Author's response to reviews

Title: Risk factors for delirium in acutely admitted elderly patients: a prospective cohort study

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Author's response to reviews: see over
MS: 1555927045716437 – Risk factors for delirium in acutely admitted elderly patients: a prospective cohort study

Thank you for reviewing our manuscript 1555927045716437 – Risk factors for delirium in acutely admitted elderly patients: a prospective cohort study. We appreciate the positive approach of the reviewers and have carefully studied all their comments and criticisms. Enclosed you will find our point-by-point response to the reviewers comments. Changes in the text are indicated in bold. In addition, we have gone through the manuscript formatting checklist, and ensured that our files are correctly formatted.

We are pleased to send you a revised version of the paper. We hope the editors will find the manuscript in its revised version acceptable for publication.

Also on behalf of the other authors,
Yours sincerely,

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Referee 1:

Major Compulsory Revisions:

1. The referee questions how reliable the use and interpretation of the MMSE is in patients with a delirium. We used 2 instruments to determine cognitive impairment: MMSE and the IQCODE. MMSE-score is based on response of the patient regarding the current state, whereas the IQCODE is based on responses of an informant who has known the patient for at least ten years. For patients who were not delirious, we applied the results of the MMSE score to classify cognitive impairment. Whereas for patients with a delirium, we used the combination of both instruments. In case of conflicting results, the score of the IQCODE was applied. We changed to text of the method section to clarify this topic (third paragraph page 5).

2. The referee suggests rephrasing our comment in the text regarding the finding that a decreased number of leucocytes were associated with an increased risk for a prevalent delirium, yet the number of leucocytes was within the normal range. Indeed, this number was within the normal range. Still, patients with a relatively lower number of leucocytes (compared to the patients with a relatively higher count) had an increased risk. We have adjusted our remarks on this subject in the discussion section to clarify the topic (last sentence page 9; first paragraph page 10).

3. As suggested by the referee, we have rephrased the final conclusion (in abstract and discussion section) to reduce possible confusion (last paragraph page 2; second paragraph page 10).

Minor Essential Revisions

- We have added the word early (first paragraph page 2)
- We have changed the words ‘increased functional impairment’ into ‘functional impairment’ (third paragraph page 2).
- It is now being called a fellow in geriatric medicine (first paragraph page 4).
- We have corrected this mistake, and changed it into ‘were scored’ (first paragraph page 4).

Discretionary Revision

None given by the referee
Referee 2:

Major Compulsory Revisions:

1. We have added text to the introduction section to state the results of the inconclusive findings of previous studies (last paragraph page 3, continued on page 4).

2. Within 48 hrs after acute admission a geriatric physician determined the presence of a delirium. Our definition of a delirium is given in the method section; a prevalent delirium is the presence of delirium within 48 hrs after acute admission, so the delirium could have been already present at admission, or developed within 48 hrs after admission. To avoid confusion, we have added the word prevalent throughout the manuscript. We have chosen for this definition since scoring a delirium immediately after admission might be difficult, as the assessor needs time to observe the patient; preferable a complete night and some day-time. Moreover, this definition has been applied in other studies as well, e.g. Francis – JAMA 1990;263:1097-1101. We have worded the complete manuscript to avoid any confusion, i.e. we have added the word prevalent.

3. The referee is correct that the formulation about informed consent was rather confusing; we have reworded this part in the method section (last paragraph page 4).

4. The patient population studied for the present manuscript is a random sample from a larger cohort. Due to logistic reasons, we could only include a random sample for the study regarding risk factors and genetic variation. The current manuscript contains the results regarding risk factors. During the inclusion period, 576 patients of 65 years or older were acutely admitted. 488 patients (85%) were directly admitted to our hospital (potential patients for inclusion). 182 patients were not included because no informed consent was given, or because they were not able to speak or understand Dutch or English (37%). Finally 306 patients were included. A random sample of 126 patients was selected for the current study regarding risk factors. Selected and non-selected patients were similar regarding important characteristics (age, gender and presence of delirium). Mean age of selected patients was 79.1 yrs. (SD 7.8), for the non-selected patients this was 78.1 yrs. (SD 8.5). Percentage male in the selected patients was 41% and in the non-selected patients 45%. In the selected patients, 29% had a prevalent delirium; in the non-selected patients this was 28%. We have added text regarding patient selection to the method section (last paragraph page 4) and these figures to the result section (first paragraph page 7).

5. We collect the number and type of prescribed medication, unfortunately, we did not collect the doses or whether the patients were actually taking the prescribed medication. The referee is correct that this could play a role in the lack of finding an association between medication and the risk of a delirium. We have added this subject to the discussion section (second paragraph page 9).

6. We have added the word prevalent to avoid confusion on the type of delirium studied. For a more detailed explanation see reaction nr. 2 of referee 2 as well.

7. The referee remarks that the number of patients included is rather small compared to the number of factors studied in the multivariate analyses. We included 126 patients and studied 17 different risk factors in the univariate analysis (Table 4). Just, risk factors with a p-value <0.20 in the univariate analysis were used in the multivariate analyses, resulting in 7 potential risk factors. Determining the effect of 7 different risk factors based on 126 patients is indeed numerous. Therefore, we have performed a number of additional analyses, as described in the manuscript, to evaluate possible bias.
due to the small number of patients. First, we performed both a backward and forward selection procedure to determine risk factors. Both procedures resulted into the same final model. Secondly, we repeated our multivariate analysis by applying a more liberal inclusion criterion (p<0.15 instead of p<0.10), to study whether we ‘missed’ borderline risk factors; this was not the case.

8. We have put more emphasize (discussion section) on our unexpected finding that a lower number of leucocytes is associated with a higher risk of delirium. Two patients without delirium had a very high leucocytes count. Repeating the multivariate analysis without these 2 patients resulted into a less significant effect of leucocytes count (p=0.032; instead of p=0.01). Moreover, we have adjusted our final conclusion (abstract and discussion section) (last sentence page 9, continued on page 10; last paragraph page 2; second paragraph page 10).

Minor Essential Revisions

1. We have changed this omission in the method section; we now simply state that leukocyte count was recorded (first paragraph page 5).
2. We did not record the distinction between at admission and within 48 hrs. For a more detailed explanation see reaction nr. 2 of the Major revisions as well.
3. In table 2 the number, as well as the percentage of patients, receiving different types of medication is indicated. We have added the definition of the term psychopharmaca to the method section (third paragraph page 6).
4. Taken the Katz ADL score in 3 classes, than the predictive value of cognitive impairment is the highest. Comparing just the patients with severe physical impairment (Katz ADL ≥ 7) with patients with no or hardly any physical impairment (score 4 or lower), a 14 times increased risk was found, even higher than the effect of cognitive impairment. For patients with moderate physical impairment, the risk on delirium was still high (8 fold increased), but this was less than the effect of cognitive impairment.

Discretionary Revision

1. Yes, the nurses/physicians collecting data on risk factors were blinded to the presence or absence of delirium. We have added this to the method section (second paragraph page 6).
2. We have put more emphasize on this topic in the discussion (first paragraph page 10).

Quality of written English: The text of the manuscript has been revised by a native English speaker.
Referee 3

Major Compulsory Revisions:

1. We have adopted the suggestion of the referee and adjusted the text. We use the term **prevalent delirium throughout the whole manuscript**.

2. We have put more emphasize on the distinction between risk factors for incident and prevalent delirium patients in the introduction section (last paragraph page 3 continued on page 4).

3. We have added text regarding medical ethical approval of the study and the role of the funding resource (last paragraph page 4).

4. The patient population studied for the present manuscript is a random sample from a larger cohort. Due to logistic reasons, we could only include a random sample for the study regarding risk factors and genetic variation. The current manuscript contains the results regarding risk factors. During the inclusion period, 576 patients of 65 years or older were acutely admitted. 488 patients (85%) were directly admitted to our hospital (potential patients for inclusion). 182 patients were not included because no informed consent was given, or because they were not able to speak or understand Dutch or English (37%). Finally 306 patients were included. A random sample of 126 patients was selected for the current study regarding risk factors. Selected and non-selected patients were similar regarding important characteristics (age, gender and presence of delirium). Mean age of selected patients was 79.1 yrs. (SD 7.8), for the non-selected patients this was 78.1 yrs.(SD 8.5). Percentage male in the selected patients was 41% and in the non-selected patients 45%. In the selected patients, 29% had a prevalent delirium; in the non-selected patients this was 28%. We have added text regarding patient selection to the method section (last paragraph page 4) and these figures to the result section (first paragraph page 7).

5. We have rephrased our text into a more cautious suggestion regarding the role of the found risk factors in daily clinical practice (last paragraph page 2).

Minor Essential Revisions

Throughout the whole manuscript, we have put more attention on the distinction between prevalent and incident delirium.

Discretionary Revision

Thank you for the useful suggestion regarding our finding about co-morbidity (last sentence page 8, continued on page 9).