supporting a prolonged preclinical phase of RA, increasing attention has been directed toward prevention and early intervention strategies. Potential approaches include modulation of environmental risk factors, treatment of mucosal inflammation, immunomodulatory therapies targeting autoimmunity, and close monitoring of high-risk individuals. Although definitive preventive therapies have not yet been established, understanding the sequence of immune alterations preceding RA onset may provide critical insights into disease pathogenesis and identify optimal windows for intervention before irreversible joint damage occurs (Frazzei et al., 2023; Kastbom et al., 2025).

METHODOLOGY

Study Design

This study employed a systematic review methodology following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to ensure methodological transparency, reproducibility, and scientific rigor. The primary objective of this review was to synthesize and critically evaluate the available evidence regarding early immune system changes in individuals at risk of developing rheumatoid arthritis (RA) prior to symptom onset or the development of clinically apparent inflammatory arthritis.

The review focused on identifying immunological, serological, genetic, imaging, and environmental changes associated with progression toward RA during the preclinical and prearthritis phases of disease. Particular

emphasis was placed on studies evaluating autoantibodies, cytokines, lymphocyte subsets, imaging biomarkers, mucosal immunity, viral immune responses, and environmental risk factors associated with transition from at-risk states to clinically manifest RA.
The review included peer-reviewed prospective cohort studies, nested case–control studies, and observational studies investigating individuals considered at increased risk for RA, including subjects with arthralgia, clinically suspect arthralgia (CSA), anti-citrullinated protein antibody (ACPA) positivity, rheumatoid factor (RF) positivity, nonspecific musculoskeletal symptoms, or familial predisposition to RA.

Eligibility Criteria
Studies were selected according to predefined inclusion and exclusion criteria.

Inclusion Criteria:
- **Population:** Adults identified as being at risk for rheumatoid arthritis, including individuals with arthralgia, clinically suspect arthralgia, ACPA positivity, RF positivity, nonspecific musculoskeletal symptoms, or familial/genetic predisposition to RA.
- **Exposures/Assessments:** Evaluation of early immune system changes including autoantibodies, cytokines, lymphocyte subsets, inflammatory biomarkers, viral immune responses, imaging findings, or environmental risk factors associated with RA development.
- **Outcomes:** Development of inflammatory arthritis, clinical arthritis, or rheumatoid arthritis during follow-up.
- **Study Designs:** Prospective cohort studies, nested case–control studies, observational cohort studies, or longitudinal studies with empirical data.
- **Language:** English-language publications only.
- **Publication Period:** Studies published between 2010 and 2025 to capture contemporary evidence regarding preclinical RA and immune dysregulation.

Exclusion Criteria:
- Reviews, editorials, conference abstracts, expert opinions, and non-empirical articles.
- Animal studies or laboratory-only mechanistic studies without clinical populations.
- Studies evaluating established rheumatoid arthritis without assessment of preclinical or at-risk phases.
- Duplicate publications or studies without accessible full-text articles.
- Studies lacking sufficient data regarding immune predictors or progression outcomes.

A total of 10 studies fulfilled all eligibility criteria and were included in the final systematic review.

Search Strategy
A comprehensive electronic literature search was conducted using PubMed, Scopus, Web of Science, Embase, and Google Scholar databases from inception until January 2026. The search strategy combined Medical Subject Headings (MeSH) terms and free-text keywords related to rheumatoid arthritis, preclinical disease, and immune system changes.
The Boolean search strategy included combinations of the following terms:
- (“rheumatoid arthritis” OR “preclinical rheumatoid arthritis” OR “at-risk rheumatoid arthritis” OR “clinically suspect arthralgia”)
- AND (“immune changes” OR “immune dysregulation” OR “autoantibodies” OR “ACPA” OR “rheumatoid factor” OR “cytokines” OR “lymphocyte subsets”)
- AND (“prediction” OR “arthritis development” OR “progression” OR “risk factors”)
- AND (“ultrasound” OR “power Doppler” OR “tenosynovitis” OR “subclinical inflammation”)
- AND (“prospective cohort” OR “observational study”).

Manual searches of the reference lists of included studies and relevant review articles were also performed to ensure comprehensive identification of eligible studies. Duplicate records were removed before screening.

Study Selection Process
The study selection process was conducted independently by two reviewers. All retrieved citations were imported into Zotero reference management software for organization and duplicate removal.
Titles and abstracts were initially screened for relevance according to the predefined eligibility criteria. Full-text articles were subsequently reviewed to determine final inclusion eligibility. Disagreements between reviewers were resolved through discussion and consensus. When necessary, a third senior reviewer adjudicated unresolved discrepancies.

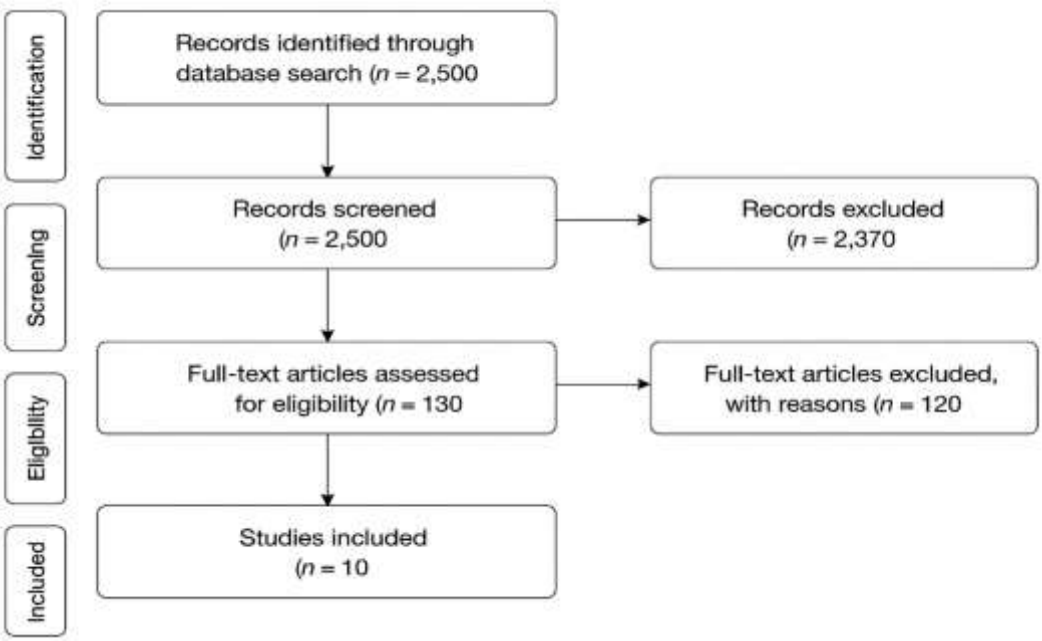

Figure 1 PRISMA Flow Diagram

Data Extraction

A standardized data extraction form was developed and pilot-tested prior to data collection. The following variables were extracted from each included study:

- Author(s), publication year, and journal.
- Country and study design.
- Sample size and participant characteristics.
- Definition of at-risk population.
- Duration of follow-up.
- Immune biomarkers evaluated (e.g., ACPA, RF, cytokines, lymphocyte subsets, EBV antibodies).
- Imaging findings (ultrasound synovitis, tenosynovitis, power Doppler signals).
- Environmental or genetic risk factors.
- Main outcomes related to arthritis or RA development.
- Quantitative measures including hazard ratios (HRs), odds ratios (ORs), confidence intervals (CIs), percentages, and predictive model performance.
- Key conclusions and predictive findings.

Data extraction was independently performed by two reviewers and cross-checked for consistency and completeness.

Quality Assessment

The methodological quality of included studies was evaluated using standardized appraisal tools according to study design.

- The Newcastle–Ottawa Scale (NOS) was used for prospective cohort and observational studies.
- Nested case–control studies were assessed using adapted NOS criteria focusing on participant selection, comparability, and outcome assessment.

Each study was evaluated across the following domains:

- Selection bias.
- Representativeness of the cohort.
- Exposure and outcome assessment methods.
- Adequacy of follow-up duration.
- Control of confounding variables.
- Statistical analysis quality.

Studies were categorized as low, moderate, or high risk of bias based on total scores and methodological rigor. Most included studies demonstrated moderate-to-high methodological quality due to prospective designs, objective laboratory assessments, and longitudinal follow-up. However, some studies were limited by relatively small sample sizes, heterogeneity in risk definitions, and variability in imaging or biomarker assessment protocols.

Data Synthesis

Due to substantial heterogeneity in study populations, biomarker assessments, follow-up duration, and outcome definitions, a narrative synthesis approach was adopted instead of quantitative meta-analysis.

The findings were synthesized thematically according to the following domains:

1. Autoantibody-related immune changes prior to RA onset.
2. Cellular immune alterations and cytokine dysregulation.
3. Imaging evidence of subclinical inflammation.
4. Environmental and infectious risk factors associated with RA development.
5. Predictive models and risk stratification approaches in at-risk populations.

Descriptive statistics including hazard ratios, odds ratios, percentages, medians, interquartile ranges, and predictive model performance measures were summarized where available. Comparative interpretation across studies was conducted to identify consistent predictors and patterns of immune dysregulation during the preclinical phase of RA.

No formal meta-analysis was performed because of heterogeneity in study design, immune biomarkers evaluated, and progression outcome definitions across the included studies.

Ethical Considerations

As this study was based exclusively on secondary analysis of previously published literature, ethical approval and informed participant consent were not required. All included studies were published in peer-reviewed journals and were assumed to have obtained institutional ethical approval before participant recruitment and data collection.

The conduct and reporting of this systematic review adhered to the principles of academic integrity, transparency, and reproducibility in accordance with PRISMA 2020 guidelines.

RESULTS

Summary and Interpretation of Included Studies on Early Immune System Changes in At-Risk Individuals Prior to Rheumatoid Arthritis Onset

6. Study Designs and Populations

The included studies consisted primarily of prospective cohort studies evaluating individuals at risk of rheumatoid arthritis (RA), particularly subjects with arthralgia, clinically suspect arthralgia (CSA), anti-citrullinated protein antibody (ACPA) positivity, rheumatoid factor (RF) positivity, or nonspecific musculoskeletal symptoms. Sample sizes ranged from 76 preclinical RA cases in Gan et al. (2015) to 9712 individuals from the general population in Nielsen et al. (2012). Most studies recruited seropositive arthralgia individuals from rheumatology clinics, while some studies evaluated population-based cohorts or nested case–control cohorts. Follow-up duration varied substantially, ranging from approximately 12 months to more than 5 years. Across studies, progression to inflammatory arthritis or RA ranged between 23% and 50% among at-risk cohorts, highlighting the importance of identifying early immunological predictors.

2. Autoantibodies and Serological Predictors

Autoantibody positivity, particularly ACPA, emerged as one of the strongest predictors of future RA development. Bos et al. (2010) demonstrated that 90% of patients who developed arthritis were ACPA positive, with ACPA positivity conferring a sixfold increased risk of arthritis development (HR = 6.0, 95% CI 1.8–19.8). High ACPA titers and dual positivity for ACPA and IgM-RF further amplified the risk. Similarly, Frazzei et al. (2025) reported that individuals with high ACPA titers had a hazard ratio (HR) of 4.65 for progression, while double positivity for ACPA and IgM-RF increased the risk nearly sevenfold (HR = 6.83). Nielsen et al. (2012) also demonstrated a dose-response relationship between RF levels and future RA, with RF levels >100 IU/Ml associated with a 26-fold increased risk of RA compared with RF <25 IU/Ml. Gan et al. (2015) identified anti-carbamylated protein (anti-CarP) antibodies in preclinical RA, reporting 26% sensitivity and 95% specificity for future RA.

3. Cellular Immune Changes and Cytokine Abnormalities

Several studies identified alterations in immune cell subsets and inflammatory mediators before clinical arthritis onset. Prajzlerová et al. (2024) demonstrated that higher percentages of CD4+ T cells, lower natural killer (NK) cell percentages, and elevated anti-CCP IgG significantly increased the probability of progression to arthritis. Their classification model identified individuals with both high anti-CCP IgG and low NK cells as the highest-risk subgroup. Cîrciumaru et al. (2024) found that elevated IL-6 levels independently predicted arthritis progression (HR = 1.5), while higher IL-15 receptor α levels appeared protective (HR = 0.6). These findings support the role of early systemic immune dysregulation in the transition from preclinical autoimmunity to overt inflammatory arthritis.

4. Imaging Biomarkers and Subclinical Inflammation

Imaging studies consistently demonstrated that subclinical inflammatory abnormalities precede clinically apparent arthritis. Van de Stadt et al. (2010) showed that ultrasound abnormalities including synovitis, power Doppler (PD) signal, and joint effusion were significantly associated with arthritis development at the joint level. Forty-five of 192 patients (23%) developed arthritis after a mean of 11 months. Rakieh et al. (2015) also identified positive ultrasound PD signal as one of the four major predictors incorporated into their risk score model. In

Cîrciumaru et al. (2024), ultrasound-detected tenosynovitis independently predicted arthritis progression with a hazard ratio of 3.4.

7. Environmental and Viral Risk Factors

Environmental exposures and viral immune responses also contributed to RA risk. Sundström et al. (2015) demonstrated that high sodium intake more than doubled RA risk among smokers (OR = 2.26, 95% CI 1.06–4.81), with 54% of the increased risk attributable to interaction between smoking and sodium intake. Fechtner et al. (2022) identified elevated Epstein–Barr virus (EBV) early antigen IgG levels in individuals before RA onset, suggesting increased viral reactivation during the preclinical phase. Elevated EBV antibody levels correlated significantly with increasing IgM-RF levels before RA diagnosis (P = 0.007), further supporting a role for chronic viral immune activation in RA pathogenesis.

Table (1): General Characteristics of Included Studies on Early Immune System Changes Prior to Rheumatoid Arthritis Development

Study	Country	Design	Sample Size	Population	Follow-up	Main Immune Marker(s)	Outcome	Key Findings
Bos et al. (2010)	Netherlands	Prospective cohort	147	Arthralgia patients positive for ACPA and/or IgM-RF	Median 28 months	ACPA, IgM-RF, Shared epitope	Arthritis development	29 patients developed arthritis; 90% were ACPA positive. ACPA predicted arthritis (HR=6.0), while IgM-RF and SE were not independent predictors.
Prajzlerová et al. (2024)	Czech Republic	Prospective cohort	207	At-risk arthralgia individuals	≥12 months	Lymphocyte subsets, anti-CCP IgG	Arthritis progression	41 individuals progressed to arthritis. High anti-CCP IgG, increased CD4+ T cells, and reduced NK cells predicted progression.
van de Stadt et al. (2010)	Netherlands	Prospective cohort	192	ACPA and/or RF-positive arthralgia	Mean 11 months	Ultrasound synovitis and PD signal	Arthritis development	45 patients (23%) developed arthritis. Ultrasound abnormalities predicted arthritis at joint level.

Frazzei et al. (2025)	Netherlands	Prospective cohort	617	Seropositive arthralgia individuals	5 years	ACPA, RF, clinical symptoms	RA development	33.7% developed arthritis. High ACPA titers and dual ACPA/RF positivity had strongest predictive value.
Nielsen et al. (2012)	Denmark	Prospective cohort	9712	General population	Up to 29 years	IgM-RF	RA development	RF >100 IU/mL associated with 26-fold increased risk of RA.
Cîrcium aru et al. (2024)	Sweden	Prospective cohort	267	Anti-CCP2-positive individuals with MSK symptoms	Median 49 months	ACPA reactivities, IL-6, IL-15Rα, ultrasound tenosynovitis	Arthritis progression	38% developed arthritis. Presence of ACPA reactivity, elevated IL-6, and tenosynovitis strongly predicted progression.
Rakieh et al. (2015)	United Kingdom	Prospective observational cohort	100	Anti-CCP-positive individuals with nonspecific MSK symptoms	Median 19.8 months	Autoantibodies, ultrasound PD signal	Inflammatory arthritis	50% developed inflammatory arthritis. High-risk score associated with 62% progression.
Fechtner et al. (2022)	USA	Case-control	166	Preclinical RA subjects and controls	Pre- and post-diagnosis samples	EBV antibodies, RF, anti-CCP	Preclinical RA immune activation	Elevated EBV IgG-EA antibodies detected before RA diagnosis and correlated with rising RF levels.
Gan et al. (2015)	USA	Nested case-control	76 RA cases	Preclinical RA sera	Before diagnosis	Anti-CarP antibodies	Future RA diagnosis	Anti-CarP-FCS antibodies were 26% sensitive

								and 95% specific for future RA.
Sundström et al. (2015)	Sweden	Nested case-control	386 RA cases, 1886 controls	General population	Median 7.7 years before RA onset	Sodium intake, smoking, anti-CCP	RA development	Sodium intake doubled RA risk among smokers (OR=2.26).

Interpretation of Key Predictive Findings

The included studies collectively demonstrate that immunological abnormalities precede the onset of rheumatoid arthritis by several years. Autoantibody positivity, particularly high ACPA titers and combined ACPA/RF positivity, consistently emerged as the strongest serological predictor of future RA. In Bos et al. (2010), 26 of the 29 individuals who developed arthritis were ACPA positive, while Frazzei et al. (2025) reported that individuals with both ACPA and IgM-RF positivity had nearly seven times the risk of progression.

Beyond autoantibodies, several studies highlighted substantial cellular immune dysregulation prior to symptom onset. Prajzlerová et al. (2024) demonstrated that altered lymphocyte populations, especially elevated CD4+ T cells and reduced NK cells, contributed significantly to prediction models. Similarly, Cîrciumaru et al. (2024) identified elevated IL-6 and ultrasound-detected tenosynovitis as independent predictors of arthritis progression.

Imaging modalities further supported the concept of subclinical inflammation preceding clinical arthritis. Ultrasound abnormalities including synovitis, PD signal, and tenosynovitis were repeatedly associated with future arthritis development in van de Stadt et al. (2010), Rakieh et al. (2015), and Cîrciumaru et al. (2024). These imaging findings suggest that localized synovial inflammation develops during the preclinical stage before overt arthritis becomes clinically detectable.

Environmental and infectious triggers may also contribute to the transition toward clinical disease. Sundström et al. (2015) demonstrated a synergistic interaction between smoking and sodium intake in increasing RA risk, while Fechtner et al. (2022) identified evidence of increased Epstein–Barr virus reactivation before RA onset, suggesting chronic immune stimulation may accelerate autoimmunity progression.

DISCUSSION

The findings of this systematic review support the concept that rheumatoid arthritis develops through a prolonged preclinical phase characterized by progressive immune dysregulation before the appearance of clinically apparent synovitis. Across the included studies, multiple immunological, serological, imaging, and environmental abnormalities were consistently associated with increased risk of inflammatory arthritis and RA development. These findings align with the evolving disease continuum model proposed by Tracy et al. (2017), Rantapää-Dahlqvist and Andrade (2019), and O'Neil et al. (2024), which describes RA as a multistage autoimmune process beginning years before diagnosis.

One of the most consistent findings across the reviewed studies was the strong predictive value of anti-citrullinated protein antibodies (ACPAs). Bos et al. (2010) demonstrated that ACPA positivity was associated with a sixfold increased risk of arthritis development, while high ACPA titers further amplified progression risk. Similarly, Frazzei et al. (2025) identified high ACPA titers and dual ACPA/RF positivity as among the strongest independent predictors of arthritis progression. These findings reinforce previous evidence showing that ACPAs emerge years before disease onset and may represent one of the earliest detectable hallmarks of RA-related autoimmunity (Kokkonen et al., 2011; Sokolove et al., 2012).

The role of rheumatoid factor was also supported, although RF alone appeared to have lower predictive specificity compared with ACPAs. Bos et al. (2010) found that IgM-RF independently showed weaker association with arthritis development, whereas Nielsen et al. (2012) demonstrated a dose-dependent increase in future RA risk with progressively elevated RF concentrations in the general population. Individuals with RF levels exceeding 100 IU/mL exhibited markedly increased long-term RA risk, particularly among smokers. These observations suggest that RF may contribute synergistically with other immune abnormalities rather than functioning as an isolated predictive biomarker.

The present review also highlights the importance of diversification and maturation of autoimmune responses during the preclinical period. Sokolove et al. (2012) demonstrated that epitope spreading of autoantibodies precedes progression to RA, indicating expansion of autoreactive immune responses over time. Furthermore, Kissel et al. (2022) observed increased glycosylation of ACPA variable domains before arthritis onset, suggesting structural evolution of autoantibodies during disease progression. These findings support the hypothesis proposed by Heutz et al. (2025) that autoimmune mechanisms evolve sequentially and become increasingly pathogenic as individuals transition toward clinically manifest RA.

Several studies included in this review demonstrated that immune dysregulation extends beyond humoral autoimmunity to involve significant cellular immune alterations. Prajzlerová et al. (2024) identified increased CD4+ T-cell percentages together with reduced T-cell and natural killer (NK) cell populations in individuals progressing to arthritis. These findings suggest impaired immune regulation and altered adaptive immune activation during the preclinical phase. Similar observations were discussed by De Hair et al. (2014), who proposed that synovial immune activation may occur even before clinically detectable arthritis develops.

Inflammatory cytokine dysregulation was another major finding identified in at-risk populations. Cîrciumaru et al. (2024) demonstrated that elevated IL-6 levels independently predicted progression to ACPA-positive RA, while reduced IL-15 receptor α levels were also associated with increased progression risk. These findings support the concept that systemic inflammation develops before overt synovitis becomes clinically apparent. O'Neil et al. (2024) and Tracy et al. (2017) similarly emphasized that inflammatory mediators likely contribute to the transition from asymptomatic autoimmunity to symptomatic inflammatory disease.

Subclinical inflammation detected through imaging modalities emerged as a particularly important predictor of future arthritis. Van de Stadt et al. (2010) demonstrated significant associations between ultrasonographic abnormalities—including synovitis, joint effusion, and power Doppler signals—and subsequent arthritis development at both joint and patient levels. Rakieh et al. (2015) similarly showed that positive power Doppler ultrasonography significantly improved prediction models for inflammatory arthritis progression in anti-CCP-positive individuals. These findings reinforce previous evidence summarized by van Boheemen and van Schaardenburg (2019), highlighting imaging biomarkers as valuable tools for identifying individuals approaching imminent disease transition.

The reviewed studies also support the concept that mucosal immune activation and microbial exposures contribute to RA pathogenesis. Gomez-Bañuelos et al. (2020) identified exposure to Aggregatibacter actinomycetemcomitans before symptom onset as a potential contributor to progression toward RA. This finding aligns with theories proposing that periodontal inflammation and mucosal citrullination initiate systemic autoimmune responses in genetically susceptible individuals. Rantapää-Dahlqvist and Andrade (2019) further emphasized the central role of mucosal sites in the earliest stages of RA-related autoimmunity.

Environmental factors also appeared to significantly influence disease development. Sundström et al. (2015) demonstrated that high dietary sodium intake significantly increased RA risk among smokers, particularly in anti-CCP-positive and shared epitope–positive individuals. These findings suggest synergistic interactions between environmental exposures and genetic susceptibility. Tanner et al. (2019) additionally demonstrated increased progression risk among first-degree relatives of RA patients, supporting the importance of familial predisposition and inherited susceptibility factors.

The potential contribution of viral immune dysregulation was highlighted by Fechtner et al. (2022), who reported elevated Epstein–Barr virus early antigen antibodies in individuals during the preclinical period of RA. Increased EBV antibody responses were associated with elevated IgM-RF levels before RA diagnosis, suggesting repeated viral reactivation may contribute to immune activation and autoantibody development. These findings support longstanding hypotheses linking viral infections to RA pathogenesis through molecular mimicry, chronic immune stimulation, or impaired immune regulation.

Another important finding of this review was the role of novel autoantibodies beyond ACPAs and RF. Gan et al. (2015) demonstrated that anti-carbamylated protein antibodies were detectable prior to RA diagnosis and were associated with future disease development. Although their predictive value alone was modest, these antibodies may improve overall risk assessment when combined with established serological biomarkers. This observation supports the increasingly recognized heterogeneity of autoimmune responses during preclinical RA development.

Risk stratification models integrating multiple clinical and immunological variables showed promising predictive accuracy across several studies. Rakieh et al. (2015), Duquenne et al. (2023), and Prajzlerová et al. (2024) demonstrated that combining serological markers, imaging findings, symptom characteristics, and immune cell profiles substantially improved prediction of inflammatory arthritis progression. These findings are clinically important because they support individualized risk assessment and may facilitate targeted monitoring or preventive interventions for high-risk individuals.

The reviewed evidence also reinforces the concept of a "window of opportunity" during the prearthritis phase of RA. Kastbom et al. (2025) and Frazzei et al. (2023) emphasized that early identification of immune dysregulation may allow implementation of preventive strategies before irreversible joint damage occurs. The ability to identify individuals with imminent progression risk could eventually support interventions targeting autoimmunity, mucosal inflammation, or environmental risk factors during the earliest disease stages.

Despite significant advances, substantial challenges remain in translating preclinical biomarkers into routine clinical practice. Heterogeneity among at-risk populations, differences in biomarker assessment methods, and variability in progression timelines complicate standardization of prediction models. Additionally, not all seropositive individuals progress to RA, indicating that additional unidentified protective or modifying factors likely influence disease evolution. Heutz et al. (2025) highlighted the need for longitudinal studies examining the temporal sequence of immune alterations in greater detail.

Overall, the findings of this systematic review indicate that early immune changes in at-risk individuals involve complex interactions among autoantibodies, cellular immune dysregulation, cytokine activation, environmental exposures, microbial triggers, and subclinical inflammation. Collectively, these abnormalities contribute to

progressive loss of immune tolerance and transition toward clinically apparent rheumatoid arthritis. Future research should focus on refining predictive models, identifying modifiable pathogenic pathways, and evaluating targeted preventive interventions capable of interrupting disease progression before irreversible inflammatory arthritis develops.

CONCLUSION

This systematic review demonstrates that rheumatoid arthritis is preceded by a prolonged phase of immune dysregulation characterized by the presence of autoantibodies, inflammatory cytokine activation, altered lymphocyte profiles, environmental risk exposures, and subclinical imaging abnormalities. Among the identified predictors, anti-citrullinated protein antibodies, high anti-CCP titers, dual ACPA/RF positivity, and ultrasonographic evidence of synovitis consistently showed strong associations with progression to inflammatory arthritis and RA. Additional factors including anti-carbamylated protein antibodies, Epstein–Barr virus immune responses, IL-6 elevation, smoking, dietary sodium intake, and familial predisposition further contributed to disease risk, highlighting the multifactorial nature of preclinical RA pathogenesis.

The reviewed evidence supports the concept that clinically apparent rheumatoid arthritis represents the final stage of a complex and evolving autoimmune process that begins years before diagnosis. Integrating serological, imaging, cellular, genetic, and environmental markers may improve early identification of individuals at highest risk for progression. These findings have important implications for the development of preventive strategies and targeted early interventions during the prearthritis phase. Future longitudinal studies and standardized predictive models are needed to optimize risk stratification and facilitate implementation of precision prevention approaches aimed at reducing the burden of rheumatoid arthritis.

Limitations

Several limitations should be considered when interpreting the findings of this systematic review. First, substantial heterogeneity existed among the included studies regarding study populations, definitions of at-risk status, follow-up duration, biomarker assessment methods, and outcome measures, limiting direct comparison between studies. Second, many studies included relatively small sample sizes or highly selected populations, which may affect the generalizability of findings to broader at-risk populations. Third, differences in laboratory assays, imaging protocols, and cutoff values for serological positivity may have introduced variability in predictive performance across studies. Fourth, the observational design of included studies precludes establishment of definitive causal relationships between immune abnormalities and RA development. Finally, only English-language publications were included, which may have introduced language and publication bias.

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