Author’s response to reviews

Title: The importance of increased awareness for delirium in elderly patients with rib fractures after blunt chest wall trauma: a retrospective cohort study on risk factors and outcomes

Authors:

Ties Janssen (tjanssen@amphia.nl)
Elmand Hosseinzoi (ehosseinzoi@amphia.nl)
Dagmar Vos (dvos@amphia.nl)
Eelco Veen (eveen@amphia.nl)
Paul Mulder (pgh.mulder@hccnet.nl)
Adrianus van der Holst (josvanderholst@hotmail.com)
Lijckle van der Laan (lvanderlaan@amphia.nl)

Version: 1 Date: 14 May 2019

Author’s response to reviews:

Mr. Guangde Tu
Editor
BMC Emergency Medicine

Breda, 7 May 2019

Dear Sir,

The authors would first of all like to express their gratitude to the reviewers for reviewing our manuscript. We have tried to adequately address all points mentioned in the reviewers’ comments. Revisions have been kept by using ‘track changes’.
Please find attached detailed comments on all matters that required attention according to the reviewers.

Thank you for receiving the revisions of our manuscript. Please let us know when things remain unclear or additional changes should be made.

We appreciate your time and look forward to your response.

On behalf of all the authors,

Sincerely,

Ties Lukas Janssen, M.D.

Department of surgery
Amphia Hospital, Breda
The Netherlands

Reviewer #1

Abstract

1. Suggest rephrasing this to state there is no known investigation around……rather than "to our knowledge". Using that phrase doesn't demonstrate that you have actually reviewed the literature to fact check etc. "To our knowledge, this study is the first to investigate risk factors of delirium in elderly patients with rib fractures after trauma.

- We agree with the reviewer here and have changed this as requested. We removed ‘to our knowledge’ from the sentence (line 28).

To clarify, we have added ‘physical impairment’ and ‘nutritional impairment’ to the sentence (lines 39-40). We also changed the capital P to a lower case p in the entire manuscript.

“Independent risk factors for delirium were increased age, physical impairment (lower KATZ-ADL score), nutritional impairment (higher SNAQ score) and the need for a urinary catheter, with odds ratios of 1.07, 0.78, 1.53 and 8.53 respectively.”

"The 6-month mortality in delirious patients was nearly twice as high as in non-delirious patients; however, differences did not prove significant” Rephrase to did not reach statistical significance.

- We have changed this as requested (line 46-47).

Introduction:

"After sustaining rib fractures, hospitalization is often required due to severity of the associated injuries and the need for proper pain management." - suggest rephrase to "adequate pain management".

- Thank you for this suggestion, we agree that adequate would be the right word here. We have changed this as requested (line 70).

To our knowledge, this study is the first to investigate risk factors of delirium in elderly patients with rib fractures after trauma." Suggest rephrasing this to state there is no known investigation around……rather than "to our knowledge". Using that phrase doesn't demonstrate that you have actually reviewed the literature to fact check etc.

- As mentioned earlier, we agree with the reviewer here. We have changed the sentence in lines 79-80:

“No previously published research has investigated risk factors and outcomes of delirium in elderly patients with rib fractures specifically.”

Methods

Why did you choose patients older than 65 years?

- In our country, people are still considered ‘senior citizens’ or ‘elderly’, when they are over 65 years of age. We agree with the reviewer that this definition can or maybe should change to people over 70 years of age, since the population is aging and people become older. However,
since we wanted to investigate the incidence of delirium in elderly patients, we included all patients over 65 years of age.

Pain management and therapy were based on the Visual Analogue Score - you need a reference for this sentence.
- We apologize, this is sloppy. We have added the following reference to the sentence and reference list:


The need for ICU admission - was this unplanned ICU admission?
- It was. We have changed the sentence in line 143 and added ‘unplanned’ to this line. We have also added ‘unplanned’ in Table 2 and 3 and to line 292.

Results:
Remove the word "significantly" from the text. The p value should speak for itself.
- We have removed ‘significantly’ twice in the first paragraph (line 192 and 193).

The variables shown in Table 1 with a p-value below 0.30 were selected to simultaneously enter the first logistic regression model as explanatory variables for delirium - this is methods, rather than results
- Thank you for pointing that out. This was already described in the methods section in lines 173 -177. We wanted to repeat this briefly to help the reader interpret the results, however we agree this is (partly) superfluous. We have therefore deleted ‘as explanatory variables for delirium’ from the sentence in line 198.

Discussion
Remove the sentence "To our knowledge, no previous studies have been published...."
- We agree with the reviewer that this does not need to be expressed again here. We have removed the sentence from the discussion (line 251-252).

In a recent study by O'Connell et al. (insert the date it was published rather than use the word recent)

- We have changed ‘recent’ to ‘2018’ (line 255).

The sentence starting "In a recent study by O'Connell et al….." belongs in the background, not discussion. This goes to your justification that there isn't any other work done in this field.

- We understand that this can be confusing. However, we stated earlier in the introduction: “No previously published research has investigated risk factors and outcomes of delirium in elderly patients with rib fractures.”

O’Connell et al. described the effects of different types of analgesia on the incidence of delirium, rather than investigating outcomes and risk factors after delirium. These are both different things and we therefore did not change this statement.

We also believe this should be in the discussion section, since we compare the incidence of delirium of our study with three other studies, one of which is O’Connell’s study.

Although hypothesized……you have not clearly stated the hypotheses in the methods a finding considered by the authors to be relevant, even though this difference was not statistically significant. - perhaps state that this finding is clinically significant rather than what you think

- We agree that this is irrelevant when not mentioned before. We have deleted ‘Although hypothesized’ from this sentence (line 266).

Nearly a quarter of patients undergoing surgery for a fractured hip develop a delirium - suggest deleting this paragraph, doesn't really add anything

- We agree with the reviewer here. We have removed this sentence (lines 315-316) from the text and changed the sentence in lines 318-322:
“This lack of significance is likely explained by the small number of patients undergoing surgery, since opposite to the treatment of other trauma-related fractures such as hip fractures, the main treatment for rib fractures is adequate pain management and respiratory support [39-41].”


- We thank the reviewer for these references. We have added Kourouche to the reference list (#40) and changed the sentence in lines 343–349:

“When acutely admitting an elderly patient with rib fractures due to blunt chest wall trauma, increased awareness for delirium is recommended. This awareness, together with identification of patients most at risk and primary preventive measures such as those stated in the HELP guidelines [45], might be able to lower the incidence of delirium. When admitting elderly patients with rib fractures, proper adequate pain management, respiratory support and chest physiotherapy [41], together with and early consultation of a geriatrician at admission, are advised.”

We have also added Kourouche as a reference in the sentence in lines 318-322.

“...since opposite to the treatment of other trauma-related fractures such as a hip fractures, the main key components of the treatment for of rib fractures is adequate pain management and respiratory support [39-41].”

We would also like to thank the reviewers for the second reference, however we feel this study does not add valuable information to the current study. This study focusses primarily on pneumonia after blunt chest wall trauma, but does not include delirium in the results.

Reviewer #2

METHODS
Please add some basic hospital demographics (number of ED presentations per year, population covered by hospital) to inform the reader of the type of hospital in which the study was completed.

- As requested, we have provided extra information regarding the hospital demographics (lines 96-101):

“...admitted two a level II trauma centre and tertiary teaching hospital in Breda, the Netherlands. The Amphia Hospital is centred in a large crowded region and the hospital covers about 400,000 inhabitants. Each year 20,000 patients visit the emergency department for surgically related diseases; more than half of them are trauma patients. Over 1500 trauma patients are admitted each year and treated for their fractures.”

Are the SNAQ / KATZ tools routinely recorded in medical records and if so, give details of how they are completed and by whom. Also, please add some detail re their reliability and validity, if this information is available in previous research. I'm guessing it may not be for the study cohort (elderly patients with rib fractures), but is there data for similar cohorts?

- Yes, for all patients that are admitted to the hospital, a SNAQ and KATZ score is recorded in the electronic patient data files. These questionnaires are completed when admitted to the wards and are performed by nurses. Both screening tools have been found to be reliable when performed by ward nurses. We have added “...routinely scored by ward nurses at admission to the wards..” in lines 111-112. We have also added a reference19 regarding the validity of the KATZ score. The reference regarding SNAQ already shows validity of this score.


Did you include dementia / conditions associated with cognitive decline / psychological co-morbidities - eg depression / previous psychosis as these may lead to increased risk of delirium in the elderly? If not, can I suggest adding a sentence to the limitation section

- We agree with the reviewer that excluding these patients would be a big limitation. However, we did not exclude patients with cognitive impairment. They are presented in Table 1 and this is stated in lines 108-109. Additionally, stated in lines 264-268, this variable was not found to be a risk factor for delirium and was deleted from the model early on.
Was a CT thorax routinely available (especially in LET patients) and if not, did you rely on CXR results? Was there always imaging available for the LET patients? If not, were these patients not included in the study? This may be worth adding to your limitations section, as we know that imaging is not fool-proof and such studies are always at the mercy of this fact.

- We agree with the reviewer here. CT thorax was routinely available, however not all patients are in need of a CT thorax and only get a chest X-ray, in accordance with hospital protocols. We acknowledge the fact that chest X-rays are less accurate and the number of fractured ribs can be underestimated and additional injuries may be missed. We have therefore added the following lines and references to the limitations section (lines 330-334):

“Although routinely available, hospital protocols do not require a CT thorax to be made for every trauma patient. The number of rib fractures and additional injuries in most patients were diagnosed using a conventional x-ray. Previous research has shown that the number of rib fractures can be underestimated or rib fractures can even be missed when only using a chest x-ray for diagnosis1,2.”


We have also added a few lines to the methods section (lines 126-127):

“Thoracic CT-scans were routinely available, however were performed only when conventional chest X-rays were inconclusive.”

Did you use the imaging reports that were written at the time of injury, or did you re-look at CT / CXR findings? If so, who conducted this for you?

- Imaging reports from the radiologist at the time of admission were used and images were not reassessed. We have therefore added the following lines to the methods section (lines 128-129):

“Imaging reports from the radiologist at the time of admission were used and images were not reassessed.”

It may help the reader if you include some brief details of your anti-psychotics protocol.

- As requested, we have added a few lines to the manuscript (lines 138-140):
“Cognitively impaired patients, patients with delirium in history and frail patients were given prophylactic haloperidol. A geriatrician was consulted to confirm diagnosis when delirium was suspected and started therapeutic haloperidol.”

What was your inclusion / exclusion criteria? It may help the reader if you explicitly state these at the start of the methods section. Did you exclude patients with dementia / cognitive decline?

- No exclusion criteria were used. As stated in lines 95 - 97: “..all patients aged ≥65 years with one or more rib fractures after blunt trauma, admitted two a level II trauma centre and tertiary teaching hospital in Breda, the Netherlands, between July 2013 and June 2018.” .. were included in the research. Patients with cognitive impairment were also included in the research, as mentioned in previous comments.

In your outcomes section - what is the reliability / validity of the DOSS?

- Literature is inconclusive about the validity of the DOSS. Specificity rates are around 90%, sensitivity rates however vary from 56% to 91%1,2. This difference is explained by the different subtypes of delirium. A hypoactive delirium is harder to recognize than a hyperactive delirium. The hypoactive form is present in over 40% of the cases and unrecognized in over half of these cases3. We have added a paragraph to the limitations section highlighting this (lines 336-340):

“The DOSS was used to screen for delirium by ward nurses. Recent validation studies have shown inconclusive results, with sensitivity rates varying from 56% to 91% [23, 43]. This difference is likely explained due to difficulty in diagnosing the hypoactive subtype of delirium. This subtype is present in over 40% of cases and is unrecognized in over half of these cases. [44]”

23. Nurses’ Recognition of Hospitalized Older Patients With Delirium and Cognitive Impairment Using the Delirium Observation Screening Scale: A Prospective Comparison Study


You state additional adverse events were included as an outcome, can you please list what complications you included as an adverse outcome briefly in your methods:

- Literally any deviation from the normal postoperative course (Clavien-Dindo grade I) was scored here. We have added a sentence to the paragraph (lines 161-162):

  “Any deviation from the normal postoperative course was considered an additional adverse event.”

Statistical analysis - stats are not my strong point, but then this may be the case for a lot of the readers of your manuscript. Why did you use a p-value of 0.30 as a cut off for inclusion in the MV analysis? Just add a reference to justify your choice, as some previous guidelines state that all variables should be included.

In terms of your analysis, please can you outline how you selected your variables (ie were they chosen a priori and based on previous literature) and also, please state how you decided on your sample size? Consider the 'Events per Variable' guidelines. You seem to have studied many variables, for only a relatively small number of events (outcomes). If this is the case, please add a sentence to your limitations to acknowledge this fact.

- We have chosen to use the conventional maximum likelihood method for logistic model fitting with selection of explanatory variables for delirium based on the p-values of the estimated regression coefficients (log odds ratios). As the number of candidate explanatory variables is much too large to include them all in a model for explaining 47 delirium cases in 181 patients a vigorous selection based on the p-value is necessary by setting some boundary $\alpha$ while at the same time avoiding to include only variables that happen to have an incidental extreme effect in our data set. Harrell1 proposes to use an $\alpha$ that is far from the traditional choices of 0.05 or 0.10. Steyerberg et al.2 mention that $\alpha = 0.50$ is a reasonable choice for deleting variables. However by choosing $\alpha = 0.50$ the number of variables selected into the model is still too large compared to the number of 47 delirium cases in our data. This is the reason why we decided to use an in-between value of 0.30 for $\alpha$, realizing that there is some arbitrariness in any choice of $\alpha$.


A power calculation was not performed as we used all available patients that were electronically registered as of 2013. Information on the consequences of a type-2 error lies in the estimated
95% confidence limits of the odds ratios. Candidate explanatory variables were selected based on clinical relevance.

All other variables studied, as presented in Table 1 and Table 2, are informative. For this kind of information, in contrast to the model that was created, ‘Events per Variable’ guidelines do not apply.

Can you justify why you didn't impute your missing data.

- Missing data was not imputed because either the data that was missing was infrequent or there was too much data missing to impute.

RESULTS

Please can you state what additional injuries were sustained by patients - or were they all isolated blunt chest wall trauma.

- The additional injuries that were recorded were injuries in the thorax and lungs, such as lung contusion, flail chest, pneumothorax and hemothorax. These were considered most important and are all reported in Table 2. By taking into account the ISS score, the number and severity of injuries were included in the analysis. We do not believe that adding these additional injuries to the manuscript would make things clearer; however we do agree with the reviewer that for completeness, these may have been recorded. Most patients had isolated rib fractures, however some of the additional injuries that occurred were fractures of the clavicle and humerus.

I got a bit confused as to why the age and KATZ scores were dichotomised (lines 205-208 and 211-215). Again, this may need to be simplified for readers who are not statisticians (like myself).

- The variables age and KATZ-ADL were not dichotomized here. We investigated a possible interaction between those variables, to see if they influence each other. We calculated the p-value for this interaction, which was close to significance (p=0.059). Even though this was not statistically significant, this was relevant to take into account. In the end, this basically means that if both variables are entered in the model together, they influence each other. With increasing age, the effect of a lower KATZ-ADL on the primary outcome (delirium) decreases. Similarly, with decreasing KATZ-ADL score, the effect of age on the primary outcome decreases as well.
Overall, the results seem to address too many outcomes for this type of study. I think the secondary outcomes are potentially slightly confusing the flow of the manuscript. This is only a suggestion, but would the study be improved by simply studying the onset of delirium, without the secondary outcomes? I think the study is strong enough with just the primary outcome and you certainly answer your research question (within the paper's title) by just doing this.

- We thank the reviewer for this suggestion and respect their opinion, however we feel that the outcomes after delirium are also highly relevant and important. As discussed earlier, outcomes and risk factors of delirium in rib fractured patients have not been investigated before. Delirium is a frequent complication, as shown in the current study (25% of cases). By also looking at the outcomes after delirium, the importance of increased awareness is emphasized (as stated in the paper’s title; to which the reviewer referred). Within this study, we demonstrate the extent of the problem, the risk factors for the problem and ‘why’ we think it is a problem (the outcomes after delirium).

DISCUSSION -

This section reads very well and is an interesting conclusion to a well-designed and informative study. I particularly like the recommendations for practice section, as a clinician who manages these patients on a daily basis. If you do decide to reduce the number of outcomes investigated, then this may need a bit of editing in line with that.

- As discussed above, we did not reduce the number of outcomes and have therefore not edited the recommendations section.

My only comment regarding the discussion is that the limitations section seems a bit limited! This may be more comprehensive following my suggested changes to the manuscript.

- We agree that the limitations section was limited. By adding several comments as discussed above, we feel we have adequately addressed important limitations to this study.