Author’s response to reviews

Title: Validation of Addenbrooke’s Cognitive Examination III for detecting mild cognitive impairment and dementia in Japan

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Version: 1 Date: 26 Feb 2019

Author’s response to reviews:

Answer to Editor

Comment 1. Please include the positive and negative likelihood of ratios in the results.

Response 1. Thank you for your pointing this out. We modified our manuscript as follows.

Before (Methods)

The optimal cut-off scores for identifying dementia and MCI were determined as the scores that led to the maximal accuracy of classification. Subsequently, positive and negative predictive values were estimated at different prevalence rates (5%, 10%, 20%, and 40%) for each optimal cut-off score.
After (Methods)

The optimal cut-off scores for identifying dementia and MCI were determined as the scores that led to the maximal accuracy of classification. Subsequently, positive predictive values (PPV) and negative predictive values (NPV) were estimated at different prevalence rates (5%, 10%, 20%, and 40%) for each optimal cut-off score.

Before (Results)

The optimal cut-off score of ACE-III-J for discriminating MCI patients from controls was 88/89 (sensitivity 0.77, specificity 0.92), and those of the HDS-R and MMSE were 24/25 (sensitivity 0.57, specificity 0.89) and 26/27 (sensitivity 0.61, specificity 0.86) (Table 4), respectively.

The AUCs of ACE-III-J, HDS-R, and MMSE for diagnosing dementia were 0.938 (0.915–0.960), 0.881 (0.847–0.915), and 0.881 (0.847–0.914), respectively. The AUC of ACE-III-J was significantly larger than those of HDS-R and MMSE (ACE-III-J vs. HDS-R, P<0.001; ACE-III-J vs. MMSE, P<0.001). For discriminating dementia patients from MCI and controls, the optimal cut-off score of ACE-III-J was 75/76 (sensitivity 0.82 and specificity 0.90), and those of HDS-R and MMSE were 20/21 (sensitivity 0.67, specificity 0.89) and 23/24 (sensitivity 0.64, specificity 0.87), respectively (Table 4).

After (Results)

The optimal cut-off score of ACE-III-J for discriminating MCI patients from controls was 88/89 (sensitivity 0.77, specificity 0.92), and those of the HDS-R and MMSE were 24/25 (sensitivity 0.57, specificity 0.89) and 26/27 (sensitivity 0.61, specificity 0.86), respectively. The PPV and NPV of ACE-III for identifying MCI at different prevalence rates were 5% (PPV 0.35, NPV 0.99), 10% (PPV 0.52, NPV 0.97), 20% (PPV 0.72, NPV 0.94), and 40% (PPV 0.87, NPV 0.86) (Table 4).

The AUCs of ACE-III-J, HDS-R, and MMSE for diagnosing dementia were 0.938 (0.915–0.960), 0.881 (0.847–0.915), and 0.881 (0.847–0.914), respectively. The AUC of ACE-III-J was significantly larger than those of HDS-R and MMSE (ACE-III-J vs. HDS-R, P<0.001; ACE-III-J vs. MMSE, P<0.001). For discriminating dementia patients from MCI patients and controls, the optimal cut-off score of ACE-III-J was 75/76 (sensitivity 0.82 and specificity 0.90), and those of HDS-R and MMSE were 20/21 (sensitivity 0.67, specificity 0.89) and 23/24 (sensitivity 0.64, specificity 0.87), respectively. The PPV and NPV of ACE-III for identifying dementia at different prevalence rates were 5% (PPV 0.30, NPV 0.99), 10% (PPV 0.48, NPV 0.98), 20% (PPV 0.67, NPV 0.95), and 40% (PPV 0.85, NPV 0.88) (Table 4).
Comment 2. What are the implications of the findings if someone screens positive to MMSE and not for ACE-III?

Response 2. Thank you for your pointing this out. We modified our manuscript as follows.

Before (Discussion)
Thus, we consider that ACE-III-J provides a more useful and precise instrument than MMSE and HDS-R for diagnosing MCI and dementia.

Several non-English versions of the ACE-III have been reported [11, 13, 14, 28].

After (Discussion)
Thus, we consider that ACE-III-J provides a more useful and precise instrument than MMSE and HDS-R for diagnosing MCI and dementia. However, in 19 of the subjects, screening results for dementia are positive in MMSE but negative in ACE-III. Six of the 19 persons were diagnosed as dementia. Even if a person takes a score that exceeds the cut-off score in ACE-III, it is necessary to consider the possibility of dementia if the MMSE score of the person is below the cut-off score for dementia in MMSE.

Several non-English versions of the ACE-III have been reported [11, 13, 14, 28].

Comment 3. Briefly add comments in the discussion section individuals with low MCI scores developing or progressing to dementia from the findings of this study.

Response 3. Thank you for your pointing this out. We modified our manuscript as follows.

Before (Methods)
Subsequently, positive and negative predictive values were estimated at different prevalence rates (5%, 10%, 20%, and 40%) for each optimal cut-off score.

After (Methods)
Subsequently, positive and negative predictive values were estimated at different prevalence rates (5%, 10%, 20%, and 40%) for each optimal cut-off score.
Correlation between the CDR sum of box (CDR SoB) score and ACE-III scores was evaluated using Spearman’s correlation coefficient. A value of p<0.05 was accepted as significant.

Before (Results)

The internal consistency reliability for ACE-III-J was high (Cronbach’s coefficient =0.870).

After (Results)

The internal consistency reliability for ACE-III-J was high (Cronbach’s coefficient =0.870).

ACE-III scores and CDR sum of boxes

Spearman’s correlation analysis of the scores of the CDR SoB and the ACE-III scores revealed that there was a significant correlation between them (correlation coefficient= -0.396, p< 0.001) in MCI patients.

Before (Discussion)

In this study, ACE-III-J total score also differentiated dementia patients from those with MCI with high accuracy (AUC, 0.938).

This study has several limitations.

After (Discussion)

In this study, ACE-III-J total score also differentiated dementia patients from those with MCI with high accuracy (AUC, 0.938).

In the cases diagnosed with MCI in this study, the higher the CDR SoB scores were, the lower the ACE-III scores were. Kim et al. reported that the CDR SoB score is useful for predicting the progression to dementia in amnestic MCI individuals. MCI cases with a low ACE-III score may be particularly susceptible to developing dementia in the future [31].

This study has several limitations.
Answer to reviewer 1

Comment 1. On page 5, the authors explain why the ACE III was created to follow on from the ACE-R, its predecessor. It is true that there are some psychometric reasons for this but the main reason was because of the copyright issues around the use of the MMSE, which was embedded in the ACE-R. Therefore the ACE III had to remove the MMSE items and introduced alternatives. I think this needs to be mentioned.

Response 1. Thank you for your pointing this out. We modified our manuscript as follows.

Before (Background)

For example, spelling of the word “WORLD” backwards can be substituted for subtraction of serial 7s from 100 in ACE-R, but these two items are known to present different challenges [10].

Therefore, the original authors developed a new version of ACE, namely ACE-III [6].

After (Background)

For example, spelling the word “WORLD” backwards can be substituted for subtraction of serial 7s from 100 in ACE-R, but these two items are known to present different challenges [10]. Most importantly, ACE-R included several elements of the MMSE. Due to copyright issues, it has become difficult to keep using ACE-R. [11]

Therefore, the original authors developed a new version of ACE, namely ACE-III [6].

Comment 2. It is not specifically a problem of this paper but I do worry that there is potential circularity in this method of evaluating the properties of instruments of this kind. Ideally the clinical diagnostic assessment should be independent of the cognitive tests that are being evaluated, but this is probably not realistic in practice and I suspect it has not occurred in this study. Instead, it is more likely that the data from the cognitive tests have contributed towards the diagnostic decisions as to which patients were normal or had MCI or dementia. If this is so, then surely we would expect there to be differences on ACE III (and MMSE and HDS-R) scores between the 3 groups. It's a general problem of this type of study, I think. I think a comment on this issue would be helpful.
Response 2. This is very important point; thank you for your comment. We modified our manuscript as follows.

Before (Discussion)

Second, the participants in this study were outpatients at a university memory center. Thus, the reliability and applicability of ACE-III-J in community samples need further study. Regardless of these shortcomings, ACE-III-J is an accurate instrument to detect MCI and dementia, and can be easily used in clinical settings.

After (Discussion)

Second, the participants in this study were outpatients at a university memory center. Thus, the reliability and applicability of ACE-III-J in community samples need further study. Third, we diagnosed dementia comprehensively including not only MMSE and HDS-R scores but also total living functions. However, it is undeniable that a potential circularity problem may exist. Regardless of these shortcomings, ACE-III-J is an accurate instrument to detect MCI and dementia, and can be easily used in clinical settings.

We had our manuscript edited by a native English speaker.