

## Key Literature – Serum Calprotectin<sup>1</sup>

### Guidelines<sup>3</sup>

- **Fautrel, B. et al.** EULAR/PReS Recommendations for the Diagnosis and Management of Still's Disease, Comprising Systemic Juvenile Idiopathic Arthritis and Adult-Onset Still's Disease. *Annals of the Rheumatic Diseases* **2024**, *83* (12), 1614–1627. <https://doi.org/10.1136/ard-2024-225851>.

“RS2: marked elevation of serum IL-18 and/or S100 proteins<sup>1</sup> (e.g., calprotectin) strongly supports the diagnosis, and therefore should be measured if available.”

- **Romano, M. et al.** The 2021 EULAR/American College of Rheumatology Points to Consider for Diagnosis, Management and Monitoring of the Interleukin-1 Mediated Autoinflammatory Diseases: Cryopyrin-Associated Periodic Syndromes, Tumour Necrosis Factor Receptor-Associated Periodic Syndrome, Mevalonate Kinase Deficiency, and Deficiency of the Interleukin-1 Receptor Antagonist. *Annals of the Rheumatic Diseases* **2022**, *81* (7), 907–921. <https://doi.org/10.1136/annrheumdis-2021-221801>.

“The clinical workup of systemic inflammation should include CRP, ESR and CBC with differential; if available SAA and S100<sup>1</sup> proteins may be assessed.”

### Reviews<sup>3</sup>

- **Reshadmanesh, T. et al.** Circulating Levels of Calprotectin as a Biomarker in Patients With Coronary Artery Disease: A Systematic Review and Meta-Analysis. *Clinical Cardiology* **2024**, *47* (7), e24315. <https://doi.org/10.1002/clc.24315>.
- **Festa, E. et al.** Synovial Calprotectin in Prosthetic Joint Infection. A Systematic Review and Meta-Analysis of the Literature. *Archives of Orthopaedic and Trauma Surgery* **2024**. <https://doi.org/10.1007/s00402-024-05416-0>.
- **Carnazzo, V. et al.** Calprotectin: Two Sides of the Same Coin. *Rheumatology (Oxford)* **2024**, *63* (1), 26–33. <https://doi.org/10.1093/rheumatology/kead405>.
- **Romand, X. et al.** Systemic Calprotectin and Chronic Inflammatory Rheumatic Diseases. *Joint Bone Spine* **2019**, *86* (6), 691–698. <https://doi.org/10.1016/j.jbspin.2019.01.003>.
- **Abildtrup, M. et al.** Calprotectin as a Biomarker for Rheumatoid Arthritis: A Systematic Review. *Journal of Rheumatology* **2015**, *42* (5), 760–770. <https://doi.org/10.3899/jrheum.140628>.

### Preanalytics and Harmonization

- **Deley, R. et al.** EDTA Plasma for Measuring Circulating Calprotectin: A Matrix to Avoid!; Dresden, **2025**.  
“EDTA plasma as a matrix for serum calprotectin should be avoided. Serum is the best matrix for assessing clinical samples since values are higher and show less statistical variation.”
- **Deley, R. et al.** A New Recombinant and Native Calprotectin Formulation: A Step Forward towards Standardization of Circulating Calprotectin Assays; Dresden, **2025**.

“Native and recombinant calprotectin can be used to standardize circulating calprotectin assays.”

### Pediatric Rheumatology

#### Systemic juvenile idiopathic arthritis/ Still's disease (sJIA/SD)

- **Elhani, I. et al.** Inflammatory Biomarker Analysis Confirms Reduced Disease Severity in Heterozygous Patients with Familial Mediterranean Fever. *RMD Open* **2024**, *10* (4), e004677. <https://doi.org/10.1136/rmdopen-2024-004677>.<sup>2</sup>

“Serum calprotectin and S100A12 levels are elevated in familial Mediterranean fever following a genedose effect and reflect disease activity. Serum calprotectin and S100A12 could be used to monitor disease activity in FMF.”

<sup>1</sup>Calprotectin, a S100 protein, is also known as S100A8/A9 or MRP8/14

<sup>2</sup>In these studies, the BÜHLMANN sCAL® ELISA assay or the Quantum Blue® sCAL assay was used. Both assays are standardized differently to BÜHLMANN sCAL® turbo and have been discontinued.

<sup>3</sup>In these publications no BÜHLMANN assays were used.

- **Foell, D. et al.** A Novel Serum Calprotectin (MRP8/14) Particle-Enhanced Immuno-Turbidimetric Assay (sCAL Turbo) Helps to Differentiate Systemic Juvenile Idiopathic Arthritis from Other Diseases in Routine Clinical Laboratory Settings. *Mol Cell Pediatr* **2023**, *10* (1), 14. <https://doi.org/10.1186/s40348-023-00168-0>.

“sCAL turbo a rapid, automated immunoturbidimetric assay can differentiate systemic JIA from key mimics like infections and leukemia within hours using a serum calprotectin cutoff of 10,5 µg/mL (84% sensitivity, 94% specificity), making early targeted therapy decisions feasible in routine clinical practice.”

- **Park, C. et al.** MRP8/14 Serum Levels as Diagnostic Markers for Systemic Juvenile Idiopathic Arthritis in Children with Prolonged Fever. *Rheumatology (Oxford, England)* **2022**, *61* (7), 3082–3092. <https://doi.org/10.1093/RHEUMATOLOGY/KEAB729>.<sup>2</sup>

“This large-scale study validates serum calprotectin as a superior diagnostic biomarker for differentiating systemic JIA from other febrile conditions in children, demonstrating better accuracy than ferritin or ESR and confirming the robust performance of both commercial ELISA and rapid point-of-care (LFIA) tests.”

- **Boyko, J.** Measurement of Blood Calprotectin (MRP-8/MRP-14) Levels in Patients with Juvenile Idiopathic Arthritis. *Reumatologia* **2017**, *55* (1), 10–14. <https://doi.org/10.5114/reum.2017.66682>.<sup>2</sup>

“Serum calprotectin is markedly elevated in systemic JIA—especially at new onset—and closely reflects clinical and laboratory disease activity, making it a powerful biomarker for diagnosing sJIA and monitoring flares and treatment response.”

## Juvenile Idiopathic Arthritis (JIA)

- **Codes-Méndez, H. et al.** Diagnostic Accuracy of Serum Calprotectin Measured by CLIA and EIA in Juvenile Idiopathic Arthritis: A Proof-of-Concept Study. *Front. Pediatr.* **2024**, *12*, 1422916. <https://doi.org/10.3389/fped.2024.1422916>.<sup>2</sup>

“This proof-of-concept study demonstrates that serum calprotectin, measured by either CLIA or EIA, is more sensitive than CRP and ESR in identifying active JIA and establishes an optimal cut-off for active disease at 2.3 µg/ml (using JADAS-27 criteria)”

- **Sumner, E. J. et al.** Use of MRP8/14 in Clinical Practice as a Predictor of Outcome after Methotrexate Withdrawal in Patients with Juvenile Idiopathic Arthritis. *Clin Rheumatol* **2022**, *41* (9), 2825–2830. <https://doi.org/10.1007/s10067-022-06165-4>.<sup>2</sup>

“This report highlights serum calprotectin’s clinical utility as a risk-stratification tool, showing that a low level (4 µg/ml) in patients with inactive JIA predicted a 12-month flare-free period after methotrexate withdrawal”

- **La, C. et al.** Serum Calprotectin (S100A8/A9): A Promising Biomarker in Diagnosis and Follow-up in Different Subgroups of Juvenile Idiopathic Arthritis. *RMD Open* **2021**, *7* (2), e001646. <https://doi.org/10.1136/rmdopen-2021-001646>.<sup>2</sup>

“This research highlights serum calprotectin’s dual role as a key prognostic tool in JIA where CRP fails, identifying high levels as a predictor of successful treatment response in active disease and, conversely, as a strong predictor of future flares in patients who are clinically in remission.”

- **Boyko, Y.** Measurement of Blood Calprotectin (MRP-8/MRP-14) Levels in Patients with Juvenile Idiopathic Arthritis. *Reumatologia* **2017**, *55* (1), 10–14. <https://doi.org/10.5114/reum.2017.66682>.<sup>2</sup>

“Serum calprotectin levels are significantly higher in sJIA (median 13.8 mg/ml) compared to polyarticular (median 3.8 mg/ml) and oligoarticular (median 2.5 mg/ml) demonstrating that its levels can be used to measure subclinical disease activity and as a therapeutic response marker.”

- **Alberdi-Saugstrup, M. et al.** Low Pretreatment Levels of Myeloid-Related Protein-8/14 and C-Reactive Protein Predict Poor Adherence to Treatment with Tumor Necrosis Factor Inhibitors in Juvenile Idiopathic Arthritis. *Clin Rheumatol* **2017**, *36* (1), 67–75. <https://doi.org/10.1007/s10067-016-3375-x>.<sup>2</sup>

“Low basal serum calprotectin levels in JIA patients predict low bDMARD therapeutic response, whereas high basal serum calprotectin predicts high bDMARD therapeutic response.”

<sup>2</sup>In these studies, the BÜHLMANN sCAL® ELISA assay or the Quantum Blue® sCAL assay was used. Both assays are standardized differently than BÜHLMANN sCAL® turbo and have been discontinued.

- **Bohr, A.-H. et al.** Lipoprotein Cholesterol Fractions Are Related to Markers of Inflammation in Children and Adolescents with Juvenile Idiopathic Arthritis: A Cross Sectional Study. *Pediatr Rheumatol* **2016**, *14* (1), 61. <https://doi.org/10.1186/s12969-016-0120-6>.<sup>2</sup>

“In this cross-sectional study of 210 JIA patients, most of whom had low disease activity, serum calprotectin was identified as a key inflammatory marker linked to cardiovascular risk, showing a significant negative correlation with protective HDL-cholesterol and a positive correlation with central fatness (waist-to-height ratio)”

- **Anink, J. et al.** MRP8/14 Serum Levels as a Predictor of Response to Starting and Stopping Anti-TNF Treatment in Juvenile Idiopathic Arthritis. *Arthritis Res Ther* **2015**, *17* (1), 200. <https://doi.org/10.1186/s13075-015-0723-1><sup>2</sup>

“High levels of baseline serum calprotectin are associated with good response to TNFi treatment, whereas elevated serum calprotectin levels at discontinuation of TNFi (etanercept) are associated with higher chance to flare.”

- **Rothmund, F. et al.** Validation of Relapse Risk Biomarkers for Routine Use in Patients with Juvenile Idiopathic Arthritis. *Arthritis Care Res (Hoboken)* **2014**, *66* (6), 949–955. <https://doi.org/10.1002/acr.22248><sup>2</sup>

“Serum calprotectin can be used as a prognostic tool to predict relapse risk in JIA patients allowing stratification of decisions to stop or maintain therapy after remission.”

## Adult Rheumatology Rheumatoid Arthritis (RA)

- **Hurnakova, J. et al.** Serum Calprotectin May Reflect Inflammatory Activity in Patients with Active Rheumatoid Arthritis despite Normal to Low C-Reactive Protein. *Clin Rheumatol* **2018**, *37* (8), 2055–2062. <http://doi.org/10.1007/s10067-018-4091-5>.<sup>2</sup>

“Approximately 50% of RA patients have normal CRP. This study shows that serum calprotectin can discriminate RA patients with clinically active disease and normal CRP from patients in remission (low disease activity with normal CRP) and from healthy subjects. Serum calprotectin can correctly classify clinically active patients despite normal CRP in 71-74% of patients.”

- **Hurnakova, J. et al.** Relationship between Serum Calprotectin (S100A8/9) and Clinical, Laboratory and Ultrasound Parameters of Disease Activity in Rheumatoid Arthritis: A Large Cohort Study. *PLoS ONE* **2017**, *12* (8), e0183420. <https://doi.org/10.1371/journal.pone.0183420>.<sup>2</sup>

“In this large-cohort study of 160 RA patients, serum calprotectin was demonstrated to be a superior biomarker to CRP, proving to be a better predictor of objective Power Doppler ultrasound-defined synovitis and, unlike CRP, also serving as an independent, significant predictor of the purely clinical CDAI score.”

- **Hurnakova, J. et al.** Serum Calprotectin (S100A8/9): An Independent Predictor of Ultrasound Synovitis in Patients with Rheumatoid Arthritis. *Arthritis Res Ther* **2015**, *17* (1), 252. <https://doi.org/10.1186/s13075-015-0764-5>.<sup>2</sup>

“In this cross-sectional study of 37 rheumatoid arthritis patients, serum calprotectin was found to be a superior and independent predictor of active, ultrasound-detected power Doppler synovitis ( $R^2=0.765$ ) compared to C-reactive protein ( $R^2=0.496$ ).”

- **García-Arias, M. et al.** Calprotectin in Rheumatoid Arthritis: Association with Disease Activity in a Cross-Sectional and a Longitudinal Cohort. *Mol Diagn Ther* **2013**, *17* (1), 49–56. <https://doi.org/10.1007/s40291-013-0016-9>.<sup>2</sup>

“Calprotectin levels strongly correlate with clinical and laboratory assessments of joint inflammation and also decrease in response to treatment, indicating that calprotectin is a promising marker for assessment and monitoring of disease activity in patients with RA.”

<sup>2</sup>In these studies, the BÜHLMANN sCAL® ELISA assay or the Quantum Blue® sCAL assay was used. Both assays are standardized differently than BÜHLMANN sCAL® turbo and have been discontinued.

- **Andrés Cerezo, L. et al.** Decreases in Serum Levels of S100A8/9 (Calprotectin) Correlate with Improvements in Total Swollen Joint Count in Patients with Recent-Onset Rheumatoid Arthritis. *Arthritis Res Ther* **2011**, *13* (4), R122. <https://doi.org/10.1186/ar3426>.

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“In this first-ever study of treatment-naïve, recent-onset rheumatoid arthritis patients, serum calprotectin not only normalized after 3 months of conventional therapy but, unlike CRP, its decrease was a significant independent predictor of improvement in the total swollen joint count.”

## Spondyloarthritis (SpA and PsA)

- **Rademacher, J. et al.** Biomarkers Reflecting Disturbed Gut Barrier under Treatment with TNF Inhibitors in Radiographic Axial Spondylarthritis. *RMD Open* **2024**, *10* (4), e004752. <https://doi.org/10.1136/rmdopen-2024-004752>.<sup>2</sup>

“Investigating the gut-joint axis in radiographic axial spondylarthritis, this study of 121 patients found that serum calprotectin and LBP—markers of intestinal inflammation and bacterial translocation—were elevated in active disease and decreased significantly with one year of TNF inhibitor therapy, correlating strongly with disease activity (ASDAS, CRP) and treatment response.”

- **Levitova, A. et al.** Clinical Improvement and Reduction in Serum Calprotectin Levels after an Intensive Exercise Programme for Patients with Ankylosing Spondylitis and Non-Radiographic Axial Spondylarthritis. *Arthritis Res Ther* **2016**, *18* (1), 275. <https://doi.org/10.1186/s13075-016-1180-1>.<sup>2</sup>

“Intensive exercise is equally effective in improving disease activity (ASDAS-CRP) and spinal mobility (BASMI) in patients with both non-radiographic and radiographic axial spondyloarthritis, and that this clinical improvement is mirrored by a significant reduction in serum calprotectin levels in both groups.”

- **Cypers, H. et al.** Elevated Calprotectin Levels Reveal Bowel Inflammation in Spondylarthritis. *Annals of the Rheumatic Diseases* **2016**, *75* (7), 1357–1362. <https://doi.org/10.1136/annrheumdis-2015-208025>.<sup>2</sup>

“Serum and fecal calprotectin represent surrogate markers for microscopic bowel inflammation in SpA. Results suggest that serum and fecal calprotectin measurements in addition to CRP may be useful in identifying patients with SpA at higher risk of subclinical bowel inflammation who might benefit from further invasive checkups.”

## Prosthetic Joint Infection (PJI)

- **Alkadhem, M. F. et al.** Synovial Calprotectin Is Superior to Synovial Leukocyte Count in Excluding Chronic Periprosthetic Joint Infections, a Retrospective Cohort Study. *Journal of Arthroplasty* **2024**. <https://doi.org/10.1016/j.arth.2024.02.064>.<sup>2</sup>

“This retrospective cohort study identifies synovial calprotectin as the superior biomarker for excluding chronic periprosthetic joint infection, achieving a 100% negative predictive value at a 50 mg/L cutoff and outperforming the diagnostic accuracy of synovial leukocyte count.”

- **Bottagisio, M. et al.** Evaluation of Synovial Calprotectin by Using a Lateral Flow Test for the Diagnosis of Prosthetic Joint Infections. *Diagnostics* **2023**, *13* (4), 741. <https://doi.org/10.3390/diagnostics13040741>.<sup>2</sup>

“Lateral flow calprotectin test for synovial fluid is a valuable biomarker (80% sensitivity, 94% specificity) that correlates strongly with synovial leukocyte counts (rs=0.69) for diagnosing prosthetic joint infections.”

- **Ackmann, T. et al.** Serum Calprotectin: A Potential Biomarker to Diagnose Chronic Prosthetic Joint Infection after Total Hip or Knee Arthroplasty. *Scientific Reports* **2022**, *12* (1). <https://doi.org/10.1038/S41598-022-09724-6>. (BÜHLMANN® fCAL turbo assay was used)

“Serum calprotectin is a very cost-efficient biomarker which reliably distinguishes patients with chronic periprosthetic infection and aseptic failure of hip and knee prostheses.”

<sup>2</sup>In these studies, the BÜHLMANN sCAL® ELISA assay or the Quantum Blue® sCAL assay was used. Both assays are standardized differently than BÜHLMANN sCAL® turbo and have been discontinued.

- **Wouthuyzen-Bakker, M. et al.** Synovial Calprotectin: A Potential Biomarker to Exclude a Prosthetic Joint Infection. *The Bone & Joint Journal* **2017**, 99-B (5), 660–665. <https://doi.org/10.1302/0301-620X.99B5.BJJ-2016-0913.R2>.<sup>2</sup>

“This pilot study on periprosthetic joint infection (PJI) identifies synovial fluid calprotectin as an excellent biomarker for excluding chronic PJI, achieving a 97% negative predictive value and high accuracy (AUC 0.94) using a rapid, cost-effective lateral flow immunoassay.”

## Other disease areas

- **Stascheit, F. et al.** Calprotectin and Neurofilament Serum Levels Correlate with Treatment Response in Myasthenia Gravis under Intensified Therapy—A Pilot Study. *Journal of Autoimmunity* **2025**, 157, 103476. <https://doi.org/10.1016/j.jaut.2025.103476>.

“Serum calprotectin strongly correlates with clinical outcomes in myasthenia gravis showing that it has potential as a marker for monitoring therapeutic efficacy.”

- **Lee, A. et al.** Assessment of Antiphospholipid Antibodies and Calprotectin as Biomarkers for Discriminating Mild from Severe COVID-19. *Clinical Laboratory Analysis* **2021**, 35 (11), e24004. <https://doi.org/10.1002/jcla.24004>.<sup>2</sup>

“Serum calprotectin levels were significantly elevated in severe COVID-19 cases.”

- **Sakuma, M. et al.** Myeloid-Related Protein-8/14 in Acute Coronary Syndrome. *International Journal of Cardiology* **2017**, 249, 25–31. <https://doi.org/10.1016/j.ijcard.2017.09.020>.<sup>2</sup>

“This study demonstrates that in acute coronary syndrome, serum calprotectin (MRP-8/14) is significantly elevated in the coronary artery blood of patients with aspirated thrombus, correlates strongly with the leukocyte activation marker myeloperoxidase, and induces tissue factor expression in endothelial cells, positioning it as a key biomarker at the interface of inflammation and thrombosis.”

- **Mangold, A. et al.** Coronary Neutrophil Extracellular Trap Burden and Deoxyribonuclease Activity in ST-Elevation Acute Coronary Syndrome Are Predictors of ST-Segment Resolution and Infarct Size. *Circulation Research* **2015**, 116 (7), 1182–1192. <https://doi.org/10.1161/CIRCRESAHA.116.304944>.<sup>2</sup>

“This comprehensive study demonstrates that Neutrophil Extracellular Traps (NETs) form the scaffold of coronary thrombi in ST-elevation acute coronary syndrome (STE-ACS), finding that high NET burden (and increased components like serum calprotectin) correlates negatively with treatment success (ST-segment resolution) and positively with infarct size, while endogenous Deoxyribonuclease (DNase) activity is protective by accelerating thrombus lysis.”

- **Peng, W. H. et al.** Increased Serum Myeloid-Related Protein 8/14 Level Is Associated with Atherosclerosis in Type 2 Diabetic Patients. *Cardiovasc Diabetol* **2011**, 10 (1), 41. <https://doi.org/10.1186/1475-2840-10-41>.<sup>2</sup>

“This study reports that elevated serum calprotectin levels in diabetic patients are independently associated with the presence and severity of coronary artery disease (CAD) and correlate positively with the early atherosclerosis marker, carotid intima-media thickness (IMT), even in patients without clinically overt CAD.”

<sup>2</sup>In these studies, the BÜHLMANN sCAL® ELISA assay or the Quantum Blue® sCAL assay was used. Both assays are standardized differently than BÜHLMANN sCAL® turbo and have been discontinued.