Author’s response to reviews

Title: Intervention to improve the appropriate use of polypharmacy for older patients with hip fractures: an observational study.

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Author’s response to reviews:

Dear Editor,

Thank you very much for your valuable comments and for giving us the opportunity to revise our manuscript. Please find below our responses to the reviewers’ comments. All changes in the paper are highlighted in yellow.

This revised manuscript was edited by a native English speaker at American Journal Experts.

Kinds regards,

Junpei Komagamine

Response to Reviewer #1

Comment 1: What was the follow-up period and how were outcome measures collected? I could not find this information in the manuscript but think this is important for interpreting the findings. In particular, were outcome measures collected only from the single hospital or directly from the patients included in the study (or through some other means)? This information is needed to assess to what extent all of the outcomes were captured. I also wonder if the length of follow-up was long enough for outcomes to accrue.

Response: We added information regarding the data collection in the methods section. The data were collected from the electronic medical records of Tochigi Medical Center. Therefore, we collected data from the database of a single center without direct contact with patients. We think
that this is one of the major limitations of this study. Furthermore, the short length of follow-up and a high rate of loss to follow-up are also limitations. However, given that the one-year mortality of hip fracture patients is 20-30%, we believe that the effect of intervention on mortality could be evaluated in the short-term.

Comment 2: I think that it would be helpful for some of the variables in Table 1, such as number of medications and number of PIMS, to be presented in categories (rather than with means/SD). I think this would make it easier for readers to see the frequency of use and some of the differences across groups.

Response: Thank you for your comments. According to your suggestion, we changed Table 1.

Comment 3: What was usual care? It looked like a number of patients in this group also experienced a decrease in PIMs. It would be helpful to know more about what happened to this group - and if possible, why so many refused the intervention.

Response: Thank you for your comments. We added information regarding usual care in the methods section. However, it is unclear why PIMs tended to decrease even in the usual care group. In our hospital, orthopedic surgeons consulted internists (n = 5) or cardiologists (n = 2) for the complicated medical problems of hip fracture patients. All consultants (either internists or cardiologists) in our hospital were interested in problems related to polypharmacy among older patients. Thus, it is possible that medical consultations affected the number of PIMs. In our study, among the 46 patients who were approached by pharmacists, 14 patients (30.4%) refused to participate in the polypharmacy intervention. It is unclear why so many refused the intervention because the reasons for refusal were not routinely documented. However, previous randomized controlled studies for deprescribing in elderly patients with polypharmacy also reported that over 30% of eligible patients refused to undergo deprescribing and were thus excluded from study. Therefore, the refusal rate in past studies is consistent with the results of our study.

Comment 4: Can the authors provide any insight on why so many PIMs were still in use on discharge among the intervention group?

Response: The final decision to stop or change unnecessary or inappropriate medications was made by internists through shared decision making with patients. Therefore, patient preference affected the decision. For example, patients were often reluctant to stop some medications, such as benzodiazepines.
Comment 5: I wonder if there are sufficient numbers for this analysis. Several of the confidence intervals are very wide, including on the primary outcome. I think that this issue may need some attention.

Response: We agree with your comment, and we stated this issue in the limitations section. The small sample size was one of the major limitations in this study. Nonetheless, our findings are consistent with the results of past meta-analyses showing that medication review did not improve patient-relevant outcomes, although few studies included in past meta-analyses targeted hip fracture patients (Br J Clin Pharmacol 2015;80(1):51-61).

Response to Reviewer #2

Comment 1: Authors stated this was a retrospective observational study but this looks like 'a prospective interventional study'.

Response: We apologize for the confusion. Our study was a retrospective observational study without any contact with patients. We clarified the study design to add more detailed information regarding the study in the methods section.

Comment 2: Regarding statistical analysis; survival analysis is needed for either mortality or primary composite outcomes rather than logistic regression analysis.

Response: Thank you for your comment. According to your suggestion, we re-collected and re-analyzed data. The comparison between the intervention group and the usual care group for primary composite outcome (death or any new fracture) and its components was analyzed using the Cox proportional hazard model and the Kaplan-Meier method. These results are shown in Figure 2 (primary composite outcome) and an additional file 1 (Figure S2-S6).

Comment 3: In results section the authors stated that 'This result did not change after adjusting for confounding factors at baseline (data not shown)'. Regression analysis is of great importance for this study. Therefore the models have been used for regression analysis should be detailed.

Response: Thank you for your suggestion. This information is now presented in Table S1 (an additional file 2).
Response to Reviewer #3

Comment 1: Please provide figures in the abstract, for example regarding the number of deaths/fractures and the number of drugs in the comparison groups, that is, not only p-values and odds ratios.

Response: Thank you for your comment. According to your suggestions, we added this information in the abstract.

Comment 2: The expression "inappropriate polypharmacy" is odd, and could be replaced. In fact, the number of drugs in the medication list is a quite good surrogate variable for the burden of disease (Fam Pract 2013; 30(2): 172-8), but a poor indicator for quality of drug treatment (Eur J Clin Pharmacol. 2015;71(3):363-8]) These aspects need to be discussed in the introduction and discussion, as well as made clear in the abstract. Further, most studies reporting prevalence of polypharmacy, focus on "potentially" inappropriate medications, which is not equal to inappropriate drug treatment. Indeed, drugs generally considered inappropriate can be appropriate at the individual level.

Response: We agree that potentially inappropriate medications are not equal to those that are inadequate at the individual level. The term "inappropriate polypharmacy" was removed from our manuscript.

Comment 3: In the study, a cut-off of five medications was used for inclusion. Please describe the rationale for this cut-off. Further, the method to estimate the number of drugs needs to be clarified. Were the patients simply asked? Or is there a central electronic system for prescribed medications for each individual in Japan? And were both drugs used regularly and as needed counted?

Response: Our hospital started the polypharmacy intervention to improve the appropriateness of polypharmacy among older patients hospitalized in an orthopedic ward. However, there was no universal standard definition of polypharmacy. Therefore, we selected a cut-off of five medications based on past research (J Clin Epidemiol 2012;65:989-995). Medications were determined based on a comprehensive medication history performed by a pharmacist. Unfortunately, there is no central electronic system for prescribed medications for each individual in Japan. As-needed medications were included, although medications that were used for apparent transient disease or symptoms were excluded. This information was added in the methods section.
Comment 4: In the present study, only potentially inappropriate drugs were targeted. It is important to acknowledge that undertreatment may also be a problem.

Response: Thank you for your comment. A statement about this problem was added in the discussion section. We are aware that this is an important issue that should be resolved. Considering problems about prescribing omission, we plan to start a prospective randomized controlled trial to evaluate another strategy for inappropriate medications and prescribing omissions to improve patient outcomes among orthopedic hospitalized patients.

Comment 5: Who assessed that a medication was unnecessary? And on what basis? Indeed, the intervention could be further described.

Response: Internal medicine physicians assessed whether a medication was unnecessary. Detailed information regarding the intervention was added in the methods section.

Comment 6: Several systematic reviews and meta-analyses have shown that interventions targeting the medication list do not improve patient related outcomes reflecting the net effect of drug treatment. These could be cited, e.g. Br J Clin Pharmacol. 2014;78(3):488-97 and Br J Clin Pharmacol. 2015;80(1):51-61.

Response: Thank you for your suggestion. We added these meta-analyses to the references.

Comment 7: In the present study, although not statistically significant, the odds ratio for death was >1 (like in several meta-analyses). This could be discussed. Indeed, on page 14, last line: this study does not support that the intervention can be performed safely.

Response: We agree with your comment. Moreover, concerns about this issue were one of the reasons we conducted this study. This polypharmacy intervention in our hospital was started by another internal medicine physician. However, one of the authors in this study (JK) became suspicious about the effectiveness of this intervention on patient outcomes. Furthermore, we were aware of several meta-analyses showing that, although not statistically significant, medication review tended to increase mortality, as you indicated. A statement about this issue was added in the discussion section.

Comment 8: Did the participants provide informed consent? Or was informed consent waived in the ethics approval? Eligible participants were approached by a pharmacist, and if the patient
declined participation, he/she was included in the control group. Ethical consideration regarding this procedure could be discussed.

Response: We apologize for the confusion. In this study, we were not required to obtain individual informed consent because we used de-identified data from medical records and did not contact patients.

Comment 9: Please provide a flowchart of patients in the wards, including patients with <5 drugs and reasons for exclusions.

Response: A flowchart of patients in this study was added as Figure 1.

Comment 10: Pharmacists’ non-dispensing role is a matter of debate. Please describe the role of this profession in Japan. This information would facilitate the interpretation of the results for the reader. Indeed, although the American Geriatric Society may recommend a multidisciplinary team to perform medication reviews, other countries may have chosen other ways to achieve rational and safe use of medicines. Further, the conclusion that comprehensive geriatric care is needed to improve patients’ clinical outcomes cannot be derived from the present study, and relevant references need to be cited to reflect the state of knowledge.

Response: Thank you for your comment. According to your suggestions, we added detailed information regarding the non-dispensing role of pharmacists in Japan in the methods section. Furthermore, as you said, the conclusion that comprehensive geriatric care is needed to improve patients’ clinical outcomes cannot be derived from the present study. Therefore, we removed this sentence from the conclusion.

Comment 11: Why did the authors choose Beers criteria and how applicable are these in the Japanese setting?

Response: In Japan, few methods to evaluate the appropriateness of medications among older patients have been tested or validated. However, some studies found that the Beers’ criteria might be applicable in a Japanese setting. Furthermore, the Beers’ criteria is used the most frequently in Japanese research. Few Japanese studies have used other criteria, such as the MAI or STOPP criteria. Therefore, we selected the Beers’ criteria. This information was added in the methods section.
Comment 12: Surprisingly many drugs were withdrawn at discharge, as the intervention patients had 9.2 drugs at admission and 4.5 at discharge. For example, 10 intervention patients had a PPI at admission and 4 patients at discharge. Did the authors evaluate what happened after discharge, that is, was PPI represcribed? Or did gastro-intestinal bleedings or rebound symptoms occur? How often were other withdrawn drugs represcribed?

Response: Given the significant increase in potentially inappropriate medication use after intervention observed in a previous study (J Am Geriatr Soc 2017;65:e33-e38), it is important to evaluate changes in medications after an in-hospital intervention. However, we did not evaluate this issue due to the lack of accurate information about medications after discharge. Therefore, how often withdrawn drugs were represcribed after discharge was not known. It was also unclear how often gastrointestinal bleedings or rebound symptoms occurred after discharge, although readmission rate during the study period was not different in the two groups.

Comment 13: The authors state, as a limitation of the study, that the follow-up period was relatively short. Can an effect in the longer term be expected for a onetime polypharmacy intervention?

Response: We think that polypharmacy intervention, which is focused mainly on deprescribing in our hospital, might not be effective for improving patient outcomes. However, deprescribing intervention often results in a reduction in the total number of medications. It is important in terms of cost and ecology to safely reduce the number of medications among older patients. However, it is unclear whether deprescribing is safe in the long term. Given that medications prescribed to the elderly are often targeted at disease prevention, we believe that the harmful effects of deprescribing cannot be captured in the short-term period.