Author's response to reviews

Title: Mortality and cause of death in hip fracture patients aged 65 or older - a population-based study

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Version: 4 Date: 2 October 2010

Author's response to reviews: see over
Reviewer's report

Title: Mortality and cause of death in hip fracture patients aged 65 or older – a population-based study
Version: 2 Date: 22 June 2010
Reviewer: Marc-Antoine Krieg

Reviewer's report:
In this manuscript, the authors aimed to assess the excess of mortality after a hip fracture in elderly men and women from Western Finland compared to the general population. They also planned to analyze causes of death comparing sex, fracture types, and hip fracture subjects with the general Finnish population.

Even if many data and review have been published about mortality after a hip fracture, this topic is of importance as it remains under-recognized for patients and politics in many countries.

Thank you for this comment. We have now included this comment in the Introduction (p. 4, 3rd paragraph).

The global long term excess of mortality compared to the general population showed in this study is very impressive. However, there are several aspects that have to be improved to reach a sufficient level of interest.

Major Compulsory Revisions
Globally, the text has to be extensively reviewed by the authors in order to improve its style, to avoid repetitions. It also needs to be reviewed by an English spoken person. This is of major importance to make it more attractive for readers.

The text has been revised, the discussion has been shortened, and the text has been edited by native English–speaking editors, as suggested.

It is difficult to know if the choice to consider only the "ultimate" cause of death per subject is correct. Indeed, it is well known that hip fracture patients usually have co-morbidities which could influence the risk to die. For example, for a patient with dementia, the cause of death could be a pulmonary disease or a neoplasm. Therefore, the prevention message remains uncompleted. And for a prevention message, the authors must be more precise than for example pulmonary diseases.

This issue is now discussed in the Discussion (p. 13, 2nd paragraph). The authors agree that the prevention of these deaths is difficult due to co-morbidities.

In the last paragraph of the discussion, the authors have mentioned the importance of nutritional intervention. This is probably one of the major messages they could give (muscle impairment would have been another topic), but malnutrition or frailty have not been investigated in this study. From a clinical point of view, it would have been important to consider the patient within its global medical conditions for prevention counseling, not only the ultimate cause of death.
Although we agree that nutritional intervention and muscle impairment are important to consider, these topics were beyond the scope of this study because we did not have any data on these variables. These topics are not discussed in detail to avoid increasing the length of the discussion, which had to be shortened in the revised version.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Not suitable for publication unless extensively edited

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:** I declare that I have no competing interests

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**Reviewer's report**

**Title:** Mortality and cause of death in hip fracture patients aged 65 or older – a population-based study

**Version:** 2  **Date:** 7 July 2010

**Reviewer:** Jian Sheng Chen

**Reviewer's report:**

The paper presents the results of a prospective cohort study evaluating mortality and causes of death in 428 patients after a hip fracture surgery. The authors reported that age and gender adjusted mortality was higher in the 428 patients than in the general population; and the increased risk persisted over 9 years of the follow up. They also observed that the two most common causes of death after hip fracture were diseases of the circulatory system and dementia, and male patients were more likely to die from the two causes compared to female patients. The authors concluded that long-term optimal treatment of all major comorbidities shall be provided to patients with a hip fracture.

The manuscript could be strengthened by addressing following issues:

- **Major Compulsory Revisions**

  1. The questions posed by the authors are not well defined. The aims stated in the introduction were “to evaluate mortality and cause of death in patients sustaining a hip fracture over both the short and long-term …”. In fact, the authors focused on reporting (1) age-adjusted HR of men to women for different causes of death and (2) age- and sex-adjusted HR of cervical fracture patients to trochanteric fracture patients for different causes of death in the results. These works do not appear to fit the study aim well. Do the authors want to evaluate patterns of death after hip fracture or to identify risk factors for death in hip fracture patients?

    The aims of our study are now stated more precisely in the Introduction (p. 4, 3rd paragraph).

  2. Issues related to identifying mortality risk factors in the cohort of 428 patients (Results, 3rd – 6th paragraphs) are (1) not adjusting for potential confounders such as comorbidities at baseline, (2) not checked for proportional hazard assumption and (3) multiple testing. One regression model (e.g. models for hip fracture types) can be used to evaluate differences
between sexes as well as differences between fracture types. If proportional hazards assumption did not hold over the whole time period (9 years), it should be split at some time points to give more homogeneous time periods, in which the assumption might hold and hence the hazard ratio could validly be estimated. Also, the authors might consider use competing risks analysis treating different death causes as competing risk.

Thank you for pointing out these important aspects.

2(1) Unfortunately, we are not able to evaluate comorbidities between hip fracture patients and the general population due to the retrospective registry-based study setting. The limitations of the retrospective study setting are now discussed in more detail in the Discussion (p. 13, 2nd paragraph). The analyses of hip fracture patients were not adjusted for comorbidities at baseline because we did not have data e.g. on the duration of comorbidities that may have substantial impact on disease sequelae. In addition, we did not have any data on disease incidence during the follow-up.

2(2) Except for HR at 30 days, the 95% confidence intervals for different follow-up time points overlapped; hence, we consider the proportional hazards assumption to be valid within the limits of the confidence intervals. In addition, we checked the proportional hazards assumption using a Kaplan-Meier curve (Figure A) and log cumulative hazard function (Figure B). The curves are quite parallel, which indicates that the proportional hazards assumption is valid.
Figure A  Kaplan-Meier analysis of sex difference of mortality
We decreased the amount of multiple testing by determining cause-specific mortality for the entire follow-up instead of uneven time periods with small numbers of events. Mortality at different time points and by cause of death for both sexes was analyzed with both age-adjustment (n=428) and age- and fracture-type adjustments (n=407 because fracture type was missing in 21 patients). Based on Table A, the results of both analyses are similar; hence, we chose to present age-adjusted results in the manuscript to avoid dropping any patients from the analyses.

Mortality risks in cause-of-death analyses differ from those presented in the first version of our manuscript because of a previous incorrect comparison of events and censored values. (Patients with a specific cause of death were incorrectly compared with surviving patients, and patients who died from some other cause of death were excluded from analysis.) We have now reanalysed the disease-specific survival data and included patients who died from some other cause of death as censored values in disease-specific survival models.

**Table A:** Adjusted mortality risk of men compared to women at different time points and by cause of death during the entire follow-up

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**Figure B** log cumulative hazard function analysis of sex difference of mortality
<table>
<thead>
<tr>
<th>Time point of follow-up</th>
<th>With age-adjustment n=428</th>
<th>With age- and fracture-type adjustment n=407</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 days</td>
<td>2.12 (1.12-4.01), 0.021</td>
<td>2.45 (1.24-4.87), 0.010</td>
</tr>
<tr>
<td>6 months</td>
<td>1.99 (1.26-3.15), 0.003</td>
<td>2.14 (1.32-3.47), 0.002</td>
</tr>
<tr>
<td>1 year</td>
<td>1.92 (1.27-2.90), 0.002</td>
<td>2.10 (1.36-3.24), 0.001</td>
</tr>
<tr>
<td>3 years</td>
<td>1.83 (1.40-2.51), &lt;0.001</td>
<td>1.99 (1.44-2.76), 0.001</td>
</tr>
<tr>
<td>7 years</td>
<td>1.57 (1.21-2.04), &lt;0.001</td>
<td>1.67 (1.28-2.19), 0.001</td>
</tr>
<tr>
<td>End of follow-up</td>
<td>1.55 (1.21-2.00), &lt;0.001</td>
<td>1.65 (1.28-2.14), 0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>With age-adjustment n=428</th>
<th>With age- and fracture-type adjustment n=407</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory system disease</td>
<td>2.17 (1.11-4.24), 0.023</td>
<td>2.23 (1.16-4.43), 0.017</td>
</tr>
<tr>
<td>Malignant neoplasms</td>
<td>2.15 (1.02-4.54), 0.044</td>
<td>2.18 (1.02-4.68), 0.045</td>
</tr>
<tr>
<td>Circulatory system disease</td>
<td>1.71 (1.18-2.49), 0.005</td>
<td>1.83 (1.23-2.71), 0.003</td>
</tr>
<tr>
<td>Digestive system disease</td>
<td>0.47 (0.10-2.13), 0.327</td>
<td>0.45 (0.1-2.07), 0.308</td>
</tr>
<tr>
<td>Dementia, Alzheimer’s disease</td>
<td>1.11 (0.55-2.24), 0.776</td>
<td>1.19 (0.58-2.44), 0.631</td>
</tr>
<tr>
<td>Other</td>
<td>1.24 (0.60-2.55), 0.564</td>
<td>1.40 (0.67-2.91), 0.370</td>
</tr>
</tbody>
</table>

Competing risks analysis between causes of death was not considered in this phase of our study because the main focus was on analyzing cause of death between sexes and fracture types. However, this might be an interesting issue in future studies.

3. Discussion, 1st paragraph - “The principal finding of the present population-based study conducted in one central hospital district was that mortality after hip fracture surgery was increased for up to 9 years.”. - Based on the present study, it is not possible to determine the
duration of the increasing mortality attributable to hip fracture. It is possible that the increased risk observed at 9 years is solely due to the increased mortality in the first few years.

Thank you for this comment. This statement has been removed from the text throughout the manuscript.

4. Discussion, 14th paragraph – “To reduce mortality after hip fracture, efforts are needed to identify the patients at increased risk, i.e. men with circulatory system disease and dementia and patients with a cervical hip fracture based on the present study.” - This statement is not adequately supported by the data. How do the authors conclude from the data that men with circulatory system disease and dementia are at increased risk of death after hip fracture?

This statement has been removed from the text. Our data do not support statements concerning the prevention of deaths.

- Minor Essential Revisions
5. Comparing death rate of hip fracture patients with the age and sex adjusted rate of the general population will at least result in an overestimated risk of death due to hip fracture. Hip fractures occur more often in persons who have a greater number of medical and functional deficits and therefore higher chances of dying even without the fracture. This limitation should be stated.

This limitation is now stated in the Discussion (p. 13, 2nd paragraph).

6. Issues related to reporting are:
a. Abstract, 3rd paragraph - “Age-adjusted mortality after hip fracture surgery was higher in men than in women from the beginning till the end of the follow-up with a hazard ratio (HR) of 2.12 (95% confidence interval [CI] 1.12-4.01) in men and HR 1.55 (95% CI 1.21-2.00) in women.” - What was HR of 2.12 for men and HR of 1.55 for women compared to? Where do the results come from?

This sentence has been corrected in the Abstract (p. 3, 3rd paragraph).

b. Table 1 – Information such as follow up time, died during follow up, underlying cause of death and place of death do not belong in baseline patient characteristics.

The term ‘Patient Characteristics’ is now used instead of ‘Baseline Patient Characteristics’ in Table 1 and in the Results (p. 8).

c. Table 2 – Consider adding one column for RR of death for hip fracture patients compared to the general population.

This column has been added to Table 2.

d. Figure 1 – Presenting different HRs for men compared to women for different time points implies that proportional hazards assumption for sex does not hold over the whole time period. If this was the case, HRs in the figure were not estimated validly.
As stated in 2(2), except for HR at 30 days, we consider proportional hazards assumption to be relevant within the limits of confidence intervals.

- Discretionary Revisions
The authors should consider comparing risk of death of hip fracture patients with the same age residents in the Satakunta district since there are regional differences in mortality in Finland.

This issue is now mentioned in the Discussion (p. 13, 2nd paragraph).

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**
I declare that I have no competing interests

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**Reviewer's report**

**Title:** Mortality and cause of death in hip fracture patients aged 65 or older – a population-based study

**Version:** 2  **Date:** 22 July 2010

**Reviewer:** Juhana Leppilahti

**Reviewer's report:**
Methods: 33 patients were excluded which may cause a bias to the results. More exact flow charts of these excluded patients are needed (gender, age, fracture type, mortality)?

Data on the 33 excluded patients have been added to the text (p.5), but mean age could not be verified due to missing death data. Additional data on 21 patients with missing hip fracture data are listed on page 8.

Discussion is perhaps too long and should be shortened.

The Discussion has been revised and shortened as suggested.

Writing style is acceptable.
This retrospective population based study has, however, many limitations. Data on patient comorbidities may not be fully comprehensive. The manuscript does not include information on postoperative complications and functional recovery.

There are regional differences of mortality and comorbidities between Western and Eastern Finland. Would it give less bias to select the population only from Western Finland?
Due to the registry-based study setting, the data on comorbidities cannot be fully comprehensive. These limitations and the problems inherent to a retrospective study are now discussed more extensively in the revised Discussion (p. 13).

Does this manuscript offer new aspects to the mortality topic? We know, that several studies have published concerning mortality after hip fractures. It is known that at 50 years of age the total lifetime risk for hip fracture is almost 40% for women and 13% for men (Lane et al 2006). Several studies have shown that mortality after hip fracture is higher in males than females. In the study of Jacobsen et al. (1992) patients aged 65 years and older were divided into four age groups (65-74, 75-84, 85-94 and over 95 years). Mortality was higher in males in all age groups and increased in older patients.

The increased mortality after hip fracture has been well documented in previous studies. A focus of this study, however, was to evaluate cause-of-death by sex and fracture type.

Many authors have also suggested that greater prefracture comorbidity among men may be largely responsible for the observed gender difference. Nutritional status, osteoporosis, and functioning also play a role. In addition Huuskonen et al. reported already at 1999 that Finnish male hip fracture patients had increased mortality 3 times higher than age matched Finnish male population.

The possible reasons for the sex differences in mortality are now discussed in the Discussion (p. 10-11).

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests:
'I declare that I have no competing interests'