Author's response to reviews

Title: Mortality and Complications of Hip Fracture in Young Adults: A Nationwide Population-based Cohort Study

Authors:

Chien-Fu Jeff Lin (cflin.ntpu@gmail.com)
Cheng-Chun Wu (ccwu.cmu@gmail.com)
Wen-Miin Liang (wmliang@mail.cmu.edu.tw)
Chang-Bi Wang (superjacker@msn.com)
Chi-Fung Cheng (jimmy.bbww@hotmail.com)
Yu-Jun Chang (yichang.cmu@gmail.com)
Hsi-Chin Wu (wuhc@www.cmuh.org.tw)
Tsai-Hsueh Leu (thleu.wfh@gmail.com)

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Authors: 
Jeff Chien-Fu Lin: cflin.ntpu@gmail.com
Cheng-Chun Wu: ccwu.cmu@gmail.com
Chi Lo: lochichilo@gmail.com
Wen-Miin Liang: wmliang@mail.cmu.edu.tw
Chi-Fung Cheng: jimmy.bbww@hotmail.com
Chang-Bi Wang: superjacker@msn.com
Chi-Fung Cheng: jimmy.bbww@hotmail.com
Yu-Jun Chang: june@cch.org.tw
Hsi-Chin Wu: wuhc@www.cmuh.org.tw
Tsai-Hsueh Leu: thleu.wfh@gmail.com

Version: 2 Date: 05 September 2014

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We thank all the reviewers for their comments. Reviewer #2 suggested using competing risk analysis. Therefore, we reanalyzed the database, including subjects from 2000-2008, using competing risk analysis. In the original manuscript, the subjects were selected from 1999-2008; however, the reason that we did not include subjects in 1999 in our new analysis was due to the expiration of the right to use the data for the year 1999. 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 our manuscript based on the reviewers’ comments and we have described these changes for each response below.

Reviewer #1:
1. The author should report the mortality and complication during hospitalization, cause of death, and identify mortality related with hip fracture.

Ans:
(a) We have reported the complication number and rate during hospitalization in Supplementary Table 2 and in result (Page 8, lines 9-10). The complication rate during hospitalization was 4.51%. We did not find any mortality during hospitalization. One reason was the very low death rate among young adults. Another reason was that, traditionally, people in Taiwan often choose to die at home rather than in hospital. Almost all patients in Taiwan are thus sent home 1 or 2 days before their death.

(b) We reported the causes of death in Supplementary Table 1 (Page 7, lines 16-17). The major causes of death were chronic liver disease and cirrhosis (15.44%) and major accidents (10.74%).

(c) We could not confirm whether mortality was related to hip fracture using our database. Our database was a nationwide repository of national health insurance claims and data of NHI beneficiaries, rather than a registry of hip surgery patients. Therefore, it was not possible to use any variables to provide a solid correlation between mortality and hip fracture.
2. How can the author know about the outcome in subjects who lost follow-up and how many patients lost the follow-up. Need to add in the result section
Ans: Our database covered more than 99% of residents in Taiwan. All subjects were followed up until death, exit from the NHI program, or the end of 2010. (See Page 4, lines 10-11, 17-18) Unless subjects emigrated from Taiwan, there would be no subjects lost to follow-up. We believe that less than 0.1% of subjects were lost to follow-up.

3. The author should mention the factors that adjusted in Table 3.
Ans: We have revised Table 3. The reported “adjusted hazard ratios” were adjusted for all factors listed in Table 3 using multivariable analysis. (See Notes in Table 3)

4. The result from this study differed from meta-analyses particularly the type of operation. Internal fixation in this study was lower complication than arthroplasty, the author should discuss more in term of biomechanical, or technic of operation.
Ans: We reanalyzed the database by using competing risk analysis. We found internal fixation had a non-significantly lower hazard ratio than that of arthroplasty.

We think age is the key reason that explains the differences between our results and previous results. Young adults have a lower death rate and are healthier than elderly subjects. Most previous studies discussed elderly patients with hip fracture. These fragile elderly patients will inevitably have a higher death rate. Among the elderly, arthroplasty had higher mortality rates during the follow-up. However, the significantly higher competing death rate among the elderly resulted in fewer subjects exposed to the risk for complications (such as delayed infection and revision) during the follow-up. (References: James J. Dignam and Maria N. Kocherginsky, Choice and Interpretation of Statistical Tests Used When Competing Risks Are Present, Journal and Oncology 2008, 26(24), 4027-4034) In addition, the elderly often have osteoporosis, neurovascular, mental disorders, and live alone or in nursing homes. Therefore, elderly patients with internal fixation have more mechanical complications than young adults within 1 year after the index surgery. Overall, the meta-analysis found that internal fixation was associated with a higher complication rate than arthroplasty among the elderly. We discuss hip fracture among young adults aged between 20-40 years old who had a significantly different rate of hip fracture compared with that of elderly patients reported in previous studies. When the competing death rate is relatively low among young adults, the effect from the competing death on complications would be minimal. Internal fixation was performed with close
reduction using multiple pins/cannulated screws and we do not think biomechanical or technical aspects of the operation caused different complication rates between internal fixation and arthroplasty among young adults. (See page 11, lines 13-18)

5. Some typing errors have been found and please correct. type of operation.
Ans: We have corrected all typos in the revised manuscript.

Reviewer #2:
Major compulsory revisions
1) Abstract-
1.1: p2 “Charlson” is misspelled throughout the text. The English is also incorrect in many places throughout the manuscript. In particular, one doesn’t say “larger number of Charlson comorbidity index”. A better phrase would be “higher or greater Charlson comorbidity index”.
Ans: We have corrected this as well as all other typos throughout the revised manuscript.

1.2: P2 It is not clear what difference the authors mean when they use the terms implant and arthroplasty?
Ans: We have changed these two names to “internal fixation implant”, including all fixation devices (pins/screws, dynamic hip screws), for internal fixation, and “prostheses” for arthroplasty in the revised manuscript (See page 6, lines 8-10).

1.3: Please define these in the manuscript. Were all the hip fractures traumatic? Or were some low trauma osteoporotic fractures? This should be clarified.
Ans: In our database, more than 99% of hip fractures were caused by high-energy trauma in young adults. We had already excluded pathologic fracture, including osteoporotic fracture, in our analysis. (See page 5, lines 5-10)

2) Background-
2.1: p3 The authors state the aim of the study was to assess long term complications but in fact they have assessed short and long term complications.
Ans: We assessed both short- and long-term surgical complications. We have described this in the revised manuscript. (See page 4, lines 2-4)

3) Methods
3.1: p5 When was the end of the study? Please specify.
Ans: Our database covers more than 99% of residents in Taiwan. All subjects were followed up to death, exit from the NHI program, or the end of 2010. (See Page 4, lines 17-18)

3.2: What was the loss to follow up rate? How was this determined and how did you know when loss to follow-up occurred?
Ans: All subjects were followed up to death, exit from the NHI program, or the end of 2010. Unless subjects emigrated from Taiwan, there were no subjects lost to follow-up. We believe that less than 0.1% of subjects were lost to follow-up. All dates of death and dates of subjects exiting the NHI program were stored in the database.

3.5: P5 Outcome measures discusses the 90 day outcomes but not longer term outcomes. This becomes confusing as to what is going to be examined eg 5 and 10 yr complication free rate. Please detail these also in the methods.
Ans: We have modified our definition of complications in the Methods. (See Page 6, lines 2-8) Complication-free time was a composite outcome and was defined as the duration from the index date to the date that the first post-operative complication occurred. The post-operative complications included the occurrence of one or more complications, including (i) death within 90 days after the index date, (ii) acute medical complications requiring admission to hospital for treatments within 90 days after the index date, and (iii) surgical complications requiring admission to hospital for additional surgical treatments after the index date. The acute medical complications included stroke, acute myocardial infraction, acute renal failure, pneumonia, pulmonary embolism, and sepsis that occurred within 90 days after the index date. Surgical complications included surgical site infection, internal fixation implant failure, malunion/nonunion, second hip fracture on the same side or contralateral side, dislocation, avascular necrosis of the femoral head, or osteoarthritis during the follow-up period.

3.5: P6 Subjects who died within 90 days couldn’t have suffered a complication and are different from those alive without complication yet they are treated in the same way. Death could be considered a complication. Please consider doing a competing risk analysis with death as the competing risk.
Ans: We reanalyzed the database, including subjects from 2000-2008, using competing risk analysis. The major results and conclusions were not notably changed. However, there were some minor changes of the numerical values.
3.6: In the multivariate (not multiple) analyses, were comorbidity(ies) analysed as separate individual comorbidity(ies) or as a Charlson score?
Ans: Charlson score was used to analyze the comorbidity(ies).

4) Results-
4.1: Where are the 90 day results that were detailed in the methods?
Ans: We regret causing the reviewer any confusion in the original manuscript. We have modified our definition of the post-operative complications in the Methods. (See Page 5, line 20, Page 6, lines 1-2) Complication-free time was a composite outcome and was defined as the duration from the index date to the day that the first post-operative complication occurred.

4.2: P7 When discussing risk factors for complication rates (and for survival rates) was this for the overall 10 year follow up or was this for 90 days. The results presented are confusing in this respect.
Ans: Again, we regret the confusion caused in the original manuscript. Risk factors were for the overall 11-year follow-up. This has been clarified in the revised manuscript.

4.3: Did cervical fracture result in more hemiarthroplasties? In other words was the effect on complication free rate due to the type of fracture or the type of operation? Are they collinear?
Ans: Less than 5% of the subjects in our database received arthroplasty. Cervical rupture was associated with a slightly higher rate of hemiarthroplasty. We also agree with the reviewer’s opinion that the effect on the complication-free rate might have been due to the type of fracture or the type of operation or interaction. However, the sample size for arthroplasty was too small to provide a robust test for the interaction.

4.4: P8 Please define terms “implants removed” vs “implants converted to arthroplasty or revision arthroplasty”. How can implants be removed without being converted to arthroplasty or revision arthroplasty?
Ans: Sorry for the confusion of the terms “implant” and “prosthesis”. In the revised manuscript we have changed these two terms to “internal fixation implant”, including all fixation devices (pins/screws, dynamic hip screws), for internal fixation, and “prostheses” for arthroplasty in the revised manuscript.
Subjects receiving internal fixation implant might have had screw backout, malunion, skin irritation, or infection. And these subjects often received internal fixation implant removal operation without converting to arthroplasty in our database. A few subjects with arthroplasty also did not receive revision arthroplasty after prosthesis removal operation in our database. Asian populations appear to show some differences from Western populations in this regard.

4.5: What risk factors caused removal of implants versus other complications? With the large numbers you have, you could explore some more interesting associations.
Ans: We thank the reviewer for this valuable comment, which raises interesting issues. Due to the space restriction of most journals, we could not address this topic in detail. However, we are currently collecting more clinical variables to assess these associations, which we hope to analyze in future studies.

4.6: Please state numbers of people that were available at different follow up times (this could be done at the bottom of the figures).
Ans: We have modified the figure in the revised manuscript. (See Figure 1)

5) Discussion-
5.1: p9 the same risk factors are stated for both survival and complication rate but this is not the case. It would be easier for the reader to group those risk factors that are the same and those that are different.
Ans: Thank you for this comment. We have revised our manuscript accordingly. We found that the number of CCI comorbidities was a risk factor for both death and complications. Male gender and older age were only statistically significant risk factors for survival. Moreover, fracture type was the only statistically significant risk factor for complications. (See Page 9, lines 15-18)

5.2: The overall discussion is quite tedious and restating findings in the literature. These should be grouped where similar and comparisons drawn with the present study detailing differences and discussing why there may be differences.
Ans: Thank you for bringing this to our attention. We have revised the manuscript accordingly. (See Page 11, line 19, Page 12, line 1)

5.3: Table 1 Please include a column indicating significant differences in risk factors between cervical and trochanteric fractures.
Ans: We have added p-values to Table 1. (See Table 1)

5.4: Table 3 please specify what the adjusted survival analyses were adjusted for.
Ans: We have revised Table 3. The reported “adjusted hazard ratios” were adjusted for all the factors listed in Table 3 using multivariable analysis. (See Notes in Table 3)

5.5: Please have the text reviewed by a native English speaker prior to resubmission for grammatical and spelling errors.
Ans: Thank you for this comment. We have had our revised manuscript checked by a native English speaker.