

Peer Review

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

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Reviewer comments to the authors

Manuscript title: *"Cystatin C at the Crossroads: Unraveling a Multidimensional Biomarker in Alzheimer's Disease and Cognitive Decline."*

Dear Authors,

Thank you for the opportunity to review your manuscript. Your work provides a well-written and comprehensive narrative overview of cystatin C (CysC) as a biological modulator and biomarker in Alzheimer disease (AD) and cognitive decline. The manuscript is generally understandable and supported by relevant references. The topic is contemporary, and the manuscript has the potential to be used by researchers and clinicians.

However, several issues should be tackled to enhance the scientific validity and contribution of the value. My detailed comments are listed below.

Major comments

1. Need for deeper critical analysis.

The manuscript summarizes the existing findings without critically elaborating on the strength, limitations, or inconsistencies of the literature. Considering the complexity of CysC biology, a more analytical approach is required.

- a. Please discuss the conflicting results, particularly regarding whether high CysC is harmful, protective, or compensatory.
 - b. Consider adding a brief section indicating key controversies and gaps in the evidence.
1. Need for updated mechanistic literature.

Mechanistic sections mainly depend on older references. Please include newer research (2018-2025) to cover:

- a. Neuroinflammatory role of CysC
- b. Autophagy and lysosomal pathway
- c. Vascular dysfunction

This will modernize the review and reflect the current scientific setting.

1. Lack of visual synthesis.

According to the multidimensional role of CysC, the review would greatly benefit from figures or schematics.

It is recommended to add:

- a. A conceptual diagram illustrating CysC mechanisms in AD.
- b. A figure depicting the association between CysC and cognition.
- c. A summary table of CST3 genetic variants and functional implications.

These would improve readability and scientific communication.

1. Novelty of the review is limited.

To reinforce the manuscript's contribution:

- a. Compare CysC with emerging AD biomarkers (GFAP, NfL, p-tau species).
- b. Discuss whether CysC adds diagnostic utility within the AT(N) framework.
- c. Explore how CysC could be integrated into a blood-based biomarker panel.

Minor comments

1. Redundancy

Some paragraphs repeat similar information about protease inhibition, A β binding, and autophagy. Consider consolidating overlapping sections.

1. Several sentences are long or overly broad and can benefit from simplification.
2. You mentioned a stronger effect of CysC in the Asian population but do not discuss potential genetic or environmental contributors. Please expand briefly.

Thank you again for this submission. I hope these comments help refine and enhance your work.

Sincerely,

Reviewer

Declarations

Potential competing interests: No potential competing interests to declare.