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Peer Review

Review of: "Cystatin C at the Crossroads: Unraveling a Multidimensional Biomarker in Alzheimer's Disease and Cognitive Decline"

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Dear authors:

The strengths of this paper are:

- The topic is of interest since not only recent publications but also academic/professional sources aim to establish early diagnosis of Alzheimer's disease and cognitive decline. Moreover, Cystatin C is undoubtedly a potential biomarker.
- The work is meticulously written, highlighting several valuable issues of cystatin C.
- This review is relevant to the biomedical field and, in particular, to early diagnosis.

Suggestions to improve the paper:

1. Figures with diagrams showing where Cystatin C acts in the neuroinflammation and/or neurodegeneration pathways could be included.
2. The criteria used to select the studies presented in Tables 1 and 2 should be clarified. In addition, other recent references should have been included.
3. A concise critical analysis (strengths and weaknesses) of each trial would also be appropriate. While limitations are discussed in general terms in the section "Limitations of Current Evidence and Methodological Challenges," some of these could be included in the section on the critical analysis of the trials.
4. Since Cystatin C is a potential biomarker for Alzheimer's disease and neurodegeneration, a brief overview of currently used biomarkers and technologies would be helpful for readers. Presenting

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the advantages, disadvantages, and complementarities of Cystatin C compared to these biomarkers would add clarity to the paper. This would provide valuable information to specialists in the biomedical field, and to physicians in particular, about current options.

5. The main molecular pathways involved should be discussed in detail. In particular, the signalling pathways affected by this biomarker. A diagram would be helpful.
6. Since cystatin C also acts outside of cysteine protease pathways, at cell surface receptors, understanding its correlation with neurodegeneration would contribute to a greater knowledge of this biomarker.
7. Some research on the interaction of cystatin C with oxidative stress and the immune system, and its potential role in neuroinflammation and neurodegeneration, should be included to improve the paper.

I hope that these suggestions/recommendations will contribute to the knowledge of this potential biomarker for the academic/professional benefit of readers in the biomedical field. Also for future research.

Sincerely,

Prof. Dr. Alicia B. Pomilio

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Declarations

Potential competing interests: No potential competing interests to declare.