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# C-reactive protein level association with future cardiovascular events assessed by different risk scores among rheumatoid arthritis patients.

--Manuscript Draft--

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Dear Editor,

Enclosed please find the manuscript entitled “C-reactive protein level association with future cardiovascular events assessed by different risk scores among rheumatoid arthritis patients.” for consideration for publication in EJIM as a response to the Letter of Noriaki Kou and colleagues entitled “An elevated C-reactive protein level was associated with cardiovascular events among rheumatoid arthritis patients: What’s next? https://doi.org/10.1016/j.ejim.2022.11.032”

The article has not been published and is not under consideration for publication elsewhere;

**Disclosures:** Authors declare that they have no financial or non- financial competing interests.

The manuscript has been read and approved by all the Authors

Yours sincerely,

Gian Luca Erre, MD PhD

**C-reactive protein level association with future cardiovascular events assessed by different risk scores among rheumatoid arthritis patients.**

We appreciate the interest of Noriaki Kou and colleagues [1] in our article [2], and we fully agree that beside disease activity, therapies, and systemic inflammation other non-traditional cardiovascular risk factors such as extra-articular manifestations and positivity for anti-citrullinated peptide antibodies (ACPA) and rheumatoid factor (RF) would negatively impact on the risk of future cardiovascular events in the RA population.
In our manuscript [2] we use the Expanded Cardiovascular Risk Prediction Score for Rheumatoid Arthritis (ERS-RA) over other cardiovascular risk scores being interested to explore the relationship of C-reactive protein both with the predicted 10-year risk score and each RA-specific cardiovascular risk factor included in the score. In our cohort of RA patients, nor the ACPA neither the RF positivity were associated with the 10-year risk of future cardiovascular events, assessed by the ERS-RA score, in univariate analysis; Therefore, these factors were not included in the final multivariate regression model.
Moreover, the paucity of data on extra-articular manifestations registered at baseline did not allow us to confirm whether the risk of future cardiovascular events assessed by ERS-RA is associated with the presence and the severity of visceral complications in RA, as suggested by Noriaki Kou and colleagues [1].

Noriaki Kou and colleagues also contemplate that different cardiovascular risk scores may show a diverse association with C-reactive protein concentrations [1]. To verify this hypothesis, we assessed the significance of the correlation between C-reactive protein concentrations and the 10-year cardiovascular risk calculated with the "Progetto CUORE" [3, 4], and the "SCORE-2" [5] algorithms. The "Progetto CUORE" risk score, based on Italian population, estimates the 10-year risk of major fatal and non-fatal CV events based on age, sex, diabetes, smoke, total cholesterol and systolic blood pressure. The SCORE-2 algorithm calculates the 10-year risk of fatal and non-fatal cardiovascular events based on age, gender, smoking habits, total cholesterol, HDL-cholesterol and systolic blood pressure. The SCORE-2 algorithm recognizes Italy as a "moderate-risk country. According to the recommendations of the EULAR (European Alliance of Associations for Rheumatology) the risk prediction models should be adapted for patients with RA by a 1.5 multiplication factor [6].
Compared with the average 10-year risk of future cardiovascular events assessed by the ERS-RA score of 12.9 ± 10%, the EULAR-adapted "Progetto CUORE" and "SCORE-2" calculated 10-year risks were 6.5 ± 7.6% and 7.5 ± 4.6%, respectively.
As summarized in Table 1, C-reactive protein level was not significantly associated with the expected risk of future cardiovascular events measured by "Progetto CUORE" and "SCORE-2" algorithms. Therefore, it is conceivable, that the magnitude of association, if any, between the systemic inflammation and the specific risk equation can be influenced, at least in part, by the number and type of risk factors included in the algorithm (e.g., the risk factor "diabetes" is comprised in the "ERS-RA" and "Progetto CUORE" equations, but is not incorporated in the SCORE-2 risk model). Furthermore, the sample sizes of RA patients to which the risk scores have been applied is also different due to specific entry criteria, a condition that may have introduced further heterogenicity in the results.
To conclude, we appreciate the opportunity to discuss the association between systemic inflammation and the risk of future cardiovascular events assessed by different cardiovascular scores in the RA population.
We expect that this analysis can be a step to fill in gaps of knowledge in the field of cardiovascular risk assessment in populations with rheumatological diseases, and will assist clinicians in the management of cardiovascular risk of their RA patients.

**References**

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**Table 1** Multiple regression

| | **ERS-RA** n= 1, 251 | | **CUORE** n= 820 | | **SCORE2** n= 845 | |
|---|---|---|---|---|---|---|
| | Coefficient | 95% CI, *p* | Coefficient | 95% CI, *p* | Coefficient | 95% CI, *p* |
| CRP | 0.006 | 0.000 to 0.012, 0.03 | 0.001 | -0.003 to 0.006, 0.56 | 0.0005 | -0.001 to 0.002, 0.65 |
| btsDMARD | -0.000 | -0.003 to 0.002, 0.89 | -0.001 | -0.003 to 0.0004, 0.13 | -0.0008 | -0.001 to 0.0002, 0.13 |
| only csDMARD | 0.002 | -0.002 to 0.007, 0.37 | 0.004 | 0.0008 to 0.049, 0.013 | 0.002 | 0.0005 to 0.004, 0.010 |

A multiple linear regression (ENTER method) was performed for the dependent variable (ERS-RA, Progetto Cuore, SCORE-2 score) using a multiple imputation analysis. CRP, C-reactive protein every 10 mg/L increment; btsDMARD use, biological and targeted synthetic disease modifying anti-rheumatic drug; csDMARD, conventional synthetic disease modifying anti-rheumatic drug.