Author’s response to reviews

Title: Exosomal microRNAs as potential circulating biomarkers in gastrointestinal tract cancers: A systematic review protocol

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Author’s response to reviews:

Re: Manuscript no # SYSR-D-17-00172 entitled " Exosomal microRNAs as potential circulating biomarkers in gastrointestinal tract cancers: A systematic review protocol"

Dear Editor in Chief, Systematic Reviews

On behalf of the authors, we are very pleased to receive the valuable comments of reviewers. We have amended the manuscript in line with the reviewers’ suggestions and therefore a revised manuscript is now being submitted. In order to accelerate the re-review process, all changed and modified parts of revised manuscript have been highlighted with yellow background. We hope it warrants the readership and is acceptable for publication in “Systematic Reviews”.

We are looking forward to hearing from you in due course.

Yours sincerely,

Dr Zahra Madjd
Reviewer reports:

Reviewer #1: This manuscript is a systematic review protocol that will consolidate the literature in the field of exosomal microRNAs as potential circulating biomarkers in gastrointestinal tract cancers. In a research area that is expanding, this review may be timely and help focus future research if conducted well.

1- A generally well written protocol although minor typos have crept in. This manuscript would benefit from an explicit reasoning of how this review differs from the review cited that was published in early 2017.

Reply:

- According to review's comments, recently a published review showed that the exosomal miRNAs could be detected and isolated from body fluids such as saliva. This review had merely given an overview on exosomal miRNAs as diagnostic markers GI cancers with focus on the origin and trafficking of exosomes between cells, techniques to isolate exosomal miRNAs, micoRNAs and exosomal miRNAs expression. In the current systematic review,
we focus on studies that have been evaluated circulating exosomal miRNAs as non-invasive biomarkers in serum of patients with primary GI tumors, the clear reasoning concerning how this systematic review differs from the previously published review is mentioned in the manuscript, at the end of the introduction section (page 3 line 107 to 120)

2- Clarification also required from the authors in the abstract, background and aims that the potential diagnostic or predictive (or even prognostic) use of biomarkers in this context is related to recurrent cancer.

Reply:

For more clarification, the ABSTRACT, BACKGROUND and AIMS are revised in the manuscript based on the reviewer's comments. (page 1 line 33-39, page 2 line 89-91 and 94-96)

- The Cochrane handbook, mentioned in the methods, is missing from the reference list. The methods are generally sound and dependent on the data identified and extracted from the literature.

Reply:

Given the diversity of cancer types and different reported exosomal miRNAs across the studies, we anticipate that we cannot perform a meta-analysis, therefore we deleted the sentence which refers to the Cochrane handbook in the manuscript.

Reviewer #2: General comments:

I thought that the protocol was generally well written and outlines an interesting systematic review of studies that have investigated the micro RNA profiles of serum exosomes in GI cancers.
Minor comments:

* The authors state that the review will be reported in line with PRISMA-P, however this guideline refers to the protocol only and not the completed review. The authors should state the correct reporting guidelines for their review.

Reply:

According to reviewer's comments, it should be noted that this manuscript is merely the protocol of our systematic review and we still did not carry out data extraction and evaluation of the included studies. Therefore, we will report this systematic review protocol in line with the Preferred Reporting Items for Systematic Reviews (PRISMA-P) guidance. (page 4 line 148). The PRISMA Flow Diagram will be applied to describe the flow of information through the different phases of the systematic review in final systematic review article.

* There are some citations that appear in the body of the text that are not included in the reference list. For example, in the risk of bias assessment section (page 5 line 14) citations are mentioned by Hoy et al and Werfali et al. These (and any others) should be included in the reference list

Reply:

- To reply the above comment, the following references (references number 46 and 47) has been included in the reference list of manuscript, as bellow;


* I am not certain that the Discussion section (Page 6 lines 5-18) is necessary for a protocol or that it adds to the content

Reply:

According to reviewer's comments, it seems that it is not necessary to mention the discussion section in the protocol article, but this is according to the journal’s style for a systematic review protocol article.
Major comments:

* I feel that the strategy for data synthesis is confused and needs some further thought. For example, page 5 line 28-29 states that outcomes will be reported as descriptive statistics without conducting meta-analysis. However, the subsequent paragraphs in that sub-section seem to describe the plans for meta-analysis. I think the authors need to be clearer about their plans for data synthesis. If they believe that meta-analysis will not be possible, or will not be informative, then I would rather see details of a planned narrative synthesis of the results.

However, if there are to be formal meta-analyses, perhaps the authors should state that meta-analysis is planned providing sufficient data are available. Also, as the authors expect there to be considerable heterogeneity, I would rather see plans to investigate some stated hypotheses of the possible causes of heterogeneity stated in advance. I think this would be preferable to what is stated at present, which is for statistical heterogeneity to be assessed and then unspecified, post hoc analyses conducted to try to identify the sources of that heterogeneity.

* I may have missed it but PRISMA-P asks for details of planned assessment of the strength of the body of evidence (e.g. using GRADE) but that appears to be missing from the protocol. The authors should consider adding this or stating why it is not being proposed here.

Reply:

Given the considerable variability among cancers and the difficulty in detecting common exosomal miRNAs and characteristics of the studies, the extracted outcomes will be summarized and reported using descriptive statistics without conducting any meta-analyses, therefore the “Strategy for data synthesis, sensitivity analysis, and analysis of subgroups or subsets” has been revised in the manuscript based on the reviewer's comments. The quality of evidence for each main outcome will be determined based on the GRADE system as bellow; (page 5 line 218-224, page 5 line 228-229, page 6 line 232-234).

Ref:
