Author's response to reviews

Title: Mortality and Complications after Hip Fracture among Elderly Patients Undergoing Hemodialysis

Authors:

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Version: 3
Date: 28 February 2015

Author's response to reviews: see over
Author's response to reviewers

Title: Mortality and Complications after Hip Fracture among Elderly Patients Undergoing Hemodialysis

Authors:
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Version: 2 Date: 28 February 2015
Author’s response to reviews: see over
The Biomed Central Editorial Team

Object: MS: 711141021523663 - Mortality and Complications after Hip Fracture among Elderly Patients Undergoing Hemodialysis

We thank all the reviewers for their valuable responses. We have revised our manuscript based on the reviewers’ comments and we have described these changes for each response below.

Reviewer's report
Title: Mortality and Complications after Hip Fracture among Elderly Patients Undergoing Hemodialysis
Version: 2 Date: 17 January 2015
Reviewer: Matthias Klingele
Reviewer's report:
see attached file

… From these data they conclude that the overall mortality and complication rates of hemodialysis subjects after surgery for hip fracture are higher compared to non-hemodialysis subjects.

This conclusion is understandable with respect to the shown data. … However, this raises several interesting questions, representing major revisions:

1. Risk for mortality depends on renal function and raises over the time being dependent on dialysis. Therefore, data showing more details are needed (e.g. time on dialysis, residual urinary output). Moreover, as you indicate in the limitations, several important risk factors such as BMI as a potential sign for malnutrition are not available. The conclusion should take this into account.

Ans: Thank you for these valuable comments. In this study, we mainly compare hip fracture patients with and without hemodialysis. The database used in this study is a nationwide repository of national health insurance (NHI) claims and data of NHI beneficiaries, rather than a registry of hip surgery or dialysis patients. Because of the study design adopted in this analysis, many subjects had received hemodialysis before they entered the NIH program. Therefore, we could not obtain the first time of dialysis for all subjects. If we excluded these subjects, we would exclude more than 25% of the total subjects which would reduce the study power to assess the long-term follow-up effects. We are planning to conduct a new prospective study to
compare dialysis patients with and without hip fracture with comparable duration of dialysis in terms of mortality and complications.

We also consider risk factors such as renal function and BMI to be very important. However, it was not possible to use variables such as residual urinary output, BMI, and malnutrition status and arrive at solid conclusions. In addition, we do not regularly measure residual urinary output before operation in controls with hip fracture. We have addressed these limitations in discussion section on page 15, lines 7-10 and have modified our conclusion section on page 15, line 20 and page 16, line 1, as followed:

1. **Page 15:** “Although we used a matched cohort design and conducted a multivariable analysis to examine risk factors, many risk factors, such as pre-operative joint function/condition, renal function, smoking status, body mass index, bone mineral density, lifestyle, comorbidity severity, and quality of life, were not available for adjustment.”

2. **Page 15-16:** “Further prospective studies which include important risk factors are necessary to more precisely quantify the adjusted effect of hemodialysis.”

2. **Serious illnesses such as cancer affecting mortality (and possibly also the occurrence of postoperative complications) were not given or excluded. This aspect should be developed and demonstrated.**

**Ans:** Thank you for this comment. We actually included cancer subjects without specifying those cancer subjects in the first manuscript. We have re-analyzed data and revised numerical values. The major results and conclusions were not notably changed as a result of the new analysis. However, there are some minor changes of the numerical values. We have revised the numeric values in Table 1 and Table 3. And we have modified our methods section on page 7, lines 7-9 and our results section on page 8, lines 15-17, as followed:

1. **Page 7:** “The comorbidities of a subject were retrieved before or at the time of the index day and included hypertension, diabetes, chronic heart disease, chronic pulmonary disease, cerebrovascular disease, chronic liver disease, and cancer.”
1. **Page 8**: “We found that dialysis, older age, male, trochanteric fracture, hemiarthroplasty, and comorbidities such as diabetes mellitus, chronic heart disease, chronic liver disease, and cancer were significant risk factors for mortality.”

3. In table S1 medical complications after surgery are shown. Interestingly, in the HD group 29% and 23% had acute renal failure after 1 and 3 months, respectively. This should be explained.

   **Ans:** Thank you for this comment. We had addressed this finding in the discussion section on **page 14, lines 1-14** (refer to references 35-40), as followed:

   1. **Page 14**: “Among hemodialysis subjects, we found that 29% and 23% of 474 and 646 subjects with at least one medical complication within one and three months, respectively, had acute renal failure. Most research on the incidence and causes of acute renal failure after major surgery is based on studies of patients who received cardiac or vascular surgery [35-40]. Previous studies found that older age, higher BMI, diabetes, hypertension, chronic obstructive pulmonary disease, liver disease, hyperlipidemia, malnutrition, abnormal renal function, use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), diuretics, nonsteroidal anti-inflammatory agents, infection, emergency/urgent surgery, and high-risk surgery were related to acute renal surgery after major surgery [35-40]. Various risks contributed to acute renal failure in dialysis patients after surgery for hip fracture, including comorbidities, co-medications, dialysis time before or after surgery, perioperative abnormal laboratory value, optimal time for surgery, type of anesthesia, type of operation, and intraoperative management, and these variables are likely similar to those associated with increased risk of acute renal failure following major cardiac or vascular surgery.”

4. Optional: It would be very interesting to compare dialysis patients with and without hip fracture with comparable duration of dialysis in terms of mortality. Furthermore, in the discussion those comparisons are cited.

   **Ans:** Thank you for these comments. We are currently working on a study to compare dialysis patients with and without hip fracture in terms of mortality and
complications. It is a complex multi-state problem including dialysis, fracture, death after fracture, complication after fracture, and death after complication. Due to the space restriction of most journals, we could not address this topic in details. We hope to analyze this in future studies.

**Level of interest:** An article of importance in its field  
**Quality of written English:** Acceptable  
**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 interest
Reviewer's report

Title: Mortality and Complications after Hip Fracture among Elderly Patients Undergoing Hemodialysis

Version: 2  Date: 20 January 2015

Reviewer: Maria Fusaro

Reviewer's report:

Comments to the Authors:

-pg 4 line 37: the term the renal osteodystrophy is not correct: you have to change it (eg: Mineral Bone Disorders)

Ans: Thank you for this comment. We have revised our manuscript accordingly.

-pg 5 line 64 and 65: you have to add the percent to absolute numbers

Ans: Thank you for this comment. We have revised our manuscript accordingly.

-pg 22 and 24; table 1 and table 3: the authors should to specify what kind of disease are included in Chronic heart disease (eg Atrial fibrillation and so on)

Ans: Thank you for this precious comment. We have revised Table 1 and Table 3 manuscript accordingly. Chronic heart diseases included myocardial infarction, coronary heart disease, congestive heart failure, and arrhythmia (ICD-9-CM codes 410-429 before index surgery).

-Useful elaboration data on stratification Chronic Heart disease and hip fractures

Ans: We tried to stratify chronic heart diseases in the revised manuscript, however, we found that subjects often had multiple heart diseases; for example, one subject had both old myocardial infarction and heart failure and another subject had both heart failure and arrhythmia. In addition, stratifying based on different chronic heart diseases or type of hip fracture also caused too many strata and too small a sample size in each stratum to conduct a matched design and data analysis. We hope to develop another study design to analyze these issues in future studies.

-The discussion is very poor: eg: no discussion about mineral bone disorders and their association with vascular calcifications and cardiovascular disease; no discussion about treatment and prevention bone fractures in CKD.
Thank you for this comment. We did not have clinical variables for mineral bone disorders in our database to support or verify the association with vascular calcifications and cardiovascular disease. We have addressed these limitations in discussion section on page 15, lines 7-10 and have added some discussion (refer to references 41-49) about mineral bone disorders and their association with vascular calcifications and cardiovascular disease and their treatment and prevention on page 14, lines 15-20 and page 15, lines 1-3, as followed:

1. **Page 15**: “Although we used a matched cohort design and conducted a multivariable analysis to examine risk factors, many risk factors, such as pre-operative joint function/condition, renal function, smoking status, body mass index, bone mineral density, lifestyle, comorbidity severity, and quality of life, were not available for adjustment.”

1. **Page 14-15**: “We also found that subjects with chronic heart disease had a higher hazard ratio for mortality and medical complication than those without chronic heart disease. Bone mineral disorders such as vitamin K deficiency, vitamin D deficiency, hypocalcemia, secondary hyperparathyroidism, hyperphosphatemia, bone loss, malnutrition, multiple metabolic mediators, and uremic toxins are present in nearly all dialysis subjects and are related to the risk of fracture risk, hypertension, vascular calcifications, and cardiovascular disease. Studies also found that vitamin K deficiency decreased bone mass and increased excessive vascular calcification. Rigorous corrections on bone mineral disorders and malnutrition, as well as vitamin D and K supplementation are necessary to prevent hip fracture in dialysis subjects [41-49].”

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

**Quality of written English**: Needs some language corrections before being published

**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
Reviewer's report

Title: Mortality and Complications after Hip Fracture among Elderly Patients Undergoing Hemodialysis

Version: 2 Date: 23 January 2015
Reviewer: Akihiko Kato

Reviewer's report:
Dr. Lin and coworkers examined the impact of surgical hip fracture on mortality and medical complications for 5 years using the nationwide database in Taiwan. They showed that HD patients had a significantly higher risk for all-cause mortality and first medical complication when compared to matched non-dialysis subjects. This study is interesting, because they showed that long-term outcome after hip fracture operation was poor in the HD population. However, there are some concerns in this study.

1. In this study, the authors examined the association of postsurgical outcomes with HD therapy by comparison with age-matched controls. They analyzed its impact by corrected by the parameters such as age, gender, fracture type, operation type, and comorbidities. However, as discussed, there are many other cofounders that affect postsurgical mortality. For example, sarcopenia, frailty and decreased bone mineral density are well known as potent risk factors of mortality after hip fracture. Medication for osteoporosis is also likely to improve prognosis. Since it is well known that the prognosis after surgery is poor as shown in the DOPPS (Ref #25), the authors focus on the mechanisms why HD patients are prone to complicate of medical and surgical problems after hip surgery more deeply.

Ans: Thank you for this comment. Few studies have reported long-term surgical complication rates among hemodialysis subjects with hip fracture; therefore, one of the purposes of our study was to explore the long-term surgical complications among hip fractures patients with hemodialysis. To explore long-term surgical complication rate, we needed a very large sample size such as a national health insurance database. The database used in this study is a nationwide repository of national health insurance (NHI) claims and data of NHI beneficiaries, rather than a registry of hip surgery or dialysis patients. Therefore, it was not possible to include all clinical and medication variables. We have these limitations in discussion section on page 15, lines 7-10 and have added some discussion on page 14, lines 1-14 (refer to references 35-40), page 14, lines 15-20 and page 15, lines 1-3 (refer to references 41-49), as followed:
Page 15: “Although we used a matched cohort design and conducted a multivariable analysis to examine risk factors, many risk factors, such as pre-operative joint function/condition, renal function, smoking status, body mass index, bone mineral density, lifestyle, comorbidity severity, and quality of life, were not available for adjustment.”

Page 14: “Among hemodialysis subjects, we found that 29% and 23% of 474 and 646 subjects with at least one medical complication within one and three months, respectively, had acute renal failure. Most research on the incidence and causes of acute renal failure after major surgery is based on studies of patients who received cardiac or vascular surgery [35-40]. Previous studies found that older age, higher BMI, diabetes, hypertension, chronic obstructive pulmonary disease, liver disease, hyperlipidemia, malnutrition, abnormal renal function, use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), diuretics, nonsteroidal anti-inflammatory agents, infection, emergency/urgent surgery, and high-risk surgery were related to acute renal surgery after major surgery [35-40]. Various risks contributed to acute renal failure in dialysis patients after surgery for hip fracture, including comorbidities, co-medications, dialysis time before or after surgery, perioperative abnormal laboratory value, optimal time for surgery, type of anesthesia, type of operation, and intraoperative management, and these variables are likely similar to those associated with increased risk of acute renal failure following major cardiac or vascular surgery.”

Page 14-15: “We also found that subjects with chronic heart disease had a higher hazard ratio for mortality and medical complication than those without chronic heart disease. Bone mineral disorders such as vitamin K deficiency, vitamin D deficiency, hypocalcemia, secondary hyperparathyroidism, hyperphosphatemia, bone loss, malnutrition, multiple metabolic mediators, and uremic toxins are present in nearly all dialysis subjects and are related to the risk of fracture risk, hypertension, vascular calcifications, and cardiovascular disease. Studies also found that vitamin K deficiency decreased bone mass and increased excessive vascular calcification. Rigorous corrections on bone mineral disorders and malnutrition, as well as vitamin D and K supplementation are necessary to prevent hip fracture in dialysis subjects [41-49].”
2. Did other sites of fracture such as wrist and vertebrae also relate to poor prognosis in HD patients?

**Ans:** Thank you for this comment. We did not explore the effects from other sites of fracture on prognosis in dialysis patients in this manuscript. Because many subjects with wrist or vertebrae fractures did not receive operations, we need more time and effort to validate the major complications that were related to wrist or vertebrae fractures in hip fracture patients with or without HD. We plan to work on this topic in future studies.

3. Did you measure Scr and estimate GFR in subjects not on dialysis. If so, did eGFR affect the risk of poor outcomes?

**Ans:** Thank you for this comment. We did not have renal function such as Scr and GFR in the database. Our database was a nationwide repository of national health insurance claims and data of NHI beneficiaries, rather than a prospective registry of hip fracture or dialysis patients. Therefore, it was not possible to use any variables to establish solid correlations between Scr, GFR, and the prognosis after operation for hip fracture. We have these limitations in discussion section on page 15, lines 7-10, as followed:

1. **Page 15:** “Although we used a matched cohort design and conducted a multivariable analysis to examine risk factors, many risk factors, such as pre-operative joint function/condition, renal function, smoking status, body mass index, bone mineral density, lifestyle, comorbidity severity, and quality of life, were not available for adjustment.”

**Level of interest:** An article of limited interest  
**Quality of written English:** Needs some language corrections before being published  
**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.