Biomarkers for the diagnosis and treatment of rheumatoid arthritis-a systematic review

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Abstract

Background Rheumatoid Arthritis (RA) is an autoimmune disease, symmetrically affecting the small joints. Biomarkers are tools that can be used in the diagnosis and monitoring of RA. Aim To systematically explore the role of the biomarkers: C-reactive protein (CRP), Rheumatoid factor (RF), Anti-cyclic citrullinated protein (Anti-CCP), 14-3-3η and the multi-biomarker disease activity (MBDA) score for the diagnosis and treatment of RA. Methods A systematic review of the English literature using four different databases was carried out. Results CRP>7.1 mg/L predicted poor conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) outcome in RA. Anti-CCP, CRP [?]0.3 mg/dL and RF predicted bone erosion and cartilage destruction. Combination of high 14-3-3η with RF and CRP improved the prediction of rapid erosion progression (REP). Anti-CCP was not associated with disease activity, but was associated with increased radiographic damage (r=0.46, p=0.048). RF was not associated with joint damage but correlated with ultrasound-detected bone erosion. 14-3-3η significantly correlated with inflammation, bone remodelling and osteoporosis in RA patients ($p<0.05$). 14 3 3η positively correlated with RA duration (p=0.003), disease activity and positive RF (P=0.025) and it distinguished early from established RA. Early MBDA scores correlated with later response in disease activity, after 6 and 12 weeks of treatment ($p<0.05$). MBDA score was able to differentiate between small differences in disease activity and predicted remission over one year period. Conclusion The investigated biomarkers are helpful tools in clinical practice for diagnosis, monitoring of treatment and predicting prognosis in RA patients. However, further research is still required to investigate novel biomarkers for the pre-treatment selection of potentially responsive patients before starting therapy for a precision medicine in this area.

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Abstract

Background

Rheumatoid Arthritis (RA) is an autoimmune disease, symmetrically affecting the small joints. Biomarkers are tools that can be used in the diagnosis and monitoring of RA.

Aim

To systematically explore the role of the biomarkers: C-reactive protein (CRP), Rheumatoid factor (RF), Anti-cyclic citrullinated protein (Anti-CCP), 14-3-3η and the multi-biomarker disease activity (MBDA) score for the diagnosis and treatment of RA.

Methods

A systematic review of the English literature using four different databases was carried out.

Results

CRP>7.1 mg/L predicted poor conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) outcome in RA. Anti-CCP, CRP [?]0.3 mg/dL and RF predicted bone erosion and cartilage destruction. Combination of high 14-3-3η with RF and CRP improved the prediction of rapid erosion progression (REP). Anti-CCP was not associated with disease activity, but was associated with increased radiographic damage (r=0.46, p=0.048). RF was not associated with joint damage but correlated with ultrasound-detected bone erosion. 14-3-3η significantly correlated with inflammation, bone remodelling and osteoporosis in RA patients (p<0.05). 14-3-3η positively correlated with RA duration (p=0.003), disease activity and positive RF (P=0.025) and it distinguished early from established RA. Early MBDA scores correlated with later response in disease activity, after 6 and 12 weeks of treatment (p<0.05). MBDA score was able to differentiate between small differences in disease activity and predicted remission over one year period.

Conclusion

The investigated biomarkers are helpful tools in clinical practice for diagnosis, monitoring of treatment and predicting prognosis in RA patients. However, further research is still required to investigate novel biomarkers for the pre-treatment selection of potentially responsive patients before starting therapy for a precision medicine in this area.

Key points

- Biomarkers are significant predictors of RA activity, prognosis and response to treatment.
- They are a useful tool that can be used in day-to-day clinical practice.
- Research is still required to investigate novel pre-treatment biomarkers that can select suitable patients for therapy.

Introduction

Rheumatoid arthritis (RA) is an autoimmune disease that affects the small joints, which causes pain, swelling and subcutaneous nodules around the joints resulting in a decreased quality of life.[1] RA is characterised by inflammation of the synovial membranes of the joints leading to bone erosion. [2] RA has an overall global prevalence of 0.5-1.0% in many populations with a prevalence that is twice in women than that in men and tends to be more common in the elderly. [2, 3] However, the prevalence may vary in certain populations such as that in Pima Indians and the Chippewa Indians that demonstrate a high prevalence (5.3% and 6.8% respectively) in contrast to the lower prevalence reported in China and Japan (0.2-0.3%). This suggests that as well as environmental factors, RA may have an underlying genetic predisposition to immune dysregulation. [3] The synovial membrane is composed of fibroblast-like synoviocytes (FLS) which are important in the pathogenesis of RA. Macrophages secrete cytokines such as tumour necrosis factor alpha (TNFα), interleukin-1 (IL-1) and interleukin-6 (IL-6) which stimulate FLS leading to inflammation. Activated FLS proliferate and migrate from joint to joint so commonly presents as a symmetrical polyarthritis. [4] Genetic and environmental factors cause modifications of the autoantigens. [5]Synovial injury or infection within the joint can trigger cytokine release causing inflammation leading to the citrullination of the autoantigens. [6] Modification of

autoantigens including citrullination is a result of these triggers leading to production of autoantibodies targeting citrullinated peptides. Rheumatoid factor (RF) is an IgM antibody which targets the fragment crystallisable (Fc) portion of the immunoglobulin G (IgG) forming an immune complex that promotes inflammation. [7] Anti-cyclic citrullinated peptide (Anti-CCP) target cyclic citrullinated antibodies (CCP). Extra-articular involvement results from cytokines produced within the joints causing the liver to produce more C-reactive protein (CRP) which is an inflammatory marker. [4] 14-3-3η is a protein of seven isoforms that can be elevated in RA patients and used as a unique diagnostic biomarker for RA. [8] The multi-biomarker disease activity (MBDA) score is also important for the assessment of the prognosis of RA by providing a disease activity score from 1-100 determined by the measurement of 12 biomarkers. [9] If RA is not treated, its progression and deterioration will lead to permanent destruction of the joints, resulting in reduced mobility and may cause serious complications in major organs. [8]Therefore, the early diagnosis and evaluation of RA severity, for prompt and effective intervention, is needed to significantly improve the clinical outcomes. The aim of this manuscript is to systematically review the literature for role of the following biomarkers: CRP, RF, Anti-CCP, 14-3-3η and MBDA in the diagnosis and treatment of RA and to assess whether these should be measured routinely in clinical practice.

Methods

We undertook a detailed literature search for studies that reported the role of biomarkers in RA diagnosis, response to treatment and prognosis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations. (Figure 1) Full assessment of relevant articles was conducted by searching the following databases: PubMed, OneSearch, EMBASE and Web of Science. Key words used included: 'Rheumatoid Arthritis', 'Biomarkers', 'Diagnosis', 'Treatment', 'CRP', 'Anti-CCP', 'Rheumatoid Factor', '14-3-3η', 'Outcome', 'Response to treatment', 'Disease Activity', and 'MBDA'. We reviewed all the articles initially by abstract alone. Then we performed a manual search of the citations in the relevant articles to retrieve further related studies. Relevant literature was identified and summarised separately unless there was an overlap where a study included multiple and relevant biomarkers. Due to the large amounts of literature on this topic, we have limited our research to the most recent studies published in year 2020. The inclusion criteria were: 1. Studies that investigated the impact of the biomarkers in the diagnosis, treatment or disease progression of RA. 2. Studies that reported clear and clinically relevant diagnostic or therapeutic effects of the biomarkers. The exclusion criteria were: 1. Non-English or non-human studies. 2. Studies with no clear outcome. 3. Case reports, review articles, editorials, abstracts, conference proceedings or expert opinions. Data was extracted from each study in a predesigned standardised information table that included author, study design, year of publication, country of origin, participants studied, aim of the study and the main findings. We have compared recent studies with the previous literature to draw valid conclusions. Any disagreement between authors was resolved by consensus.

Results

After exclusion of irrelevant articles, 23 studies met the inclusion criteria and were included in this systematic review. (Figure 1) The findings of these studies are summarised in Table 1. Xu K et al, retrospectively investigated the predictive value of clinical factors combined with variants of HMGB1 genes to the csDMARDS treatment outcomes. [10] They found that high CRP ($>$ 7.1mg/L) to be associated with poor outcomes (sensitivity 87.2% and specificity 60.9%). However, response to csDMARDs treatment was better in those with higher CRP. [10] Hayashi S, et al, investigated biomarkers that help in selection of RA patients suitable for treatment with tocilizumab or etanercept and found that CRP, among other factors, positively correlated with improvement in clinical outcomes making it a suitable biomarker which helps the choice of patients for such therapy. [11] CRP/albumin ration (CAR) was studied by Sunar I, et al, who demonstrated that CAR was weakly associated with RA disease activity. [12] Furthermore, CAR was also reported by He Y et al, to be significantly increased in RA patients ($p<0.01$) and positively correlated with CRP (Spearman's correlation $= 0.99$) suggesting that it could be used as an indicator of RA inflammation. [13] Similarly, CRP/prealbumin ratio (CPR) was a significant marker of disease activity and correlated positively with CRP as shown by Wang J, et al, in their retrospective analysis. The receiver operating characteristics (ROC) curves for CPR

has a high area under the curve (AUC) of 0.943 suggesting good discriminatory ability of CPR in RA patients. [14]In the large post-hoc analysis by Vanier A, et al, CRP and RF identified, as part of a matrix was a predictor of rapid radiographic progression in RA. Although the sensitivity and specificity were moderate, the AUC of 0.63 {95% confidence interval (CI) 0.55 to 0.71}, the authors concluded that the matrix might help clinicians make treatment decisions in clinical practice. [15] In addition, Takeuchi T, et al, concluded that bone erosion and cartilage destruction in RA patients treated with csDMARDs could be predicted by positive RF, anti-CCP and high CRP [?]0.3 mg/dL. [16] The incidence of the total new erosion was 29.4%, increasing in patients with positive anti-CCP to 38.4% and to 43.1% in patients with CRP [?]0.3 mg/dL and further increased to 48.4% when these two factors occurred together. [16] Also, impending Rapid Erosive Progression (REP) prediction improved by adding high 14-3-3η to RF and CRP in a cohort of 749 RA patients as prospectively investigated by Carrier N, et al, which may help to adapt treatment strategies in at-risk individuals, even those with signs of erosion. [17] Similarly, Ziegelasch M, et al, demonstrated that anti-CCP prospectively predicted radiographic damage of early RA patients, but was not associated with disease activity and recommended that close radiographic monitoring is warranted in anti-CCP positive patients with early RA, regardless of disease activity. [18] In addition to this, RA-related ultrasound changes were tested in correlation to anti-CCP levels by Tan YK et al, and found significant correlation (r=0.46, P=0.048) and predictive ability (P=0.048). [19] Area under the ROC curve based on cut-off anti-CCP level of [?]95.2 to identify patients with ultrasound erosion scores >7 (75th percentile) was 0.72 (sensitivity 83.3%, specificity 53.8%). On the other hand, RF was not associated with joint damage on ultrasound testing. [19]

CRP, RF and anti-CCP have been shown to have similar sensitivities, specificities and correlations for RA activity across different races as reported by Yuan X, et al. [20] Anti-CCP is a good diagnostic biomarker for RA as shown by different assays which demonstrated AUC of 0.89-0.91, indicating good diagnostic performance as reported by Cho J et al. [21] In a retrospective study by Pongratz G, et al, to determine factors associated with change in serum autoantibody levels including anti-CCP and RF, the association with RA activity was variable and strengthens with increase in signs of inflammation such as more morning stiffness (p=0.002), tender (p=0.01) or swollen joints (p<0.01). [22] Furthermore, positive RF and anti-CCP helped in diagnosis of early RA in combination with melanoma associated antigen genes (MAGE-1) mRNA expression rate in synovial fluid cells as demonstrated by Al-Qtaitat A, et al.[23] Hu X, et al, found that high-titre positive anti-CCP score was an independent predictor for RA recurrence within 1 year. A nomogram incorporating anti-CCP independently predicted the risk of RA recurrence with good discrimination (C-index=0.826) and good calibration. [24] In a cross-sectional analysis, Sun Y et al, reported that 14-3-3η correlated with inflammation, bone remodelling and osteoporosis in patients with RA. The level of 14-3-3η was highest in the osteoporosis group compared to the normal group (p<0.05). [25] Similarly, another study showed that 14-3-3η positively correlated with inflammation and disease risk as reported by Tu J et al. [26] 14-3-3η was significantly increased in RA patients, and ROC analysis indicated that it served as a potential predictive marker for RA risk. [26] 14-3-3η distinguished patients with established RA (disease duration >2 years) compared to early RA patients ([?]2 years) with an AUC of 0.76 (95% CI, 0.61 to 0.91). The sensitivity and specificity were 79.3% and 75.0%, respectively. 14-3-3η correlated with other inflammatory markers such as RF and anti-CCP suggesting it may serve as a biomarker for disease risk. [26] Also, a study by Hu T et al, explored the clinical value of a collagen triple helix repeat containing 14-3-3η protein as a component and found that 14-3-3η had the largest odds ratio at 5.1 (95% CI 2.1 to 12.5) for RA diagnosis. They also reported that a combination of anti-CCP and 14-3-3η has a diagnostic value of RA. The AUC of 14-3-3η, anti-CCP and RF were 0.81, 0.89 and 0.85 respectively (all P< 0.01). [27]Luedders B, et al, have shown that although the multibiomarker disease activity (MBDA) score moderately correlated with disease activity, it did not predict treatment response to methotrexate. [28]Another study by Baker J et al, demonstrated that adjusted and unadjusted MBDA score correlated similarly with clinical disease activity. Adjustment for leptin reduced the influence of adiposity, particularly among women but significantly estimated higher disease activity in thin men and women. [29] However, MBDA score predicted disease activity and response to tofacitinib treatment in RA patients as demonstrated by Razmjou A et al. [30]Jurgens M, et al, prospectively showed that MBDA could predict response to treatment of methotrexate with or without prednisolone. The improvement was faster in the first month followed by gradual improvement over the following 6 months. [31]

Ma M, et al, showed that MBDA predicted remission in RA and could differentiate between small differences in disease activity (low disease activity vs remission states). It also predicted long-term remission after one year.[32]

Discussion

This systematic review has confirmed the positive role of biomarkers in the overall management of RA. (Figure 2) The study by Xu K et al, found that CRP was a predictor for RA response to csDMARDs. Although a retrospective design, with its own limitations, it included a large number of participants (252) making its findings reasonably credible.[10] In another study, CRP has also been found to be a useful prognostic marker for response to tocilizumab treatment.[11] However, this study was limited as 196 patients were divided into 4 smaller subgroups limiting its statistical power. CAR was shown to be correlated with disease activity.[12] This finding has agreed with a previous study.[33] However, there was no correlation observed between CAR and quality of life or physical function of patients with RA which have also been observed in previous studies. [34, 35]The authors recommended that further studies are required to explore the role of CAR in RA. CAR has been shown to be associated with increased inflammation in RA patients. [13] Although limited by its cross-sectional design, these findings were previously reported.[36] The increased CAR with inflammatory markers of RA is expected as increased concentration of CAR was shown in other diseases associated with inflammation such as cancer.[37-40] CRP and RF, were part of a matrix that predicted rapid radiographic progression (RRP) in RA. [15] This study included a large number of patients (1306) and demonstrated a practical matrix for clinical use but wasn't identical to previously published matrices. [41] Although it more reliably estimates RRP risk than the previous studies, the author stated that its discriminatory power isn't yet perfect and requires further improvement. Also, bone erosion and cartilage destruction were predicted by CRP, RF and anti-CCP. [16] This study is limited by its post-hoc analysis design but is consistent with previous studies.[42] Adding 14-3-3η to positive RF and high CRP improved prediction of radiographic erosion progression (REP).[17] The strength of this study is the large sample size of real-world patients (749) with a prospective design reflecting day to day clinical practice. However, the observational design could have limited exploring whether intensive therapy in high-risk patients would prevent or delay REP. Anti-CCP has also been identified as a marker of radiographic damage, but not disease activity, being in line with a previous study. [43] RA changes detected by ultrasonography has been correlated with anti-CCP level but not RF positivity as investigated by Tan YK. [19] In contrast, a study by Yang J et al, has found that both anti-CCP and RF are correlated with ultrasound RA-related joint damage. [44]The reason for this disparity between the two studies could be due to the different populations. For example, the population of Yang's study had early RA whereas, the population of Tan's study suffered advanced disease. Therefore, there is a need for further exploration. It appears that anti-CCP is a good diagnostic marker for RA and its current different assays are consistent in sensitivity and specificity.[21]

The collective autoantibody markers for RA such as anti-CCP and RF have been shown to fluctuate with disease activity and inflammation. The higher the inflammation, the more likely the response to treatment as suggested by Pongratz G et al. [22] Although limited by its retrospective design, the heterogeneity of its population and being conducted in only one centre, the results were consistent with previous studies. [45] The diagnostic ability of anti-CCP and RF improved by the combination with MAGE-1. [23] However, large future prospective studies are still required to further investigate the diagnostic and prognostic value of the addition of MAGE-1 to the established biomarkers of RA. Anti-CCP is independently diagnostic of RA as well as a predictor of a recurrence of RA activity.[24] The prediction of RA recurrence was related to high-titre of anti-CCP and a high number of joints which support the prognostic value of anti-CCP that is consistent with previous studies.[46] 14-3-3η predicts disease activity of RA and its duration, and when combined with other biomarkers such as anti-CCP and RF, its diagnostic ability improves. [25-27] This has also been consistent with previous studies. [47] 14-3-3η is a predictor of bone remodelling and RA related osteoporosis.[25] However, this study was limited by the fact that it excluded patients on osteoporosis promoting drugs such as steroids. It may be biased by the selection of patients who fit this criterion and may not reflect on the real-life general population of RA patients. Previous studies have shown that 14-3-3η was associated with bone destruction and increased inflammation in RA patients.[48] MBDA correlated with disease activity but not

response to treatment. [28] The lack of prediction of MBDA to response to treatment was also previously demonstrated.[49] However, the response to treatment to be detected by a biomarker depends on the spectrum of disease activity from the peak to the point of remission. The higher the magnitude of change from the starting point of treatment, the more likely the biomarker will be a predictor tool as explained by Curtis et al. [50]Therefore, the finding of this study cannot be generalised, especially since a previous meta-analysis demonstrated a moderate correlation between MBDA and disease activity. [51] Also, it has been shown that MBDA is correlated with response to tofacitinib, methotrexate and disease remission. [30-32] Although MBDA is a good diagnostic biomarker, its sensitivity can be reduced by adjusting for leptin in obese women but not in thin men and women. It overestimates disease activity in obese women and underestimates it in thin men and women. As a result, with adjustment to leptin, fewer obese women and more thin men and women will be diagnosed with active disease. This study however, was limited by its small sample size (104 patients) and the lack of a standardised marker of disease activity.[29]

The strengths of this systematic review include the use of up-to-date literature published in 2020 and the global diversity of the participants in the chosen studies but limited by the small number of populations in the studies, the retrospective or cross-sectional design of some studies as well as limiting literature to the English language.

Conclusion

The biomarkers of RA appear to have significant utility in clinical practice.

CRP is useful for monitoring of disease activity and prognosis. RF in combination with CRP predicts disease activity as well as bone erosion and cartilage damage. Anti-CCP can be used in the diagnosis and prediction of recurrence of RA as well as a predictor of both radiographic and ultrasonographic changes. 14-3-3η adds to the diagnostic accuracy of the previously mentioned biomarkers. MBDA correlates with disease activity and a potential predictor of response to treatment. Therefore, based on existing evidence, these biomarkers are essential tools in our day-to-day clinical practice and should be routinely measured. However, there is a lack of literature exploring biomarkers that identify patients deemed resistant to treatment before starting therapy. Non-responders will be exposed to the potential side effects of unnecessary therapy. Therefore, there is a need for further research to explore a novel biomarker that fulfils this gap in literature.

Ethical statement

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Data availability statement

No data available as it is a review article

Author contribution

All authors have contributed equally to literature search, writing and editing of the manuscript.

References

1. Guo, Q., Wang, Y., Xu, D. et al. Rheumatoid arthritis: pathological mechanisms and modern pharmacologic therapies. Bone Res 2018; 6: 15. doi.org/10.1038/s41413-018-0016-9.

2. Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. The Lancet 2010; 376: 1094-108.

3. Silman AJ, Pearson JE. Epidemiology and genetics of rheumatoid arthritis. Arthritis Res Ther 2002; 4: S265. doi.org/10.1186/ar578.

4. Bustamante M, Garcia-Carbonell R, Whisenant KD, et al.Fibroblast-like synoviocyte metabolism in the pathogenesis of rheumatoid arthritis. Arthritis Res Ther 2017; 19**:** 110. doi.org/10.1186/s13075-017-1303-3.

5. Guo Q, Wang Y, Xu D, et al. Rheumatoid arthritis: pathological mechanisms and modern pharmacologic therapies. Bone Res 2018; 6: 15. doi: 10.1038/s41413-018-0016-9.

6. Elshabrawy HA, Chen Z, Volin MV, et al. The pathogenic role of angiogenesis in rheumatoid arthritis. Angiogenesis 2015; 18: 433-48.

7. Song YW, Kang EH. Autoantibodies in rheumatoid arthritis: rheumatoid factors and anticitrullinated protein antibodies. QJM 2010; 103: 139-46.

8. Mohamed AH, Abdellatif S, El-Noshokaty EH. Serum Level of 14-3-3η (Eta) Protein as a Diagnostic Marker for Rheumatoid Arthritis and Potential Correlation with Disease Activity. MOJ Orthop Rheumatol 2017; 7: :00280. doi:10.15406/mojor.2017.07.00280.

9. Centola M, Cavet G, Shen Y, Ramanujan S, Knowlton N, Swan KA, et al. Development of a Multi-Biomarker Disease Activity Test for Rheumatoid Arthritis. PLoS One. 2013; 8:e60635.

10. Xu K, Ren X, Ju B, et al. Clinical markers combined with HMGB1 polymorphisms to predict efficacy of conventional DMARDs in rheumatoid arthritis patients. Clinical Immunology. Clin Immunol 2020; 221: 108592. doi: 10.1016/j.clim.2020.108592.

11. Hayashi S, Matsubara T, Fukuda K, Funahashi K, Hashimoto M, Maeda T, et al.. Predictive factors for effective selection of Interleukin-6 inhibitor and tumor necrosis factor inhibitor in the treatment of rheumatoid arthritis. Sci Rep Sc 2020; 10: 16645 (2020). doi.org/10.1038/s41598-020-73968-3.

12. Sunar İ, Ataman Ş. Serum C-Reactive Protein/Albumin Ratio in Rheumatoid Arthritis and its Relationship With Disease Activity, Physical Function, and Quality of Life. Arch Rheumatol 2020; 35: 247-53.

13. He Y, Tang J, Wu B, et al. Correlation between albumin to fibrinogen ratio, C-reactive protein to albumin ratio and Th17 cells in patients with rheumatoid arthritis. Clin Chim Acta 2020; 500: 149-54.

14. Wang J, Xi H, Zhang K, et al. Circulating C-Reactive Protein to Prealbumin Ratio and Prealbumin to Fibrinogen Ratio are Two Promising Inflammatory Markers Associated with Disease Activity in Rheumatoid Arthritis. Clin Lab 2020; 66: doi: 10.7754/Clin.Lab.2019.190833.

15. Vanier A, Smolen J, Allaart C, et al. An updated matrix to predict rapid radiographic progression of early rheumatoid arthritis patients: pooled analyses from several databases. Rheumatology (Oxford) 2020; 59: 1842-52.

16. Takeuchi T, Soen S, Ishiguro N, et al. Predictors of new bone erosion in rheumatoid arthritis patients receiving conventional synthetic disease-modifying antirheumatic drugs: Analysis of data from the DRIVE and DESIRABLE studies. Mod Rheumatol 2020; 31: 34-41.

17. Carrier N, De Brum-Fernandes AJ, Liang P, et al. Impending radiographic erosive progression over the following year in a cohort of consecutive patients with inflammatory polyarthritis: prediction by serum biomarkers. RMD Open 2020; 6: e001191. doi:10.1136/rmdopen-2020-001191.

18. Ziegelasch M, Boman A, Martinsson K, et al. Anti-cyclic citrullinated peptide antibodies are associated with radiographic damage but not disease activity in early rheumatoid arthritis diagnosed in 2006–2011. Scand J Rheumatol 2020; 49: 434-42.

19. Tan YK, Li H, Allen JC, et al. Anti-cyclic citrullinated peptide but not rheumatoid factor is associated with ultrasound-detected bone erosion among rheumatoid arthritis patients with at least moderate disease activity. Int J Rheum Dis 2020; 23: 1337-43.

20. Yuan X, Cui S, Liu Y, et al. Analysis of serum rheumatoid factors in patients with rheumatoid arthritis in Han, Tibetan and Hui nationalities in Qinghai. Int Immunopharmacol 2020; 83: 106380. doi:

10.1016/j.intimp.2020.106380.

21. Cho J, Pyo JY, Fadriquela A, et al. Comparison of the analytical and clinical performances of four anti-cyclic citrullinated peptide antibody assays for diagnosing rheumatoid arthritis. Clin Rheumatol Clinical 2020; 40: 565-73.

22. Pongratz G, Frieser R, Brinks R, et al. Association between autoantibody level and disease activity in rheumatoid arthritis is dependent on baseline inflammation. Clin Exp Rheumatol 2020; 38: 691-8.

23. Al-Qtaitat A, Mwafi N, Albtoosh A, et al. A new tool for early diagnosis of rheumatoid arthritis using a combined biomarkers; synovial MAGE-1 mRNA and serum anti-CCP and R. Pan Afr Med J 2020; 36: 270. doi: 10.11604/pamj.2020.36.270.21827.

24. Hu XL, Gu Y, Wu DL, et al. A nomogram to predict recurrence of RA patients in clinical remission within one year. Eur Rev Med Pharmacol Sci 2020; 24: 9797-806.

25. Sun Y, Hong L, Gao C. The association among 14-3-3η protein, inflammation, bone remodeling and osteoporosis in patients with rheumatoid arthritis. Pakistan Journal of Medical Sciences. Pak J Med Sci 2020; 36: 872-6.

26. Tu J, Chen X, Dai M, et al. Serum levels of 14-3-3η are associated with increased disease risk, activity and duration of rheumatoid arthritis in Chinese patients. ExpTher Med 2020; 20:754-61.

27. Hu T, Liu Y, Tan L, Huang J, et al. Value of serum collagen triple helix repeat containing-1(CTHRC1) and 14-3-3η protein compared to anti-CCP antibodies and anti-MCV antibodies in the diagnosis of rheumatoid arthritis. Br J Biomed Sci 2020; 78: 67-71.

28. Luedders BA, Johnson TM, Sayles H, et al. Predictive ability, validity, and responsiveness of the multi-biomarker disease activity score in patients with rheumatoid arthritis initiating methotrexate. Semin Arthritis Rheum 2020; 50: 1058-63.

29. Baker JF, Curtis JR, Chernoff D, et al. Evaluation of the impact of age and adiposity on a multi-biomarker disease activity score before and after adjustment. Clin Rheumatol 2020; 40: doi: 10.1007/s10067-020-05508-3.

30. Razmjou AA, Brook J, Elashoff D, et al. Ultrasound and multi-biomarker disease activity score for assessing and predicting clinical response to tofacitinib treatment in patients with rheumatoid arthritis. BMC Rheumatol 2020; 4: 55. doi: 10.1186/s41927-020-00153-4.

31. Jurgens MS, Safy-Khan M, De Hair MJH, et al. The multi-biomarker disease activity test for assessing response to treatment strategies using methotrexate with or without prednisone in the CAMERA-II trial. Arthritis Res Ther 2020; 22: 205. doi.org/10.1186/s13075-020-02293-x.

32. Ma MHY, Defranoux N, Li W, et al. A multi-biomarker disease activity score can predict sustained remission in rheumatoid arthritis. Arthritis Res Ther 2020; 22: 158. doi.org/10.1186/s13075-020-02240-w.

33. Yang WM, Zhang WH, Ying HQ, et al. Two new inflammatory markers associated with disease activity score-28 in patients with rheumatoid arthritis: Albumin to fibrinogen ratio and C-reactive protein to albumin ratio. Int Immunopharmacol 2018; 62: 293-8.

34. Garip Y, Eser F, Bodur H. Health-related quality of life in rheumatoid arthritis: comparison of RAQoL with other scales in terms of disease activity, severity of pain, and functional status. Rheumatol Int 2011; 31: 769-72.

35. Maska L, Anderson J, Michaud K. Measures of functional status and quality of life in rheumatoid arthritis: Health Assessment Questionnaire Disability Index (HAQ), Modified Health Assessment Questionnaire (MHAQ), Multidimensional Health Assessment Questionnaire (MDHAQ), Health Assessment Questionnaire II (HAQ-II), Improved Health Assessment Questionnaire (Improved HAQ), and Rheumatoid Arthritis Quality of Life (RAQoL). Arthritis Care Res (Hoboken) 2011; 63 Suppl 11: S4-13. doi: 10.1002/acr.20620.

36. Yang WM, Zhang WH, Ying HQ, et al. Two new inflammatory markers associated with disease activity score-28 in patients with rheumatoid arthritis: Albumin to fibrinogen ratio and C-reactive protein to albumin ratio. Int Immunopharmacol. 2018; 62: 293-8.

37. Zou YX, Qiao J, Zhu HY, et al. Albumin-to-Fibrinogen Ratio as an Independent Prognostic Parameter in Untreated Chronic Lymphocytic Leukemia: A Retrospective Study of 191 Cases. Cancer Res Treat 2019; 51: 664-71.

38. Shimizu T, Ishizuka M, Suzuki T, et al. The Value of the C-Reactive Protein-to-Albumin Ratio is Useful for Predicting Survival of Patients with Child-Pugh Class A Undergoing Liver Resection for Hepatocellular Carcinoma. World J Surg 2018; 42: 2218-26.

39. Zhang L, Chen QG, Li SQ, et al. Preoperative fibrinogen to prealbumin ratio as a novel predictor for clinical outcome of hepatocellular carcinoma. Future Oncol. 2019; 15: 13-22.

40. Xu WY, Zhang HH, Xiong JP, et al. Prognostic significance of the fibrinogen-to-albumin ratio in gallbladder cancer patients. World J Gastroenterol 2018; 24: 3281-92.

41. Vastesaeger N, Xu S, Aletaha D, St Clair EW, SmolenJS. A pilot risk model for the prediction of rapidradiographic progression in rheumatoid arthritis. Rheumatology 2009; 48: 1114-21.

42. Hambardzumyan K, Bolce R, Saevarsdottir S, et al. Pretreatment multi-biomarker disease activity score and radiographic progression in early RA: results from the SWEFOT trial. Ann Rheum Dis 2015; 74: 1102-9.

43. Kastbom A, Forslind K, Ernestam S, et al. Changes in the anticitrullinated peptide antibody response in relation to therapeutic outcome in early rheumatoid arthritis: results from the SWEFOT trial. Ann Rheum Dis 2016; 75: 356–61.

44. Yang J, Shao Q, Wu J. Correlation between high-frequency ultraso-nography of patients with early rheumatoid arthritis and anti-CCP antibody. Medicine (Baltimore). 2019; 98: e14083. doi: 10.1097/MD.0000000000014083.

45. Cantini F, Niccoli L, Nannini C, et al. Tailored first-line biologic therapy in patients with rheumatoid arthritis, spondyloarthritis, and psoriatic arthritis. Semin Arthritis Rheum 2016; 45: 519-32.

46. Du Y, Liu X, Guo JP, et al. Association between PADI4 gene polymorphisms and anti-cyclic citrullinated peptide antibody positive rheumatoid arthritis in a large Chinese Han cohort. Clin Exp Rheumatol 2014; 32: 377-82.

47. Gong X, Xu SQ, Wu Y, et al. Elevated serum 14-3-3eta protein may be helpful for diagnosis of early rheumatoid arthritis associated with secondary osteoporosis in Chinese population. Clin Rheumatol 2017; 36: 2581-7.

48. Zeng T, Tan L. 14-3-3eta protein: a promising biomarker for rheumatoid arthritis. Biomark Med 2018; 12: 917-25.

49. Hambardzumyan K, Bolce RJ, Wallman JK, et al. Serum biomarkers for prediction of response to methotrexate monotherapy in early rheumatoid arthritis: results from the SWEFOT trial J. Rheumatol 2019; 46: 555-63.

50. Curtis JR, Yang S, Chen L, et al. Determining the Minimally Important Difference in the Clinical Disease Activity Index for Improvement and Worsening in Early Rheumatoid Arthritis Patients. Arthritis Care Res (Hoboken). 2015; 67: 1345-53.

51. Johnson TM, Register KA, Schmidt CM, et al. Correlation of the Multi-Biomarker Disease Activity Score With Rheumatoid Arthritis Disease Activity Measures: A Systematic Review and Meta-Analysis. Arthritis Care Res (Hoboken). 2019; 71: 1459-72.

Table 1: Summary of studies exploring the relationship between biomarkers and RA diagnosis, progression and treatment. [10-32]

Study	**Population**	**Aim to:**	**Relevant Findings**
Xu K, et al, retrospective, 2020, China [10]	252 patients with RA.	Determine predictive markers of csDMARDs treatment outcomes.	CRP>7.1 mg/L, among other factors, were predictors of poor csDMARDs outcome, sensitivity 87.2%, specificity 60.9%.
Hayashi S, et al, retrospective, 2020, Japan [11]	196 patients with RA	Investigate predictive factors for successful drug therapy of RA.	CRP positively correlated with clinical outcomes of RA.
Sunar I and Ataman Ş, cross-sectional, 2020, Turkey [12]	121 patients with RA	Evaluate CRP/albumin ratio (CAR) with RA outcomes.	CAR was positively correlated with disease activity, p<0.001.
He Y, et al, retrospective, 2020, China [13]	196 patients with RA	Investigate the association of CAR with the concentration of autoantibodies in RA	Concentration of CAR was significantly increased in RA patients p<0.01and positively correlated with CRP r=0.99
Wang J, et al, retrospective, 2020, China [14]	170 RA patients and 120 healthy individuals	Investigate CRP to prealbumin ratio (CPR) to RA disease activity.	CPR was a significant marker of disease activity in RA and positively correlated with CRP
Vanier A, et al, post-hoc analysis, 2020, Austria [15]	1306 patients with RA	Develop a matrix to predict rapid radiographic progression (RRP) in RA.	RF and CRP >30mg/l were part of the matrix that predicted RRP in RA.
Takeuchi T, et al, post-hoc analysis, 2020, Japan [16]	306 patients with RA	Explore predictors of bone erosion and cartilage destruction in RA.	Anti-CCP, CRP [?]0.3 mg/dL and RF were predictors of bone erosion and cartilage destruction in RA
Carrier N, et al, prospective, 2020, Canada [17]	749 patients with inflammatory polyarthritis	Evaluate biomarkers predicting rapid erosion progression (REP).	High 14-3-3n in addition to RF and CRP improved the prediction of impending REP.
Ziegelasch M, et al, prospective, 2020, Sweden [18]	683 patients with RA	Evaluate if Anti-CCP predicts early disease activity and radiographic damage in RA	Anti-CCP not associated with disease activity over time, but with increased radiographic damage at follow-up.

Tan Y, et al, cross-sectional, 2020, Singapore [19]	30 patients with RA	Evaluate the relationship between Anti-CCP and RF with ultrasound-detected joint inflammation and bone erosion in RA	In patients with the least disease activity, anti-CCP was associated with joint damage, r=0.46, p=0.048, whereas RF was not associated with joint damage but was correlated moderately with ultrasound-detected bone erosion.
Yuan X, et al, cross-sectional, 2020, China [20]	75 RA patients and 75 healthy individuals	Compare the sensitivities and specificities of biomarkers in different races of RA patients	CRP, A-CCP and RF were all useful biomarkers for detection of RA in the 3 studied races.
Cho J, et al, assay, 2020, Korea [21]	132 patients with and 108 without RA.	Compare anti-CCP assays for diagnosing RA.	All Anti-CCP assays showed a good diagnostic performance, sensitivity 88.0% and specificity 97.2%
Pongratz G, et al, retrospective, 2020, Germany [22]	78 patients with RA	Investigate which factors are associated with RA disease activity and autoantibody levels.	Association between disease activity and change in autoantibody levels is not static and increased with increase in inflammation. Baseline inflammation is a confounder.
Al-Qtaitat A, et al, case-control, 2020, Jordan [23]	135 patients with RA and 78 normal subjects with traumatic knee joints	Evaluate serum levels of anti-CCP and RF for early RA diagnosis	There was an increase in serum RF and anti-CCP levels in RA patients in comparison to the control groups, specificity 100%, sensitivity 100%.
Hu X, et al, prospective, 2020, China [24]	167 patients with RA	Establish a nomogram which will predict outcomes of RA in clinical remission	The nomogram incorporating Anti-CCP as well as other factors helped to achieve complete remission.
Sun Y, et al, cross-sectional, 2020, China [25]	285 patients with RA	Investigate the correlation among 14-3-3n inflammation and bone remodelling in RA	14-3-3η was significantly correlated with inflammation, bone remodelling and osteoporosis in RA patients, $p<0.05$.

Tu J, et al, case-control, 2020, China [26]	45 patients with RA and 45 patients with osteoarthritis	Determine 14-3-3η association with RA risk, duration and inflammatory level.	14-3-3η positively correlated with RA duration, p=0.003 disease activity (P=0.025), 14-3-3η correlated with positive RF. 14-3-3η distinguished early from established RA.
Hu T, et al, cross-sectional, 2020, China [27]	103 patients with RA, 105 non-RA patients and 59 healthy controls	Investigate the diagnostic value of 14-3-3η compared to other markers in RA	Anti-CCP had highest specificity 94.5% and most valuable in diagnosis of RA, 14-3-3η had largest OR of 5.1, 95% CI 2.1 to 12.5 for RA diagnosis.
Luedders B, et al, prospective, 2020, USA [28]	130 patients with RA	Assess the MBDA score in RA patients treated with methotrexate	MBDA scores were found not to predict response to methotrexate.
Baker J, et al, cross-sectional, 2020, USA [29]	104 patients with RA	Assess MBDA score adjusted for confounding factors	Adjusted MBDA was not associated with adiposity, less likely to overestimate RA activity in obese women or underestimate RA activity in lean men or women.
Razmjou A, et al, prospective, 2020, USA [30]	25 patients with RA	Assess whether early MBDA scores predict later clinical response to tofacitinib in RA	Early MBDA scores correlated with later response in disease activity, after 6 weeks and 12 weeks of treatment all $p<0.05$
Jurgens M, et al, prospective, 2020, Netherlands [31]	92 patients with RA	Investigate the correlation between MBDA and disease activity in patients treated with methotrexate and prednisone	MBDA was correlated with response to treatment in RA.
Ma M, et al, prospective, 2020, UK [32]	148 patients with RA	Use the MBDA score to assess the role of biomarkers in RA remission	MBDA score was able to differentiate between small differences in disease activity and predicted remission over 1 year.

RA = Rheumatoid Arthritis, CRP = C-Reactive Protein, RF = Rheumatoid Factor, csDMARDs = conventional synthetic disease-modifying antirheumatic drugs, RCT = Randomised Clinical Trail, Anti-CCP = Anti-cyclic citrullinated peptide, CI= Confidence Interval, MBDA= Multi-biomarker disease Activity Score

Figure 1: PRISMA flow diagram.

Figure 2: Summary of the role of biomarkers in the diagnosis, treatment and prognosis of Rheumatoid arthritis. RF=Rheumatoid factor, Anti-CCP=Anti-cyclic citrullinated peptide, REP=Rapid erosive progression, US=Ultra sound, RA=Rheumatoid arthritis, CRP=C-reactive protein, csDMARDS= conventional synthetic disease-modifying antirheumatic drugs, MBDA= multi-biomarker disease activity.

49. Vastesaeger N, Xu S, Aletaha D, St Clair EW, Smolen

JS. A pilot risk model for the prediction of rapid

radiographic progression in rheumatoid arthritis.

Rheumatology 2009;48:1114–21.

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radiographic progression in rheumatoid arthritis.
Rheumatology 2009;48:1114–21.