Author’s response to reviews

Title: Prevalence of the potentially inappropriate Kampo medications to be used with caution among elderly patients taking any prescribed Kampo medications at a single centre in Japan: a retrospective cross-sectional study

Authors:

Junpei Komagamine (junpei0919@yahoo.co.jp)

Kazuhiko Hagane (drsteel@tochigi-mc.jp)

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Author’s response to reviews:

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Dear Editor:

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

Kind regards,

Junpei Komagamine
Response to Reviewer 1 (Tetsuhiro Yoshino, M.D., Ph.D.)

Major revision required

Participants and inclusion criteria

Comment: It is difficult to understand how long each patient' information was reviewed. I understood that the screened period was from Jan 1st to March 31st 2015. Then, how long did you review the chart? All of available charts or not? If the patient had long history before 2015, how did you deal with?

Response: Thank you for your comments. Since September 2014, all medical records have been electronic in our hospital, although prescription orders have been electronic for more than ten years. Therefore, all available electronic medical records charts from September 2014 to the time of the index visit were reviewed to collect past medical history information. This information has been added to the Methods section of the revised manuscript (Page 7, Lines 117-118).

Comment: Did you checked and included Kampo medications from other hospitals or clinics in your analysis?

Response: Thank you for your comments. At our hospital, physicians often document information on medications prescribed by other hospitals in the medical records at every consultation as part of routine care. Therefore, we included medications prescribed by other hospitals based on this information. Of the 1035 elderly ambulatory patients screened, 14 patients were prescribed Kampo medications by other hospitals. Of those, two patients were excluded because the names of the prescribed Kampo medications were not documented. Thus, 12 patients who were prescribed Kampo medications by other hospitals were included in this study. The information on prescriptions from other hospitals in this study might be inaccurate because prescriptions from other hospitals were determined using medical record documentation by physicians at our hospital. Therefore, this was an important limitation of this study. This information has been added to the Methods (Page 7, Lines 121-124) and Limitations (Page 18, Lines 286-289) sections of the revised manuscript.

Comment: We can find a statement "OTC Kampo medications were excluded." Did you excluded OTC medications itself or patients who were prescribed OTC Kampo medications? Next sentence contains "also", so that the meaning is difficult to interpret.

Response: We apologize for the confusion. We excluded OTC medications. We have modified the Methods section accordingly (Page 7, Lines 108-109).
Comment: It is usually very difficult to collect complete information about medications from other institutions. How did you make sure that you did NOT have missing data?

Response: Thank you for your comment. At our hospital, most internal medicine physicians are cautious about polypharmacy in elderly patients (BMC Geriatrics 2017;17:288). Therefore, physicians often check the medications prescribed at other hospitals. Furthermore, the physicians make an effort to provide comprehensive care for elderly patients by themselves to avoid multiple prescribers. In addition, some ambulatory patients participate in several registry studies conducted by National Hospital Organization-associated institutions. For these patients, medications from other hospitals are routinely documented in medical records. Nonetheless, as you noted, it was difficult to collect complete information about medications from other institutions. Therefore, this was an important limitation of this study. This information has been added to the Limitation section of the revised manuscript (Page 18, Lines 286-289).

The definition of "uncontrolled" hypertension

Comment: Hypertension is one of indications of hachimijiogan sold by Tsumura. Therefore, I think that the definition of "uncontrolled" is crucial in this analysis, and I do not agree that the number itself mean "uncontrolled". If you do not have any data of blood pressure, one option is adding one more criterion, "prescription period", in your definition of controlled or uncontrolled; e.g. if you could find that the patient was receiving 3 or more antihypertensive medications for 3 or more consecutive consultations, you defined the patient as controlled.

Response: Thank you for your valuable comments. According to your suggestion, we have redefined uncontrolled hypertension. Uncontrolled hypertension is defined as office systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg. If office blood pressure was not documented in the medical records, hypertension was judged to be uncontrolled for patients whose antihypertensive medications were increased over three or more consecutive physician visits (Page 9, Lines 144-149). Otherwise, hypertension was judged to be controlled. In addition, we performed a new statistical analysis because the definition of uncontrolled hypertension was changed.

Statistical analysis

Comment: I could not understand why you could "reduce selection bias" with your screening criterion.

Response: We apologize for the confusion. We chose a three-month screening period to include as many ambulatory patients who made a regular visit to our hospital as possible. We have
modified this section in the revised manuscript (Page 10, Lines 161-164). We apologize if we did not respond to your comments appropriately.

Comment: In the same sentence, "three consecutive months" does not make sense for me. Is it Jan to March 2015?
Response: As you noted, "three consecutive months" means "January 2015 to March 2015". We have modified this sentence in the revised manuscript (Page 10, Lines 163-164). We are sorry for the confusion.

Table 2
Comment: You can omit "Male" row.
Response: Thank you for your comment. We have omitted the “Male” row in Table 2.

Comment: The numbers of medications are discrete variables, and you need to be very cautious in calculating means. I believe medians with ranges would be better for discrete variables.
Response: Thank you for your comment. According to your suggestion, we have presented the median number of medications in the revised manuscript.

Comment: The number of Kampo medication might be 1 for most of patients, and this would affect the regression analysis. The linearity of variable might not be achieved. You should also report the proportion of patients who were prescribed two or more Kampo medications, and consider using it as a binary variable in regression analysis.
Response: Thank you for your comment. According to your suggestion, we have presented the proportion of patients who were prescribed two or more Kampo medications in the revised manuscript (Table 2). We reanalysed data by using it as a binary variable in regression analysis.

Table 3
Comment: The total mean does not make sense for me. What is it? If the number is 0.263, it is just a proportion.
Response: We apologize for the confusion. We have modified Table 3 in the revised manuscript.
Comment: You can omit "used" from the sentence, glycyrrhizae radix for CKD or by loop diuretic user.

Response: Thank you for your comment. In response to your suggestion, we have modified the sentence in Table 3.

Adverse event with potentially inappropriate Kampo medications

Comment: Did you know any cases who experienced side effect or adverse event with potentially inappropriate Kampo medications? It would be a non-surrogate marker in this analysis.

Response: Thank you for your comments. One elderly patient with hypokalemic myopathy caused by combination of loop diuretics and Glycyrrhizae radix compositions was admitted to our hospital last month. However, no patients who had experienced apparent side effects from potentially inappropriate Kampo medications were among those included in this study. To evaluate the association between the potentially inappropriate Kampo medications and adverse events, a larger sample size is likely needed. Therefore, we plan to investigate this relationship in a future study.

Minor revisions required

Comment: In scientific article, it is better for you to avoid starting sentence with abbreviation. page 6, line 105., page 8 line 129.

Response: Thank you for your comments. According to your suggestion, we have modified these sentences in the revised manuscript (Page 7, Line 108; Page 8, Line 135).

Comment: page 8, line 131. Please consider my correction below.

Used for patients with uncontrolled hypertension, or patients with tachyarrhythmia.

(Original sentence means that aconite composition is used for the treatment of hypertension, and I don't think it is what you meant.)

page 8, line 135.

or patients with liver cirrhosis.
Table 1

sya -> sha; goshajinkigan and keishikashakuyakuto.

page 10, line 162-4

This sentence has two "(in order) to".

page 10, line 163 and table 4.

Multivariable and multivariate have different meaning. You might mean multivariable.

Many

baicalensi -> baicalensis

Response: We apologize for this oversight. In response to your comments, we have corrected these points in the revised manuscript. Furthermore, this revised manuscript was edited by a native English speaker at American Journal Experts.