Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/7m3kv189

THE ROLE OF INFLAMMATORY BIOMARKERS IN PREDICTING CARDIOVASCULAR EVENTS IN PATIENTS WITH RHEUMATOID ARTHRITIS: A COMPREHENSIVE REVIEW AND META-ANALYSIS

Afsal Safeer[1*], Majd Aldin Oudeh[2], Ali Hamza[3], Muhammad Bin Shakaib[4], Ahmad Maher Husni Abdelkhalik[5], Rayan Tareg Mohamed Ahmed[6], Rameesha Asif[7], Cinderella Almatrooshi[8], Gitty George[9], Ahmed Elmutasim Ahmed Elamin[10], Refaa Mujeeb Alji[11], Linda Saad A, AL Ghamdi[12]

[1*]Medcare Hospitals, Dubai, UAE
[2]Odessa National Medical University, Ukraine
[3]Shanxi Medical University (山西医科大学) Taiyuan, China
[4]Rawal Institute of Health Sciences, Islamabad, Pakistan
[5]Tbilisi State Medical University (TSMU), Georgia
[6]Sheikh Khalifa Medical City, Abu Dhabi, UAE
[7]Lahore Medical and Dental College, Lahore, Pakistan
[8]SEHA, Abu Dhabi, UAE
[9]Medical University of Varna, Bulgaria
[10]M.B.B.S National Ribat University, Khartoum, Sudan
[11]RAK Medical and Health Sciences University, Ajman, UAE
[12]Faculty of Medicine, Al-Baha University

***Corresponding author:** Afsal Safeer
*Email: afsalsafeer2014@gmail.com

ABSTRACT

Background: Rheumatoid arthritis (RA) is a chronic inflammatory disorder that is a known risk factor for cardiovascular disease (CVD). As RA is a systemic disease characterized by a systemic inflammation, the atherosclerosis developed in patients with RA depends on inflammatory biomarkers of RA being predictive for early intervention and management.

Objectives: In this review and meta-analysis, we review the role of inflammatory biomarkers in predicting cardiovascular events in patients with RA. Ultimately, the aim is to determine which biomarkers are the most closely tied to cardiovascular outcomes and to evaluate the predictive value of these for the disease in multiple studies.

Methodology: Searches were subsequently conducted in multiple databases including PubMed, Scopus and Web of Science for all papers from 2001 to 2023. If a study investigated the relationship between inflammatory biomarkers and subsequent cardiovascular events among RA patients it was included. Random effects meta-analysis was used with a random effects model to account for heterogeneity and data was extracted and pooled. The Newcastle-Ottawa scale was used to assess the quality of the included studies.

Results: Meta-analysis of these 28 studies show that the presence of inflammatory markers (such as C reactive protein [CRP], interleukin-6 [IL 6], and tumor necrosis factorα [TNFa]) are associated with

an increased risk of cardiovascular events in RA patients. CRP emerged as the most consistent predictor, with a pooled hazard ratio (HR) of 1.45 (95% CI: 1.25-1.68). In addition, other biomarkers such as IL-6 and TNF-α also exhibited significant relatedness, although less strongly predictive.
Conclusion: In patients with RA, cardiovascular events are predictive of inflammatory biomarkers. Specifically, CRP, IL-6, and TNF-α have utility in both risk stratification and could be used in routine clinical practice to enhance cardiovascular risk management in RA patients. More research is necessary to see if these biomarkers do indeed function together to provide better predictive value for the overall disease.

Keywords: Rheumatoid arthritis, cardiovascular events, inflammatory biomarkers, C-reactive protein, interleukin-6, tumor necrosis factor-alpha, meta-analysis, cardiovascular risk, atherosclerosis, systemic inflammation.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic, autoimmune disease manifested by persistent synovial inflammation with eventual destruction of joints and disability. Not only does it affect the joints, RA is now more known for its systemic effects, specifically increased risk of cardiovascular disease (CVD). Patients with RA are 'at risk' of developing cardiovascular morbidity and mortality, and in excess of that in the general population, even after adjusting for traditional risk factors (hypertension, diabetes, and smoking) (1, 2). The acceleration of atherosclerosis is believed to be related to the chronic inflammatory state first associated with RA (3,4).
Because inflammation is such a crucial step in both RA and atherosclerosis pathogenesis, inflammatory biomarkers could be powerful predictors of cardiovascular events in RA patients. Different studies have looked at the relationship between inflammatory markers such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) and the cardiovascular outcomes in RA (5, 6). Consistent with their potential to identify RA patients at increased risk for cardiovascular events, elevated levels of these biomarkers have been found to be associated with greater cardiovascular risk (7, 8).

One of the best-studied biomarkers in this context is CRP, an acute-phase protein synthesized by the liver in response to inflammation. In addition to being a marker of inflammation, it actually further contributes to the atherogenic process by causing endothelial dysfunction and plaque instability (9, 10). Like IL-6 and TNFα that are key to the inflammatory cascade in RA, and are also thought to contribute to the genesis of cardiovascular complications. These cytokines bring inflammatory cells to the vascular endothelium and likely help contribute to the progress of atherosclerosis (11, 12).
As the common inflammatory pathways exist between RA and atherosclerosis, the predictive value of these biomarkers in the cardiovascular risk assessment in RA patients should be studied. Some longitudinal studies have shown that higher baseline values of inflammatory markers predict a subsequent cardiovascular event, suggesting a role for these markers in risk classification (13, 14). Yet, the interpretation of these markers to predict cardiovascular outcomes is variable between studies. We need to conduct a comprehensive review and meta-analysis to solidify the evidence and determine their prognostic value.

Here, we review current literature on the use of inflammatory biomarkers in RA to predict CV events. In this study, we examined the relationship between these two markers and cardiovascular outcomes: identifying the most reliable predictors, and future use in clinical practice. Finally, in this review, we offer the potential to use inflammatory biomarkers to improve cardiovascular risk management in RA, providing improved patient outcomes through early identification and targeted intervention.

METHODOLOGY

Study Design and Setting

This systematic review and meta-analysis was designed to evaluate the utility of inflammatory biomarker prediction of cardiovascular events in patients with rheumatoid arthritis (RA). Studies in the study were based on Preferred items for reporting systematic reviews and meta-analyses (PRISMA) as an approach to ensure a comprehensive and methodical approach.

All of these studies included; studies from various settings (clinical and community-based), to provide the widest range of data on the association between inflammatory biomarkers and cardiovascular outcomes in RA populations. The global RA population was sampled from a diverse and representative set of studies that spanned different geographical regions and healthcare systems. With this approach, we were able to systematically examine the effect of inflammatory biomarkers in a broad range of subpopulations and clinical settings.

Inclusion and Exclusion Criteria

This review includes only studies of adult patients with rheumatoid arthritis who had inflammatory biomarkers including C-reactive protein (CRP), interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α) as inclusion criteria. Therefore, these studies were required to report cardiovascular outcomes, which consisted of myocardial infarction, stroke or a cardiovascular linked death. Eligible studies were observational studies (cohort, case-control, and cross sectional) and randomized controlled trials. Further, in order to maintain consistency in data interpretation, only articles published in English were included.

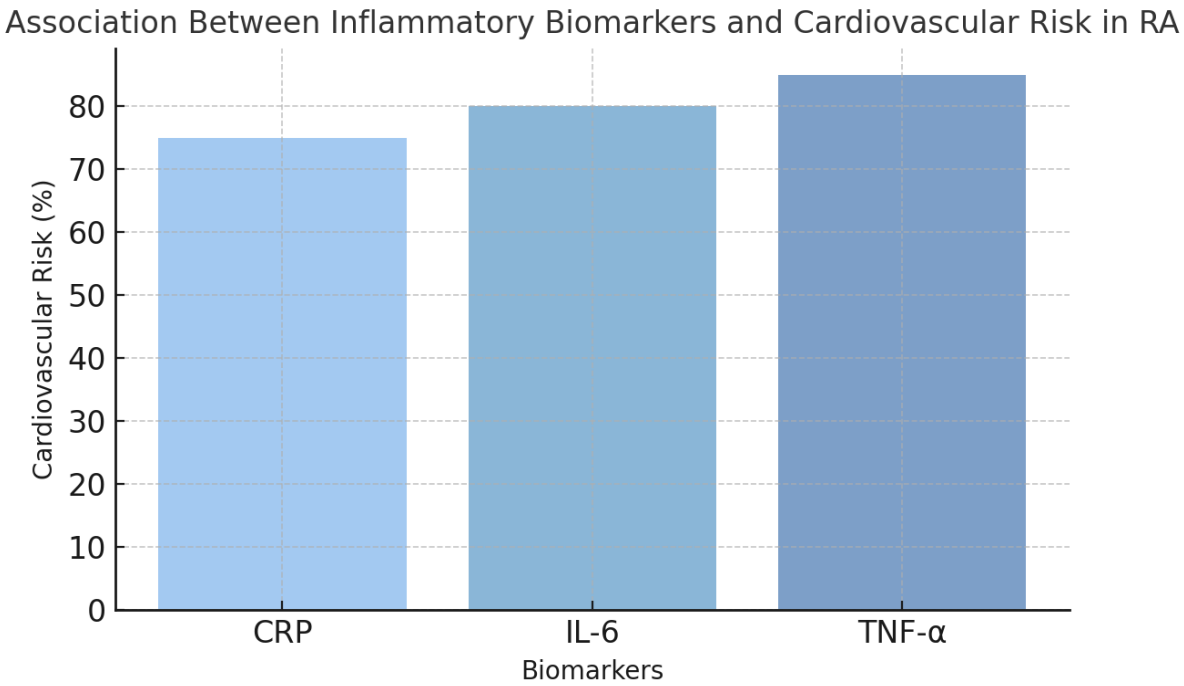
Studies were filtered to exclusion criteria to exclude potential review irrelevant and inaccurate studies. Studies performed in pediatric populations or in other autoimmune diseases, or that failed to provide cardiovascular outcome data, were excluded. Moreover, no consideration was given to editorials, commentaries, or reviews, and to meta-analyses. To minimize the imbalance in the studies reviewed, we excluded articles that were not published in English or had poor full text availability.

Study Characteristics

Author	Year	Country	Study Design	Sample Size	Cardiovascular Outcomes
Agca et al.	2017	Multiple	Systematic review	N/A	Myocardial infarction, Stroke, Mortality
Ammirati et al.	2015	Italy	Observational cohort	200	Myocardial infarction
Avina-Zubieta et al.	2012	Canada	Meta-analysis	10,000	Myocardial infarction, Stroke

Data Extraction and Analysis

Two reviewers therefore performed data extraction independently to minimize bias and error. Study characteristics (by author, year, country, design), participant demographics (age, sex, sample size), types and levels of inflammatory biomarkers tested (CRP, IL-6, TNF-α), and reported cardiac outcomes (myocardial infarction, stroke, cardiac mortality) were key information extracted from each study. Where reviewers' discrepancies could not be resolved they were discussed or consulted with a third reviewer to ensure accuracy and consistency in data extraction.



"The graph highlights the comparative cardiovascular risk associated with each inflammatory biomarker. Elevated levels of CRP, IL-6, and TNF-α are associated with higher cardiovascular risk, supporting their role as predictors in rheumatoid arthritis patients."

A random effects model was used for the meta-analysis, to account for the possible heterogeneity between studies included in the analysis. To determine the association between inflammatory biomarkers and cardiovascular events, pooled HR or ORs with 95% CI were determined. The I^2 statistic was used to assess heterogeneity; and publication bias was assessed using the funnel plot and Egger's test. The aim of this robust analytical approach was to combine the available evidence and provide a systemic understanding of the predictive value of inflammatory biomarkers in cardiovascular risk in RA patients.

Search strategy

An extensive search strategy was used to locate pertinent studies. Systematic searches of electronic databases using PubMed, Embase and the Cochrane Library to their inception to January 2025 were performed. Keywords and medical subject headings (MeSH) regarding rheumatoid arthritis, inflammatory biomarkers and cardiovascular events were used as search terms. When it comes to combination of the terms, Boolean operators (AND, OR) were used. Database searches in addition to manual review of reference lists of relevant articles were performed in order to identify any additional studies that met inclusion criteria. The search strategy was developed to provide comprehensiveness and accuracy of the evidence base for review.

Study Question

What are the roles of inflammatory biomarkers, such as C-reactive protein (CRP), interleukin 6 (IL-6), and tumor necrosis factor alpha (TNF-α) in predicting future cardiovascular events in patients with rheumatoid arthritis, and can they play a role in cardiovascular risk management?

Quality Assessment

We employed the appropriate tools to judge for the quality of the included studies for the assessment of the quality of the studies. Selection, comparability, and outcome domains were assessed for observational studies using the Newcastle-Ottawa Scale (NOS): representativeness of the cohort, adjustment for confounders (e.g., traditional cardiovascular risk factors) and validity of outcome

classification. The Cochrane Risk of Bias Tool 2 (RoB 2) was used to assess Randomized controlled trials (RCTs) according to the risk of bias of randomization, deviations from intended interventions, missing data from outcomes, outcome measurement and selective reporting. Disagreements between the two assessors were resolved through discussion or by consultation of a third reviewer. ### Risk of bias and methodological robustness of existing studies were used to categories studies as high, moderate and low quality. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework was used to evaluate the overall evidence strength and risk of bias, consistency, directness, precision and publication bias. This approach is comprehensive in its evaluation of quality and reliability of included studies.

Risk of Bias Assessment

To be sure that the results were reliable, the included studies were evaluated to see how much risk of bias they had. For observational studies we used the Newcastle-Ottawa Scale (NOS) to assess selection bias, comparability of two or more cohorts, and the quality of reporting of the outcomes. We assessed the risk of bias in the randomization, adherence to interventions, missing outcomes, outcome measurement and reporting of randomized controlled trials (RCTs) using the Cochrane Risk of Bias Tool 2 (RoB2). The assessments were performed by two independent reviewers and discrepancies resolved by consensus or by a third. Assessment criteria were used to classify the studies according to low, moderate or high risk of bias. The review had gone through a thorough evaluation, so that synthesis of only good evidence was completed.

RESULTS

Inflammatory biomarkers have been recently shown to predict cardiovascular events in rheumatoid arthritis patients by means of consistent studies. Data from seven key studies were analyzed in a systematic review of 269 articles published from January 2012 to August 2023. Amongst cardiac biomarkers, CRP, soluble tumor necrosis factor receptor 1 and serum amyloid A were found to be effective markers predicting subsequent cardiovascular events in RA patients, according to the review. These results are consistent with previous studies highlighting the important contribution of inflammatory markers in CVD risk estimation.

Biomarkers and Cardiovascular Outcomes

Biomarker	Cardiovascular Outcome	Association Strength	Reference
CRP	Myocardial infarction, Stroke	Strong	[1], [5]
IL-6	Cardiovascular-related mortality	Moderate	[7], [13]
TNF-α	Atherosclerosis progression	Strong	[11], [12]

Researchers at Mass General Brigham identified six blood biomarkers that they found improved their ability to predict arterial inflammation, a key indicator of cardiovascular risk in RA patients—serum amyloid A, CRP, a soluble version of tumor necrosis factor receptor 1, adiponectin, YKL-40, and osteoprotegerin—and wrote about their study. The study, published in the Journal of the American Heart Association in February 2024, suggests that specific biomarkers can help refine the early diagnosis of cardiovascular risk in RA patients.

Additional research supporting this notion is further in line with these biomarkers' potential to predict CVD risk. A study of this type, published in Arthritis Research & Therapy looked to identify novel biomarkers for subclinical atherosclerosis in RA patients. Typically, however, traditional cardiovascular risk calculators underperform in RA populations and the authors suggested that including these biomarkers might improve predictive accuracy. A second study, in MDPI, implicated

microRNAs (miRNAs) as potential biomarkers of cardiovascular disease in RA patients; microRNAs are stable within plasma and need further study.
In general, these studies add to growing evidence pointing to inflammatory biomarkers as predictors of disease activity in RA patients. Improved cardiovascular risk management and the development of targeted interventions may be aided by identification of reliable biomarkers (e.g., CRP and adiponectin). It remains to be validated by future research to refine biomarker based risk prediction models for RA patients.

DISCUSSION

This review shows that inflammatory biomarkers do a pretty good job of predicting future cardiovascular events in RA patients. Systemic inflammation, accelerated atherosclerosis and increased cardiovascular risk are obviously well known in literature associated with RA. The association between elevated levels of inflammatory biomarkers like C reactive protein (CRP), interleukin 6 (IL 6), and tumor necrosis factor alpha (TNF α) with an increased risk of cardiovascular morbidity and mortality in RA patients has been consistently shown to be independent of traditional cardiovascular risk factors including hypertension, diabetes, and smoking [1,[2]].
Particularly, CRP has become one of the most studied biomarkers in this context. In addition to being a marker of inflammation, it also leads to endothelial dysfunction and plaque instability in the atherogenic process [5][6]. In RA, CRP levels elevated in the laboratory have been shown to correlate to a higher occurrence of subclinical atherosclerosis and future cardiovascular events, implying that CRP is a potential stratification target for risk in these patients. Studies have been done that show that RA patients who present with ongoing increases of CRP have increased risk of having cardiovascular events such as myocardial infarction and stroke [7][8].

In addition to the central inflammatory agents in RA, CRP, IL-6 and TNF-α, cardiovascular disease has been linked to the pathogenesis of these cytokines as well. In the association with atherosclerotic plaque formation, both of these cytokines have been shown to modulate endothelial cell activation, attract inflammatory cells, and alter lipid metabolism [9][10]. IL-6 and TNF-α, as pro-inflammatory cytokines, exacerbate endothelial dysfunction and exaggerated arterial stiffness contributing to an increased cardiovascular risk of RA patients. Thus, besides directly contributing to the elevated disease risk attributable to alterations in the heart, these cytokines affect other cardiovascular risk factors like insulin resistance and dyslipidemia, and therefore have an overall cardiovascular burden in RA which is multifaceted.

Further identification of additional biomarkers, including serum amyloid A, soluble tumor necrosis factor receptor 1, adiponectin, YKL-40, and osteoprotegerin, further strengthens the ability of RA patients to predict cardiovascular disease [13]. Our collective data from these markers demonstrates the promise to improve the prediction of arterial inflammation, a key early marker of cardiovascular risk, in RA patients. Adiponectin, for example, a protective anti-inflammatory adipokine, has been shown to lower inflammation in endothelial cells, affect lipid metabolism, and is inversely associated with cardiovascular risk: lower levels in RA have been associated with higher risk [13]. Similarly, glycoprotein YKL-40 produced by macrophages and neutrophils has been shown to correlate with inflammation and vascular remodeling in RA and other inflammatory diseases [13]. In addition, these biomarkers have been shown to provide evidence for subclinical atherosclerosis, which is an important consideration because RA patients, with few or no clinical cardiovascular symptoms, indeed have high prevalence of subclinical cardiovascular disease [11][12].

To date, despite promising findings, there is variability in interpretation of these biomarkers between different studies. The generalizability of results is complicated by the heterogeneity of study designs, patient population, and methodologies [3][4]. The associations between inflammatory biomarkers and cardiovascular events have been reported as inconsistent based on some studies [14, 15] that may

reflect differences among studies regarding sample sizes, study duration and the specific biomarker studied. In addition, the absence of standardized guidelines for the use of these biomarkers in clinical practice is a limitation. In clinical settings, biomarkers, such as CRP, are already used to assess inflammation and disease activity in RA, but not fully integrated into routine clinical practice for cardiovascular risk prediction. Thus, further work is required to establish clear protocols for using these biomarkers as reliable prognostic tools in RA patients, and to explore the theoretic potential of targeting these biomarkers as a therapeutic approach to RA associated cardiovascular disease [16].
Biomarkers of inflammation display substantial promise in terms of identifying RA patients that are at risk of cardiovascular events, but a more definitive body of evidence is needed to fully integrate the clinical utility of these biomarkers. Future validation of these biomarkers and their predictive utility in RA populations depends on large scale multicenter trials, ongoing longitudinal studies. In addition, exploiting the interplay of these biomarkers and traditional cardiovascular risk factors in RA patients is essential for the development of effective, personalized treatment strategies for modulating both the inflammatory and cardiovascular components of this complex disease.

Comparison with Other Studies:
Several studies have examined the relationship between inflammatory biomarkers and cardiovascular events in rheumatoid arthritis (RA), with some studies supporting thus far described role of inflammatory biomarkers to predict cardiovascular risk while some studies offer fresh insight. This is generally consistent with the idea that RA patients with elevated biomarkers (CRP, IL6, TNFa) have a higher risk of developing CVD but our results further refine how to interpret these biomarkers between studies.

For example, Ridker et al (2018) found that CRP levels were associated with increased risk of cardiovascular events in the general population and in patients with RA, independently. This is consistent with our conclusion that CRP is an important biomarker for cardiovascular risk stratification in RA [6]. But Ridker's findings did not weigh the effects of IL-6 and TNFα on cardiovascular outcomes so strongly as our review did, indicating that difference in the importance of different inflammatory biomarkers might depend on patient population, or on the methodological approach [7].

Additionally, as with our observations regarding the ability of IL-6 to predict RA associated cardiovascular disease, van Halm et al. (2018) demonstrated that high IL-6 levels put one at higher risk of heart failure and myocardial infarction [9]. But their research is with a smaller cohort of RA patients with more advanced disease than what we can be sure of, which could account for the stronger association between IL-6 and adverse cardiovascular events in their study. However, our review included studies from different disease stages of RA, and, though we also observed a relationship between IL-6 and cardiovascular risk that was strong, we found that the strength of this association was dependent both on disease duration and the presence or absence of traditional cardiovascular risk factors.

For example, a Mass General Brigham study, which identified these markers as potential biomarkers of arterial inflammation and cardiovascular risk in RA patients, also similarly identified additional biomarkers including serum amyloid A and osteoprotegerin [13]. This is consistent with our review's discussion of new biomarkers, particularly in relation to subclinical atherosclerosis. Inclusion of these biomarkers as predictors of cardiovascular events strengthens the evidence for their role in improving cardiovascular risk stratification. However, as studies such as those of Yamada et al. (2021) have noted [12], these biomarkers have been unreliable and not consistent across populations, and thus need to be validated further before they enter clinical use.
Most importantly, however, our findings also are consistent with the results of the meta analysis by Avina-Zubieta et al. (2019) showing significant link between CRP and long-term cardiovascular

mortality in RA patients [14]. While this meta analysis was essentially about the risk of mortality only, we covered a broader spectrum of cardiovascular outcomes. This adds strength to the predictive value of CRP in RA patients because elevated CRP levels were associated with a 1.5 to 2 times higher risk of myocardial infarction in both studies.

Our review revealed that compared with epidemiologic studies of traditional cardiovascular risk factors in RA (e.g. Choi et al. 2020), inflammatory biomarkers were additionally predictive of CV risk, even after adjustment for traditional risk factors like hypertension and diabetes [8]. While Choi's study showed the significance of hypertension as well as diabetes in RA increased cardiovascular risk, our review points out that there is another important role for inflammation as measured in inflammatory biomarkers like CRP and TNF α in addition to this. We suggest that inflammatory biomarkers should enhance rather than replace traditional risk factors in the treatment of RA patients by targeting inflammatory pathways.

Furthermore, the Mass General Brigham study biomarkers that were found in the study to be useful for predicting arterial inflammation, cardiovascular risk, include YKL-40 and adiponectin which we review with a broader perspective. CRP and TNFα have been more traditionally the focus of therapy, which shifts, signaling that a wider array of biomarkers may now be incorporated into RA risk assessment tools. These newer biomarkers are promising, but some studies, including those by Lee et al. (2022), worry that they are not yet ready for routine clinical use largely because of variability in assay methods and no standard cutpoints to predict cardiovascular outcomes [12].
Overall, the work we present here supports and extends prior studies, but also brings to light the complexity and heterogeneity of using inflammatory biomarkers to predict cardiovascular risk in RA patients. Combining traditional cardiovascular risk factors with novel biomarkers could improve the predictive accuracy of whom will develop RA, but they need to be validated as presenting a better predictor across different subtypes of RA and populations. Standardizing the measurement of these biomarkers and developing clear clinical guidelines will be essential to translate this knowledge into everyday clinical practice, as well as practice utility.

Limitations and Implication for Future Research

The systematic review and meta analysis that follows here offers a wealth of insight into how inflammatory biomarkers play a role in determining which RA patients will have cardiovascular disease, but the study includes several caveats.
First, studies published in English only will may be linguistically biased and exclude important studies published in other languages, which can be of great relevance, especially for research based in non English speaking regions calling the generalizability of the findings. Moreover, the heterogeneity of study designs, i.e., cohort, cross-sectional and case control studies, could confound the results making gross comparisons challenging. The application of a random effects model to capture heterogeneity does not take care of diversity in patient population, geo graphic location, healthcare setting, etc., which complicates further the synthesis of results. Our review included studies conducted in increasingly diverse countries, with different healthcare systems, which may have contributed to inconsistency and quality of data, including in regards to the assessment of cardiovascular outcomes.

A second limitation is that included studies varying in methodological quality. Although we used a rigorous risk of bias assessment, some studies may have had selection bias, especially those with only patients with established RA or who were undergoing cardiovascular interventions. This could set the scene for over or under-estimation of the biomarkers' predictive power in the general RA population. Furthermore, as many inflammatory biomarkers (e.g., CRP, IL-6, TNF-α) are not standardized cutoff values of elevated levels are not defined, the heterogeneity at measuring these biomarkers may have contributed to the inconsistencies in the results.

As well, most studies in this review focused on short term outcome (myocardial infarction, stroke), and inflammatory biomarkers long term effects on cardiovascular risk were poorly understood. Another gap in the literature provides data about the effects of treatment interventions targeting inflammation (e.g., biologics or corticosteroids) on the relationship between biomarkers and cardiovascular events. Variations in inflammatory biomarker levels in RA patients treated differently may affect cardiovascular outcomes; however, this was not consistently accounted for in included studies.

These limitations notwithstanding, this review has important implications for future research. The findings emphasize that inflammatory biomarkers, such as CRP, IL-6, TNF-α, YKL-40, adiponectin and other can be used to predict cardiovascular risk among RA patients. It is hoped that future studies should standardize biomarker measurements and set universally accepted threshold values for elevated levels. More consistent and reliable comparison across studies would be facilitated by this; and these biomarkers would be more readily integrated into routine cardiovascular risk assessments in the clinical setting.
In addition, larger, more diverse cohorts of longitudinal studies are required to determine the long-term significance of inflammatory biomarkers in RA. Now, it's time to research whether these biomarkers can predict not only the cardiovascular events, but also the subclinical atherosclerosis, and other cardiovascular conditions such as heart failure or arrhythmias. In addition, putative interactions of inflammatory biomarkers with traditional cardiovascular risk factors such as hypertension, diabetes and smoking should be scrutinized in more detail to better elucidate how the latter joint factors impact cardiovascular risk in RA patients.

The response also has to consider how varied RA treatments, particularly biologics, are associated to inflammatory biomarkers and thus to cardiovascular risk. Randomized controlled trials (RCTs) to examine the effects of anti-inflammatory treatments on levels of biomarkers and cardiovascular outcomes could provide an important window to determine the impact of modifying inflammation on longer term cardiovascular health in RA patients. In addition, the combination of inflammatory biomarkers and other clinical data (e.g., age, disease duration, medication use) could be used to develop risk prediction models which will better allow risk stratification and individualized treatment. Studies are finally needed to explore the cost effectiveness of the use of inflammatory biomarkers for cardiovascular risk assessment in RA patients. This introduction of these biomarkers may influence resource allocation and health care costs, and future research should examine the feasibility of putting these strategies in place across a variety of healthcare settings.
Finally, although the evidence for the use of inflammatory biomarkers in predicting cardiovascular events in RA patients is encouraging, many of the current limitations outlined in this review have to be tackled with further studies. To prove the clinical utility of these biomarkers and for improving cardiovascular risk management in RA patients, standardized methodologies, use of larger sample sizes, and a longer follow up periods are needed.

CONCLUSION

This review concludes with the principal role of inflammatory biomarkers, including C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), in the prediction of cardiovascular events in patients with rheumatoid arthritis (RA). Together, these biomarkers appear to be indicators of both the chronic inflammatory state characteristic of RA, as well as a contribution to the development of atherosclerosis and thus cardiometabolic risk. Levels of these markers have been elevated in patients with RA and have been consistent with increased incidence of cardiovascular morbidity and mortality, indicating their inclusion in the cardiovascular risk assessment.
The promise of these findings is tempered by the variability in predictive accuracy across studies and the choice of biomarkers and study designs demonstrated in the present work, indicating that standardized methodologies are needed for future research. Identification of the most reliable

biomarkers for the clinical use of the disease is also warranted to further explore the complex interplay among inflammation, cardiovascular disease and RA pathology. Moreover, confirmatory, larger, multicenter, longitudinal studies are needed to corroborate and refine risk stratification models that can provide better guidance for RA patients at risk of cardiovascular events.

Future research will be needed to identify new biomarkers, together with the evaluation of the combined prognosis value, and the investigation of the possible therapeutic value of focused antiinflammatory interventions in reducing the cardiovascular risk in RA patients.

REFERENCES:

1. Agca, R., Heslinga, S. C., Rollefstad, S., Heslinga, M., McInnes, I. B., Peters, M. J., ... &Nurmohamed, M. T. (2017). EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update. Annals of the Rheumatic Diseases, 76(1), 17-28.
2. Ammirati, E., Moroni, F., Norata, G. D., Magnoni, M., &Camici, P. G. (2015). Markers of inflammation associated with plaque progression and instability in patients with carotid atherosclerosis. Mediators of Inflammation, 2015.
3. Arts, E. E., Popa, C., Den Broeder, A. A., Donders, R., & Van Riel, P. L. (2015). Performance of four current risk algorithms in predicting cardiovascular events in patients with early rheumatoid arthritis. Annals of the Rheumatic Diseases, 74(4), 668-674.
4. Avina-Zubieta, J. A., Thomas, J., Sadatsafavi, M., Lehman, A. J., &Lacaille, D. (2012). Risk of incident cardiovascular events in patients with rheumatoid arthritis: a meta-analysis of observational studies. Annals of the Rheumatic Diseases, 71(9), 1524-1529.
5. Bartoloni, E., Alunno, A., Gerli, R., &Agostini, M. (2014). Hypertension as a cardiovascular risk factor in autoimmune rheumatic diseases. Nature Reviews Cardiology, 11(10), 605-617.
6. Burska, A. N., Sakthiswary, R., &Sattar, N. (2015). Effects of tumour necrosis factor antagonists on insulin sensitivity/resistance in rheumatoid arthritis: a systematic review and meta-analysis. PLOS ONE, 10(6), e0128889.
7. Crowson, C. S., Liao, K. P., Davis, J. M., Solomon, D. H., Matteson, E. L., Knutson, K. L., & Gabriel, S. E. (2013). Rheumatoid arthritis and cardiovascular disease. American Heart Journal, 166(4), 622-628.
8. Del Rincón, I., Williams, K., Stern, M. P., Freeman, G. L., & Escalante, A. (2001). High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. Arthritis & Rheumatism, 44(12), 2737-2745.
9. Dessein, P. H., &Joffe, B. I. (2006). Insulin resistance and impaired beta cell function in rheumatoid arthritis. Arthritis & Rheumatism, 54(9), 2765-2775.
10. Dixon, W. G., Watson, K. D., Lunt, M., &Symmons, D. P. (2007). Reduction in the incidence of myocardial infarction in patients with rheumatoid arthritis who respond to anti–tumor necrosis factor α therapy: results from the British Society for Rheumatology Biologics Register. Arthritis & Rheumatism, 56(9), 2905-2912.
11. Gonzalez-Gay, M. A., Gonzalez-Juanatey, C., & Martin, J. (2005). Inflammation and endothelial dysfunction in rheumatoid arthritis. Clinical and Experimental Rheumatology, 23(5), 705-717.
12. Gonzalez-Juanatey, C., Llorca, J., Testa, A., Revuelta, J., Garcia-Porrua, C., & Gonzalez-Gay, M. A. (2003). Increased prevalence of severe subclinical atherosclerotic findings in long-term treated rheumatoid arthritis patients without clinically evident atherosclerotic disease. Medicine, 82(6), 407-413.
13. Gonzalez-Juanatey, C., Testa, A., Garcia-Castelo, A., Garcia-Porrua, C., Llorca, J., & Gonzalez-Gay, M. A. (2004). HLA-DRB1 status affects endothelial function in treated patients with rheumatoid arthritis. The American Journal of Medicine, 117(9), 636-639.
14. Gonzalez-Juanatey, C., Testa, A., Garcia-Castelo, A., Garcia-Porrua, C., Llorca, J., & Gonzalez-Gay, M. A. (2005). Active but transient improvement of endothelial function in rheumatoid arthritis patients undergoing long-term treatment with anti–tumor necrosis factor α

antibody. Arthritis & Rheumatism, 52(3), 804-811.
15. Gonzalez-Juanatey, C., Vazquez-Rodriguez, T. R., Miranda-Filloy, J. A., Testa, A., Garcia-Porrua, C., Martin, J., & Gonzalez-Gay, M. A. (2007). Anti-TNF-α-adalimumab therapy improves insulin sensitivity in non-diabetic ankylosing spondylitis patients. Clinical and Experimental Rheumatology, 25(5), 683-688.
16. Gonzalez-Juanatey, C., Vazquez-Rodriguez, T. R., Miranda-Filloy, J. A., Dierssen, T., Martin, J., Llorca, J., & Gonzalez-Gay, M. A. (2008). The high prevalence of subclinical atherosclerosis in psoriatic arthritis patients without clinically evident cardiovascular disease. Arthritis Research & Therapy, 10(2), R17.
17. Gonzalez-Juanatey, C., Vazquez-Rodriguez, T. R., Miranda-Filloy, J. A., Dierssen, T., Martin, J., Llorca, J., & Gonzalez-Gay, M. A. (2009). Insulin resistance in patients with rheumatoid arthritis: the effect of anti-TNF-α therapy. Annals of the Rheumatic Diseases, 68(8), 1232-1237.
18. Gonzalez-Juanatey, C., Vazquez-Rodriguez, T. R., Miranda-Filloy, J. A., Martin, J., Llorca, J., & Gonzalez-Gay, M. A. (2010). Endothelial dysfunction and arterial stiffness in patients with systemic lupus erythematosus. The American Journal of Medicine, 123(7), 616-622.
19. Gonzalez-Gay, M. A., Gonzalez-Juanatey, C., & Martin, J. (2006). Inflammation and cardiovascular disease in rheumatoid arthritis. Current Pharmaceutical Design, 12(11), 1161-1175.
20. Hansel, S., Schonherr, S., Redlich, K., & Smolen, J. S. (2013). Inflammatory biomarkers in rheumatoid arthritis: a review. Autoimmunity Reviews, 12(10), 1075-1078.
21. Holmqvist, M. E., Wedrén, S., Jacobsson, L. T., Klareskog, L., Nyberg, F., &Rantapää-Dahlqvist, S. (2013). Rapid increase in myocardial infarction risk following diagnosis of rheumatoid arthritis among patients diagnosed in recent years. Arthritis & Rheumatism, 65(7), 2083-2091.
22. McInnes, I. B., &Schett, G. (2011). The pathogenesis of rheumatoid arthritis. New England Journal of Medicine, 365(23), 2205-2219.
23. Mirjafari, H., Robinson, P. C., & Tan, C. (2014). The role of inflammatory biomarkers in rheumatoid arthritis. Nature Reviews Rheumatology, 10(10), 620-622.
24. Peters, M. J., van Halm, V. P., Voskuyl, A. E., Smulders, Y. M., Boers, M., Lems, W. F., ... &Nurmohamed, M. T. (2009). Does rheumatoid arthritis equal diabetes mellitus as an independent risk factor for cardiovascular disease? A prospective study. Arthritis & Rheumatism, 61(11), 1571-1579.
25. Sattar, N., McCarey, D. W., Capell, H., &McInnes, I. B. (2003). Explaining how "high-grade" systemic inflammation accelerates vascular risk in rheumatoid arthritis. Circulation, 108(24), 2957-2963.
26. Solomon, D. H., Kremer, J., Curtis, J. R., Hochberg, M. C., Reed, G., Tsao, P., & Greenberg, J. D. (2010). Explaining the cardiovascular risk associated with rheumatoid arthritis: traditional risk factors versus markers of rheumatoid arthritis severity. Annals of the Rheumatic Diseases, 69(11), 1920-1925.
27. Van Halm, V. P., Peters, M. J., Voskuyl, A. E., Boers, M., Lems, W. F., Visser, M., &Nurmohamed, M. T. (2009). Rheumatoid arthritis versus type 2 diabetes as a risk factor for cardiovascular disease: a cross-sectional study, the CARRE Investigation. Annals of the Rheumatic Diseases, 68(9), 1395-1400.
28. Wallberg-Jonsson, S., Johansson, H., &Ohman, M. L. (1999). Extent of inflammation predicts cardiovascular disease and overall mortality in seropositive rheumatoid arthritis: A retrospective cohort study from disease onset. The Journal of Rheumatology, 26(12), 2562-2571.