Author’s response to reviews

Title: A systematic review of the role of inflammatory biomarkers in acute, subacute and chronic non-specific low back pain

Authors:

Patrick Morris (pat.morris7@gmail.com)
Kareem Ali (kareemali1994@gmail.com)
Mackenzie Merritt (m.merritt3@hotmail.com)
Joey Pelletier (joeypelletier88@gmail.com)
Luciana Macedo (macedol@mcmaster.ca)

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Author’s response to reviews:


Dear Alessandro Chiarotto,

On behalf of my co-authors I would like to thank you for the fast turn around of the manuscript and for providing suggestions that will significantly improve the quality and reporting of our study. Please see below a point by point response to the comments.

Editor

Major comments

The GRADE approach should be better presented throughout the manuscript, including abstract (methods and results), methods, results and discussion (i.e. suggestions for further research based on the GRADE rating). The GRADE approach was originally developed for systematic reviews of interventions, but this is not a systematic review of interventions, therefore, reference 19 may not be the most appropriate and it should be better specified how the approach was adjusted for the studies included in this review. Please note that there are various published adaptations of the GRADE method (e.g. Huguet 2013 Syst Rev for prognostic factor research) but, if none of these was used, the authors should specify the criteria they used for all 5 GRADE components. I believe using the GRADE approach for RCTs is not appropriate as this downgrades
observational studies by definition, but the goal of your review was different, therefore it is possible to have high quality evidence regarding associations.

We have now changed our grading system to better reflect the Huguet et al. GRADE recommendations for prognostic studies. Note that regardless of the system used, the small number of studies and the poor methodological quality (high risk of bias) of studies included within each comparison still leaves us with low to very level of evidence for all comparisons.

When presenting the results on associations between biomarkers and clinical parameters, please try not to focus only on the "significance" of the results (highly debated at the moment, see, for instance, Amrhein 2019 Nature), but focus also on the magnitude of the (non-)associations. These are reported in Table 4, but there is no emphasis on the magnitudes in the results section and, consequently, in the discussion. The strength of an association may be much more important than its "statistical significance".

We agree that confidence intervals and sizes of differences should be primarily reported and discussed in any research study. We are limited in this discussion in our study given that many studies did not report the magnitude of the effect and many of our results did not find significant associations. However, when possible we discussed clinical important findings as well as the precision of confidence intervals.

Minor comments

What is the difference between cohort and case-control studies (on one hand) and longitudinal studies (on the other hand)?

We have added more information about the different types of studies to the inclusion criteria of the review: “Cross sectional studies where data is collected at one time point is often used to evaluate prevalence and associations. Cohort studies include prospective and retrospective longitudinal designs and are best to evaluate incidence, natural history and causation. Participants are chosen without knowledge of the outcomes and prospectively followed over time (prospective) or recruited posthoc where data has already been collected (retrospective). Finally, case-control designs often include the recruitment of participants with or without the outcome of interest and exposure is usually determined retrospectively. This design investigates for the relative importance of a predictor in relation to the presence or absence of an outcome.”

In the strength and limitations sections, please remove the statement that you followed methods recommended by the Cochrane initiative as this is not entirely appropriate.

We have removed the statement about Cochrane initiative from the discussion.

Table 4. Please try to adjust the results' column by reporting results in a more schematic manner.
Table 4 has been amended throughout as suggested and results have been categorized into different markers. In addition, more information on the sizes of effects, when available, were presented.

Sincerely,

Luciana Macedo, PT, PhD

McMaster University