Peer Review File

Article information: https://dx.doi.org/10.21037/apm-21-1788

RESPONSES TO REVIEWER A'S COMMENTS:

Comment 1: While the study is informative and includes novel results, it lacks clarity in the description of the methods and results.

Reply 1: Thank you for your appreciation of our manuscript. We corrected the manuscript in accordance with your comments.

Comment 2: The retrospective design is hard to understand: Is it true, that two PIM assessments were done? One time by pharmacists during enrolment of the study and another time later based on the charts? If the answer is yes, the description of the original PIM assessment is not sufficient. Did they use STOPP at all? What was the rate of PIM found in the first assessment compared to the second assessment?

Reply 2: PIM was assessed only once when the patient was admitted to the palliative care unit. It was not assessed twice. The pharmacist evaluated the drugs the patient was taking at the time of admission to the palliative care unit based on STOP vesion2. We have added more detail to the Methods, to make it easier to understand the research methods.

Changes in the text: We have added the following text to the Methods page 6, line 16 to page 7, line 16):

"PIMs detection, Pharmacists' Recommendations and Discontinuation/Changes in Medication

In our palliative care unit, the following tasks have been carried out as part of our daily work since 2019. First, when a patient was admitted, the pharmacists detected the PIMs of the medications the patient was taking using STOPP 2 criteria and recorded the details of PIMs in the medical record. Next, the pharmacists considered whether the detected PIMs should be discontinued, changed, or maintained. The pharmacists did not recommend the physician to discontinue or change the prescription if: (1) the detected PIMs were not very harmful medications, considering the overall condition of the patient; (2) the detected PIMs were important drugs for palliative care; and (3) the patient refused

to discontinue or change the medication due to psychological or emotional problems. In all other cases, pharmacists would recommend physicians to discontinue or change the medication. Then, after receiving the recommendation from the pharmacists, the physician decided whether the recommendation was reasonable or not. If the recommendation was considered reasonable, the prescription was discontinued or changed. And finally, details of this process were documented in the patient's medical record on the day of admission. In this study, we accessed the medical records of these patients retrospectively and collected demographic data and descriptions of PIMs from the medical records on the day of hospitalization."

Comment 3: The authors often wrote how many PIM changes were implemented by the physicians based on the pharmacist's recommendations. This is totally confusing because the physicians could not know about all PIM found in the retrospective chart review. They could only know of the few changes already suggested to them by pharmacists during the hospitalization of patients and of whom most were already dead the second PIM assessment was done.

Reply 3: PIMs were assessed only once when the patient was admitted to the palliative care unit. It was not assessed twice. The pharmacist assessed the medications that the patient was taking at the time of admission using the STOPP vesion2 criteria. If the pharmacist thought that the PIM detected at the time of admission should be changed, they would recommend a prescription change to the physician. Conversely, if the pharmacist thought that the detected PIM was difficult to change, they would not recommend anything to the physician. We have added text to the Methods to make it easier to understand the research methods. Please refer to reply 2 for changes in the text.

Comment 4: Page 6, sensitivity analysis: Actually it makes no sense to me to include 81 study participants in this study at all when there are 3 who did not get an initial PIM assessment. I would like to encourage the authors to do all analyses with n=78 as main analysis and drop the sensitivity analysis. In the end there should be 3 and not 5 tables.

Reply 4: Based on your comment, we have removed the description of sensitivity analysis from this manuscript.

Changes in the text: We have deleted the following from the Methods section:

"As a sensitivity analysis, we performed a univariate analysis identical to the main analysis, assuming that PIMs were detected in these cases on the day of hospitalization and were either changed or not changed based on pharmacists' recommendations."

Furthermore, we have also deleted the following from the Results section:

"Sensitivity Analysis
From October 9, 2020, to February 28, 2021, three patients aged 65 years or older were not assessed for PIMs while hospitalized. Three PIMs were detected in the case of two of these three patients. Assuming that these three PIMs were changed based on pharmacists' recommendations, the results were consistent with the main result (Table 4). Furthermore, assuming that these three PIMs were not changed, the results were consistent with the main result (Table 5)."

"Furthermore, the results of the sensitivity analysis indicated that the main result of this study was robust. This was because the main results were the same — regardless of whether the PIMs prescribed to patients whose PIMs were not assessed at the time of hospitalization from October 9, 2020, to February 28, 2021 — were assumed to have been changed based on pharmacists' recommendations."

In addition, we have deleted tables 4 and 5.

Comment 5: Table 2: Please add a column for „PIM changes by pharmacists at palliative care ward admission". I think these numbers are more relevant to understand the column "Changed PIMs" than the column "Detected PIMs at retrospective chart review", which I would name this way to make it more understandable that there were 2 times of PIM assessments.

Reply 5: We are concerned that you misunderstood that we assessed PIM twice in this study. In this study, we only assessed PIM once, at the time of admission. We believe that the reason for your confusion is the inadequate description in the Methods and Results sections of this article. Based on your comment and the comment of Reviewer B ("The sample size is rather low to allow sound conclusions in respect to the research question"), and the comments of Reviewer C ("Methods; difficult to follow and make sense of Study design needs to be elaborated on" and "A univariate analysis showed that 2 the rate of change in medications in our palliative unit was significantly lower than in 3 previous studies (Table 3) not a valid comparison"), we have substantially modified the study.

First, based on Reviewer C's comments, we narrowed down the number of previous studies to compare with our study from two to one. Then, we re-calculated the sample size needed to compare the results of our preliminary study with the results of the single prior study. The result of the sample size calculation was 220 cases. Subsequently, based on the result of the sample size calculation, we collected additional patient data and performed a univariate analysis again. Although the number of cases increased, the results did not change significantly. The rate of PIMs discontinuation or changes in the cancer patients hospitalized in the palliative care unit was lower than that of patients with other diseases. Based on the results of this last study, we have substantially revised Table 2.

Changes in the text: We have changed Table 2 (page 21, line 1 to page 23, line 1) from:

"Table 2. The classification of detected and changed PIMs.

Pharmacological classes	Detected PIMs	Changed PIMs
Total	71	18
Section A: Indication of medications	11	6
Section B: Cardiovascular system	4	2
Section C: Antiplatelet/Anticoagulant drugs	4	1
Section D: Central nervous system and psychotropic drugs	10	1
Section E: Renal system	8	1
Section F: Gastrointestinal system	4	2

Section G: Respiratory system	0	0
Section H: Musculoskeletal system	2	0
Section I: Urogenital system	0	0
Section J. Endocrine system	0	0
Section K: Drugs that predictably increase the risk of falls in older people	23	1
Section L: Analgesic drugs	5	5
Section N: Antimuscarinic/Anticholinergic drug burden	0	0

1 “

2

3 to

4

5 “Table 1. The classification of detected and discontinued/changed PIMs.

Pharmacological classes	Number of Detected PIMs by pharmacists	Number of recommendations for prescription	Number of prescriptions discontinued

		discontinued or changed by pharmacists	or changed by physicians
Total	218	65	61
Section A: Indication of medications	30	16	16
Section B: Cardiovascular system	6	3	3
Section C: Antiplatelet/Anticoagulant drugs	9	3	3
Section D: Central nervous system and psychotropic drugs	38	4	4
Section E: Renal system	21	1	1
Section F: Gastrointestinal system	9	2	1
Section G: Respiratory system	0	0	0
Section H: Musculoskeletal system	6	1	0
Section I: Urogenital system	3	1	0

Section J. Endocrine system	1	1	1
Section K: Drugs that predictably increase the risk of falls in older people	68	7	7
Section L: Analgesic drugs	23	23	23
Section N: Antimuscarinic/Anticholinergic drug burden	4	3	2

PIMs, potentially inappropriate medications “

Comment 6: Once all recommended changes are made, please let another not involved scientist check all numbers with respect to PIMs detected and changed so that they are consistent in the whole manuscript. I got very confused with different numbers in different parts of the manuscript and suspect that there are some inconsistencies.

Reply 6: After making all the changes recommended by you and Reviewers B and C, we asked Dr. Akihiro Sakashita, of the Hyogo Brain and Heart Medical Center, to check all the numbers concerning PIMs detected and changed. Dr. Sakashita has authored many papers in the field of palliative medicine and has served as a reviewer for many journals. Dr. Sakashita confirmed all the numbers concerning PIMs detected and discontinued/changed. The letter from Dr. Sakashita is attached separately. In addition, we have also included an acknowledgment to Dr. Sakashita in the manuscript.

Changes in the text 6: We have added the following text (page 15, line 4 to line 6):

We would like to express our gratitude to Dr. Akihiro Sakashita, the chief doctor of

palliative medicine of Hyogo Brain and Heart Center, who checked all the numbers regarding the detected and discontinued/changed PIMs.

RESPONSES TO REVIEWER B'S COMMENTS:

Comment 1: The authors present a cross-sectional single center cohort-study to assess the prevalence of potentially inappropriate medications (PIMs) in advanced cancer patients.
Strengths:
The research question is of relevance for clinicians and policy makers and the chosen research method adequate. The manuscript is written very well (but please notice that I am not a native speaker) and well structured. The discussion, noted liimtations and conclusions are sound. The same applies to tables and figures.

Reply 1: Thank you for your appreciation of our manuscript. We corrected the manuscript in accordance with your comments.

Comment 2: The sample size is rather low to allow sound conclusions in respect to the research question.

Reply 2: Based on your comment and the comments of Reviewer C ("Methods; difficult to follow and make sense of Study design needs to be elaborated on" and "A univariate analysis showed that 2 the rate of change in medications in our palliative unit was significantly lower than in 3 previous studies (Table 3) not a valid comparison"), we have substantially modified this study.
First, based on Reviewer C's comments, we narrowed down the number of previous studies to compare with our study from two to one. Then, we re-calculated the sample size needed to compare the results of our preliminary study with the results of the single prior study. The result of the sample size calculation was 220 cases. Then, based on the result of the sample size calculation, we collected additional patient data and performed a univariate analysis again. Although the number of cases increased, the results did not change significantly. The rate of PIMs discontinuation or changes in the cancer patients hospitalized in the palliative care unit was lower than that of patients with other diseases. Based on the results of this last study, we have substantially revised the entire paper.

Changes in the text: We have changed the following text (page 3, line 15 to page 4, line

4) from:

"Results: A total of 71 potentially inappropriate medications were detected in 475 medications administered to 81 patients. Of these, 18 medications were changed based on the recommendation of pharmacists (rate of change of medications: 25.4%). The univariate analysis results showed that this rate of change of medications was significantly lower than previous reports intended for non-cancer patients (47.7%). The rate of change of medications for benzodiazepines was extremely low, but for other drugs it was almost the same as in previous reports."

to

"Results: A total of 218 potentially inappropriate medications were detected in 1261 medications administered to 220 patients. Of these, 61 medications were discontinued or changed based on the recommendation of pharmacists (rate of discontinuation/change of medications: 28.0%). The univariate analysis results showed that this rate of discontinuation or change of medications was significantly lower than that of the previous report intended for non-cancer patients (40.6%). The rate of discontinuation/change of medications for benzodiazepines was extremely low, but for other drugs it was almost the same as in the previous report."

Furthermore, we have changed the following text (page 7, line 18 to page 8, line 11) from:

"Sample Size Calculation
Before the main study, a preliminary study was conducted on February 28, 2021. Thirty-eight patients, from the total number of patients admitted to our palliative care unit from January 1 to February 28, 2021, were included in the preliminary study. Among the subjects, 32 patients were aged 65 years or older. We extracted data related to STOPP, from the medical records of these patients on the day of admission, and found records related to STOPP in the case of 30 patients. PIMs were detected in medications brought by 16 of the 30 patients upon admission, and the total number of PIMs we detected was 29. Nine of the detected PIMs had been changed or discontinued by physicians on the recommendation of pharmacists. In similar studies by Kimura et al. (2017, 2019), 726 PIMs were detected in a total of 1,052 hospitalized patients. Of these PIMs, pharmacists recommended that 371 medications be discontinued or changed, and physicians subsequently changed 346 medications. We set αrisk to 0.05 and βrisk to 0.80 and

calculated the sample size; 81 participants were needed to compare the rate of change of medications in the previous studies with our rate of change of medications."

to

"Sample Size Calculation
To compare the PIMs' discontinued/changed rate in this study with that in the most recent previous study in which pharmacists reduced PIMs through intervention using the STOPP 2Criterion, we examined the sample size calculation. Before the main study, we conducted a preliminary study to calculate the sample size. The preliminary study was conducted on patients hospitalized in the palliative care unit from January 1 to February 28, 2021, and the medical records at the time of admission were reviewed to investigate PIMs' discontinued/changed rate. The PIMs' discontinued/changed rate was 31.0%. Based on the results of this preliminary study, the sample size required to compare the PIMs' discontinued/changed rate in this study with the PIMs discontinued/changed rate in the most recent previous study was 220. The α risk and β risk were set at 0.05 and 0.80, respectively."

Furthermore, we have changed the following text (page 10, line 1 to page 11, line 2) from:

"Incidence of PIMs
Eighty-one consecutive patients were enrolled retrospectively from February 28, 2021, resulting in the enrollment of patients admitted between October 9, 2020, and February 28, 2021. All the patients were Japanese. Seventy-five of these patients had already died, and the survival time after evaluation for the presence of PIMs was 20.8 ± 20.9 days (mean ± SD). The remaining six patients were confirmed to be alive as of June 1, 2021. Table 1 shows the characteristics of the 81 patients. One or more PIMs were found in 40 of the 81 target patients (49.9%). Four hundred seventy-five medications were prescribed to them and using STOPP, 71 were determined to be PIMs. The classification of the detected PIMs is shown in Table 2.

Pharmacists' Recommendations and Changes in Medications
Pharmacists recommended changes in 18 PIMs to physicians, which were implemented. Table 2 shows the classification of the PIMs that were changed based on pharmacists' recommendations.
The rate of change in medications was 25.4% (18/71). A univariate analysis showed that

the rate of change in medications in our palliative unit was significantly lower than in previous studies (Table 3)."

to

"Incidence of PIMs
All patients enrolled in this study were Japanese. Participants' age was 79.5±7.4 years old (mean±SD), and 131 were males and 89 were females. The most common type of cancer was gastric cancer, with 35 cases. This was followed by colorectal cancer with 32 cases and lung cancer with 29 cases.
One or more PIMs were found in 112 of the 220 target patients (50.9%). Regarding the medication, 1261 were prescribed to them, and using STOPP2, 218 were determined to be PIMs. The classification of the detected PIMs is shown in Table 1.

Pharmacists' Recommendations and Discontinuation/Changes in Medications
The pharmacists recommended physicians to discontinue or change 65 PIMs. The physician accepted the recommendations and discontinued/changed the prescription for 61 PIMs. Conversely, the physicians did not discontinue or change four PIMs, despite the recommendation of pharmacists. Table 2 shows the classification of the PIMs that were discontinued or changed based on pharmacists' recommendations.
The rate of discontinue/change in medications was 28.0% (61/218). A univariate analysis showed that the rate of discontinue or change in medications in our palliative unit was significantly lower than that in the most recent previous study (rate of discontinue/change of medications: 40.6%) (Table 2)."

Furthermore, we have changed the following text (page 11, line 8 to page 13, line 2) from:

"STOPP classifies PIMs into 13 types (7), and we detected several PIMs in Section A (Indication of medications), Section D (Central nervous system and psychotropic drugs), and Section K (Drugs that predictably increase the risk of falls in older people) in this study. The same pattern was observed in two previous studies used for comparative purposes (3, 4). However, the rate of change in medications per section seems to differ from this study. First, in Section A, 6 of 11 medications were changed in this study (rate of change of medications: 54.5%), while 56 of 113 medications were changed in the previous studies (rate of change of medications: 49.6%). Most of the PIMs classified as Section A were duplications of drugs, and our results showed no significant difference in

the possibility of correcting duplications of drugs, even for patients with end-stage cancer. However, in Section D, one out of ten medications were changed in this study (rate of change of medications: 10.0%), while 106 of 286 medications were changed in the previous studies (rate of change of medications: 37.1%). In Section K, one of 23 medications was changed in this study (rate of change of medications: 4.3%), while 51 of 113 medications were changed in the previous studies (rate of change of medications: 45.1%). The risk of falling was low, because the end-stage cancer patients hospitalized in the palliative care unit could not stand. Therefore, changing or stopping the administration of PIMs of Section K, that included medications that increased the risk of falling in elderly patients, was unnecessary.

Furthermore, most of the drugs classified in Sections D and K were benzodiazepines. The benzodiazepines used to treat patients with end-stage delirium could not be discontinued when patients were already experiencing delirium (9). Discontinuation of regularly used benzodiazepines would generate withdrawal phenomena, and cause unnecessary suffering in patients at the end of their lives (10). These reasons might have contributed to the lower rate of change of medications in this study. If we exclude PIMs classified in Sections D and K, and compare the rates of change of PIMs of this study with previous studies, 16 of 38 PIMs were changed in this study, while 189 of 385 PIMs were changed in the previous studies. The rate of reductions in prescribed PIMs, in sections other than D and K, was approximately the same."

to

"STOPP2 classifies PIMs into 13 types (16), and we detected several PIMs in Section A (Indication of medications), Section D (Central nervous system and psychotropic drugs), and Section K (Drugs that predictably increase the risk of falls in older people) in this study. The same pattern was observed in two previous studies used for comparative purposes (3, 4). However, the rate of discontinue or change in medications per section seems to differ from this study. First, in Section A, 16 of 30 medications were discontinued or changed in this study (rate of discontinuation or change of medications: 53.3%), while 11 of 22 medications were changed in the previous studies (rate of discontinuation or change of medications: 50.0%). Most of the PIMs classified as Section A were duplications of drugs, and our results showed no significant difference in the possibility of correcting duplications of drugs, even for patients with end-stage cancer. However, in Section D, 4 of 38 medications were discontinued or changed in this study (rate of discontinuation or change of medications: 10.5%), while 25 of 64 medications

were discontinued or changed in the previous study (rate of discontinuation/change of medications: 26.6%). In Section K, 7 of 68 medications were discontinued or changed in this study (rate of discontinuation/change of medications: 10.3%), while 6 of 14 medications were discontinued or changed in the previous studies (rate of discontinue/change of medications: 42.9%). The risk of falling was low, because the end-stage cancer patients hospitalized in the palliative care unit could not stand up. Therefore, changing or stopping the administration of PIMs of Section K, which included medications that increased the risk of falling in older patients, was unnecessary.
Furthermore, most of the drugs classified in Sections D and K were benzodiazepines. The benzodiazepines used to treat patients with end-stage delirium could not be discontinued when patients were already experiencing delirium (19). Discontinuation of regularly used benzodiazepines would generate withdrawal phenomena, and cause unnecessary suffering in patients at the end of their lives (20). These reasons might have contributed to the lower rate of discontinue or change of medications in this study. If we exclude PIMs classified in Sections D and K and compare the rates of discontinuation/change of PIMs of this study with those of previous studies, 50 of 112 PIMs were discontinued or changed in this study, while 23 of 55 PIMs were discontinued or changed in the previous studies. The rate of reductions in prescribed PIMs, in sections other than D and K, was approximately the same."

Comment 3: Some paragraphs are not in the correct place. For example, much of what is reported under "power calculation" are rather results.

Reply 3: Based on your comment, we have restructured the Methods. Please see reply 2 for the text changes.

Comment 4: Moreover, much of the STROBE list should be revisited. Already the first item is not correctly respected, as the title does not convey the research method. Instead, findings are already reported in the title. I recommend thorough and detailed revision.

Reply 4: Based on your comment, we have changed the title of this manuscript and revised the STROBE checklist thoroughly.

Changes in the text : We have changed the following text (page 1, line 2 to line 5) from:

"Potentially inappropriate medications for end-stage cancer patients are more difficult to

curtail on the basis of pharmacists' recommendations, than for elderly patients hospitalized for other illnesses"

to

"Potentially inappropriate medications discontinued or changed based on pharmacists' recommendations in older end-stage cancer patients receiving palliative care: a cross-sectional study"

Comment 5: Also, I recommend some more literature research to discuss and reference the most relevant literature.

Reply 5: Based on your comment and the comment of reviewers C and D, we have added 11 references and revised the Introduction significantly. In addition, we have removed references by Thomas et al. that we consider less important to the revised Introduction, and renumbered the references.

Changes in the text: We have changed the following text (page 4, line 16 to page 6, line 9), from:

"Introduction
Recently, it was reported that potentially inappropriate medications (PIMs) were associated with higher rates of hospitalization and increased the cost of health care in the elderly (1). It was also reported that pharmacists could reduce instances of prescribing PIMs for outpatients and inpatients, and their role has been emphasized (2–4). The role of pharmacists was also examined in the field of palliative care, as avoiding PIMs has been reported to reduce adverse events and fight untimely death in elderly cancer patients receiving palliative care (5, 6). However, to our knowledge, studies have not examined the extent to which pharmacists' recommendations can play a role in the reduction of the prescription of PIMs, in elderly cancer patients receiving palliative care. In the palliative care unit where this study was conducted, pharmacists routinely detect PIMs based on the Screening Tool of Older Persons' Prescriptions (STOPP) version 2, by examining the medications bought by patients on admission, and recommending physicians to change medications (7). Therefore, we designed a cross-sectional study to determine the extent to which pharmacists' recommendations can reduce the prescription of PIMs in elderly cancer patients receiving palliative care.

Kimura et al. reported how the prescription of several PIMs, based on STOPP, could have been avoided for elderly Japanese patients hospitalized for non-cancer diseases through pharmacists' recommendations (3, 4). By comparing the results of these studies with those conducted in our daily practice, we examined the extent to which pharmacists' recommendations can decrease the prescription of PIMs in elderly cancer patients receiving palliative care. We present this article following The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting checklist."

to

"Introduction

Recently, potentially inappropriate medications (PIMs) in older cancer patients have become a growing serious clinical problem, especially after Chen et al. and Mostafa et al. reported that reducing PIMs can reduce adverse events and prevent premature death in elderly cancer patients (1, 2). To reduce PIMs, it has been reported that not only physicians, who prescribe, but also pharmacists, who detect PIMs and recommend to the physicians to discontinue or change the prescription, are important (3–5). Furthermore, many researchers have reported that pharmacists can reduce PIMs for older cancer patients as well, highlighting the role of these professionals in the field of cancer medicine (6–9). However, all these studies were conducted in cancer patients receiving anticancer therapy, and there have been no reports of pharmacists contributing to the reduction of PIMs in older cancer patients hospitalized in the palliative care unit. Therefore, we designed this study to investigate whether pharmacists contribute to PIMs reduction in older cancer patients hospitalized in the palliative care unit.

Criteria such as beers criteria, OncPal, screening tool of older persons' prescriptions (STOPP), screening tool of older persons' prescriptions in frail adults with limited life expectancy (STOPPFrail), among others, have been proposed to detect PIMs (10–15). The most recent version of STOPP, STOPP version 2 (STOPP2), provides more detailed criteria for determining PIMs, including the use of blood test results (16). It is also a simple and practical criterion that can be evaluated in a few minutes by trained pharmacists (5, 17). In our palliative care unit, we use STOPP2 among other criteria for detecting PIMs, because blood tests are basically performed upon admission. In our daily clinical practice, pharmacists detect PIMs when a patient is hospitalized in the palliative care unit and recommend to the physician to discontinue or change the prescriptions to reduce PIMs. In this study, we retrospectively reviewed the patients' medical records and evaluated the PIMs' discontinuation/change rates at our palliative care unit. Furthermore,

by comparing our PIMs' discontinuation/change rates with those of a previous study, in which pharmacists reduced PIMs by intervening using the STOPP 2Criterion, we investigated whether pharmacists contribute to reducing PIMs in older cancer patients hospitalized in the palliative care unit."

Furthermore, we have added the following references and renumbered them (page 18, line 2 to page 19, line 17):

"6. Choukroun C, Leguelinel-Blache G, Roux-Marson C, et al. Impact of a pharmacist and geriatrician medication review on drug-related problems in older outpatients with cancer. J Geriatr Oncol 2021;12(1):57-63.
7. van Loveren FMAM, van Berlo-van de Laar IRF, Imholz ALT, et al. Prevalence and follow-up of potentially inappropriate medication and potentially omitted medication in older patients with cancer - The PIM POM study. J Geriatr Oncol 2021;12(1):80-84.
8. Whitman A, DeGregory K, Morris A, et al. Pharmacist-led medication assessment and deprescribing intervention for older adults with cancer and polypharmacy: a pilot study. Support Care Cancer 2018;26(12):4105-4113.
9. Nipp RD, Ruddy M, Fuh CX, Zangardi ML, et al. Pilot Randomized Trial of a Pharmacy Intervention for Older Adults with Cancer. Oncologist 2019;24(2):211-218.
10. American Geriatrics Society 2012 Beers Criteria Update Expert Panel. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2012.
11. The 2019 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc. 2019.
12. Lindsay J, Dooley M, Martin J, et al. The development and evaluation of an oncological palliative care deprescribing guideline: the 'OncPal deprescribing guideline'. Support Care Cancer 2015;23(1):71-8.
13. Gallagher P, Ryan C, Byrne S, et al. STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation. Int J Clin Pharmacol Ther 2008;46(2):72-83.
14. Lavan AH, Gallagher P, Parsons C, et al. STOPPFrail (Screening Tool of Older Persons Prescriptions in Frail adults with limited life expectancy): consensus validation. Age Ageing 2017;46(4):600-607.
15. Curtin D, Gallagher P, O'Mahony D. Deprescribing in older people approaching end-of-life: development and validation of STOPPFrail version 2. Age Ageing

2021;50(2):465-471.

17. Ryan C, O'Mahony D, Kennedy J, et al. Potentially inappropriate prescribing in an Irish elderly population in primary care. Br J Clin Pharmacol 2009;68(6):936-47."

Furthermore, we have deleted following references:

"1. Thomas R E, Thomas B C. A systematic review of studies of the STOPP/START 2015 and American Geriatric Society Beers 2015 criteria in patients ≥ 65 Years. Curr Aging Sci 2019;12(2):121-54."

RESPONSES TO REVIEWER C'S COMMENTS:

Comment 1: This manuscript has potential but the current presentation and comparisons with prior research raise concerns regarding rigour and validity of the claims being made

Reply 1: Thank you for your appreciation of our manuscript. We corrected the manuscript in accordance with your comments.

Comment 2: Title: a more succinct, objective study title required that makes reference to aim and design without summarising main findings

Reply 2: Based on your comment, we have changed the title of this manuscript.

Changes in the text: We have changed the title (page 1, line 2 to line 4) from:

"Potentially inappropriate medications for end-stage cancer patients are more difficult to curtail on the basis of pharmacists' recommendations, than for elderly patients hospitalized for other illnesses"

to

"Potentially inappropriate medications discontinued or changed based on pharmacists' recommendations in older end-stage cancer patients receiving palliative care: a cross-sectional study."

Comment 3: Suggest replacing the terms aged and elderly with “older” throughout

Reply 3: Based on your comment, we have replaced the terms aged and elderly with older throughout the manuscript.

Changes in the text: We have changed the following text (page 3, line 1 to page 4, line 14) from:

“Abstract

Background: Avoiding potentially inappropriate medications can reduce adverse events in aged cancer patients receiving palliative care. However, studies have not examined the extent to which pharmacists’ recommendations reduce the prescription of potentially inappropriate medications. Therefore, we designed a cross-sectional study to determine the extent to which their recommendations play a role in reducing the prescription of potentially inappropriate medications for elderly cancer patients receiving palliative care.
Methods: Patients brought their medications with them upon admission to the hospital. These medications were examined by pharmacists and deemed inappropriate based on the Screening Tool of Older Persons’ Prescriptions (STOPP) version 2. In this study, these 81 patients were surveyed, and the percentage of medications that were changed based on pharmacists’ recommendations was compared with the previously published results of similar studies on elderly non-cancer inpatients, using univariate analysis.
Results: A total of 71 potentially inappropriate medications were detected in 475 medications administered to 81 patients. Of these, 18 medications were changed based on the recommendation of pharmacists (rate of change of medications: 25.4%). The univariate analysis results showed that this rate of change of medications was significantly lower than previous reports intended for non-cancer patients (47.7%). The rate of change of medications for benzodiazepines was extremely low, but for other drugs it was almost the same as in previous reports.
Conclusions: In the case of elderly end-stage cancer patients receiving palliative care, compared with elderly patients hospitalized for other diseases — it was more difficult to, on pharmacists’ recommendations — change potentially inappropriate medications detected by STOPP. The low significance of discontinuing or changing benzodiazepines in subjects was a major reason it was difficult to reduce the prescription and, eventually, administer potentially inappropriate medications based on pharmacists’ recommendations.

Keywords: End-stage cancer; Potentially inappropriate medications; Screening tool of

aged persons' prescriptions criteria version 2; Benzodiazepines; Elderly patients"

to

"Abstract

Background: Avoiding potentially inappropriate medications can reduce adverse events in older cancer patients receiving palliative care. However, studies have not examined the extent to which pharmacists' recommendations reduce the prescription of potentially inappropriate medications. Therefore, we designed a cross-sectional study to determine the extent to which their recommendations play a role in reducing the prescription of potentially inappropriate medications for older cancer patients receiving palliative care.

Methods: Patients brought their medications with them upon admission to the hospital. These medications were examined by pharmacists and deemed inappropriate based on the Screening Tool of Older Persons' Prescriptions version 2 (STOPP2). In this study, these 220 patients were surveyed, and the percentage of medications that were discontinued or changed based on pharmacists' recommendations was compared with previously published results of similar studies on older non-cancer inpatients, using univariate analysis.

Results: A total of 218 potentially inappropriate medications were detected in 1261 medications administered to 220 patients. Of these, 61 medications were discontinued or changed based on the recommendation of pharmacists (rate of discontinuation/change of medications: 28.0%). The univariate analysis results showed that this rate of discontinuation or change of medications was significantly lower than that of a previous report intended for non-cancer patients (40.6%). The rate of discontinuation/change of medications for benzodiazepines was extremely low, but for other drugs it was almost the same as in the previous report.

Conclusions: In the case of older end-stage cancer patients receiving palliative care, compared with older patients hospitalized for other diseases, it was more difficult, on pharmacists' recommendations, to discontinue or change potentially inappropriate medications detected by STOPP2. The low significance of discontinuing or changing benzodiazepines in subjects was a major reason it was difficult to reduce the prescription and, eventually, administer potentially inappropriate medications based on pharmacists' recommendations.

Keywords: End-stage cancer; Potentially inappropriate medications; Screening tool of aged persons' prescriptions criteria version 2; Benzodiazepines; Older patients"

Furthermore, we have changed the following text (page 11, line 4 to page 13, line 7) from:

"Discussion

The results of this study indicate that it is more difficult to reduce the prescription of PIMs in cancer patients hospitalized in palliative care units, than in patients hospitalized with other diseases. Moreover, 75 of the 81 patients in the study were dead by June 1, 2021, when the medical files were examined. As these 75 patients died an average of 20.8 days after the date of detection of PIMs, most of the subjects were likely to have been end-stage cancer patients. In addition, the fact that they were admitted to our palliative care unit, suggests that they required intensive palliative care. Therefore, the results of this study indicate that it is more difficult to reduce PIMs in hospitalized end-stage cancer patients receiving intensive palliative care. Furthermore, the results of the sensitivity analysis indicated that the main result of this study was robust. This was because the main results were the same — regardless of whether the PIMs prescribed to patients whose PIMs were not assessed at the time of hospitalization from October 9, 2020, to February 28, 2021 — were assumed to have been changed based on pharmacists' recommendations. STOPP classifies PIMs into 13 types (7), and we detected several PIMs in Section A (Indication of medications), Section D (Central nervous system and psychotropic drugs), and Section K (Drugs that predictably increase the risk of falls in older people) in this study. The same pattern was observed in two previous studies used for comparative purposes (3, 4). However, the rate of change in medications per section seems to differ from this study. First, in Section A, 6 of 11 medications were changed in this study (rate of change of medications: 54.5%), while 56 of 113 medications were changed in the previous studies (rate of change of medications: 49.6%). Most of the PIMs classified as Section A were duplications of drugs, and our results showed no significant difference in the possibility of correcting duplications of drugs, even for patients with end-stage cancer. However, in Section D, one out of ten medications were changed in this study (rate of change of medications: 10.0%), while 106 of 286 medications were changed in the previous studies (rate of change of medications: 37.1%). In Section K, one of 23 medications was changed in this study (rate of change of medications: 4.3%), while 51 of 113 medications were changed in the previous studies (rate of change of medications: 45.1%). The risk of falling was low, because the end-stage cancer patients hospitalized in the palliative care unit could not stand. Therefore, changing or stopping the administration of PIMs of Section K, that included medications that increased the risk of falling in elderly patients, was unnecessary.

Furthermore, most of the drugs classified in Sections D and K were benzodiazepines. The benzodiazepines used to treat patients with end-stage delirium could not be discontinued when patients were already experiencing delirium (9). Discontinuation of regularly used benzodiazepines would generate withdrawal phenomena, and cause unnecessary suffering in patients at the end of their lives (10). These reasons might have contributed to the lower rate of change of medications in this study. If we exclude PIMs classified in Sections D and K, and compare the rates of change of PIMs of this study with previous studies, 16 of 38 PIMs were changed in this study, while 189 of 385 PIMs were changed in the previous studies. The rate of reductions in prescribed PIMs, in sections other than D and K, was approximately the same.

However, the rate of change in medications for PIMs in sections other than D and K, may not differ for terminal cancer patients hospitalized in the palliative care unit, compared to other patients. This suggests that even end-stage cancer patients hospitalized in the palliative care unit, may benefit from efforts to detect and reduce the prescription of PIMs using STOPP."

to

"Discussion

The results of this study show that older cancer patients hospitalized in palliative care units have more difficulty reducing PIM detected by STOPP2 than patients admitted for other diseases. STOPP2 classifies PIMs into 13 types (16), and we detected several PIMs in Section A (Indication of medications), Section D (Central nervous system and psychotropic drugs), and Section K (Drugs that predictably increase the risk of falls in older people) in this study. The same pattern was observed in two previous studies used for comparative purposes (3, 4). However, the rate of discontinuation or change in medications per section seems to differ from this study. First, in Section A, 16 of 30 medications were discontinued or changed in this study (rate of discontinuation or change of medications: 53.3%), while 11 of 22 medications were changed in the previous study (rate of discontinuation or change of medications: 50.0%). Most of the PIMs classified as Section A were duplications of drugs, and our results showed no significant difference in the possibility of correcting duplications of drugs, even for patients with end-stage cancer. However, in Section D, 4 of 38 medications were discontinued or changed in this study (rate of discontinuation or change of medications: 10.5%), while 25 of 64 medications were discontinued or changed in the previous study (rate of discontinuation/change of medications: 26.6%). In Section K, 7 of 68 medications were discontinued or changed in

this study (rate of discontinuation/change of medications: 10.3%), while 6 of 14 medications were discontinued or changed in the previous studies (rate of discontinue/change of medications: 42.9%). The risk of falling was low, because the end-stage cancer patients hospitalized in the palliative care unit could not stand up. Therefore, changing or stopping the administration of PIMs of Section K, which included medications that increased the risk of falling in older patients, was unnecessary.
Furthermore, most of the drugs classified in Sections D and K were benzodiazepines. The benzodiazepines used to treat patients with end-stage delirium could not be discontinued when patients were already experiencing delirium (19). Discontinuation of regularly used benzodiazepines would generate withdrawal phenomena and cause unnecessary suffering in patients at the end of their lives (20). These reasons might have contributed to the lower rate of discontinuation or change of medications in this study. If we exclude PIMs classified in Sections D and K and compare the rates of discontinuation/change of PIMs of this study with those of previous studies, 50 of 112 PIMs were discontinued or changed in this study, while 23 of 55 PIMs were discontinued or changed in the previous studies. The rate of reductions in prescribed PIMs, in sections other than D and K, was approximately the same.
However, the rate of discontinuation or change in medications for PIMs in sections other than D and K, may not differ for terminal cancer patients hospitalized in the palliative care unit, compared to other patients. This suggests that even end-stage cancer patients hospitalized in the palliative care unit, may benefit from efforts to detect and reduce the prescription of PIMs using STOPP2."

Furthermore, we have changed the following text (page 14, line 3 to line 10) from:

"Nevertheless, this cross-sectional study has some limitations. First, all the study participants were recruited from a single center; thus, they did not represent the general population of end-stage cancer patients. Second, all the participants were recruited from the patients hospitalized in the palliative care unit; thus, they did not represent the general population of end-stage cancer patients, including home patients and outpatients. Finally, neither this study, nor the previous studies used for comparison, are representative of the general population of elderly patients, as they were conducted on Japanese subjects. Therefore, the results must be interpreted whilst considering these limitations."

to

"Nevertheless, this cross-sectional study has some limitations. First, all the study participants were recruited from a single center; thus, they did not represent the general population of end-stage cancer patients. Second, all the participants were recruited from the patients hospitalized in the palliative care unit; thus, they did not represent the general population of end-stage cancer patients, including home patients and outpatients. Finally, neither this study, nor the previous studies used for comparison, are representative of the general population of older patients, as they were conducted on Japanese subjects. Therefore, the results must be interpreted whilst considering these limitations."

Furthermore, we have changed the following text (page 12, line 14 to line 18) from:

"Conclusion
In the records of elderly patients hospitalized with end-stage cancer and receiving palliative care, compared with those of elderly patients hospitalized for other diseases, PIMs detected by STOPP were more difficult to reduce based on pharmacists' recommendations. The low significance of discontinuing or changing benzodiazepines in subjects, was a major reason for the difficulty in reducing the prescription of PIMs based on pharmacists' recommendations."

to

"Conclusion
In the records of older patients hospitalized with end-stage cancer and receiving palliative care, compared with those of older patients hospitalized for other diseases, PIMs detected by STOPP were more difficult to reduce based on pharmacists' recommendations. The low significance of discontinuing or changing benzodiazepines in subjects, was a major reason for the difficulty in reducing the prescription of PIMs based on pharmacists' recommendations."

Comment 4: Introduction: lacks proper structure and flow; need to make better use of paragraphs to introduce the clinical area of relevant to this study, the role of pharmacists and then the particular gap in the literature that this study plans to address – at present all of this is squashed into the opening paragraph
Describing reference 1 as recent in opening statement is not accurate (it was published in 2015)
"However, to our knowledge, studies have not examined the extent to which pharmacists'

recommendations can play a role in the reduction of the prescription of PIMs, in elderly cancer patients receiving palliative care." It would be nice to see a statement like this backed up by a review as opposed to the authors' knowledge which could be prone to bias. See recent scoping review interventions to optimise medication prescribing and adherence in older adults with cancer by Murphy et al (Res Social Adm Pharm. 2021 Apr 17;S1551-7411(21)00134-0. doi: 10.1016/j.sapharm.2021.04.011) which shows that pharmacists were involved in various interventions but none of the included studies referred to patients receiving palliative care.
The appropriateness of STOPP criteria to a palliative population needs to be discussed
I don't follow the reference to Kimura et al. and its relevance to this study and why the results are being compared against it – this does not seem like a valid comparison

Reply 4:

Based on your comment and the comments of reviewers A and D, we have added 11 references and revised the Introduction significantly. In addition, we have removed references by Thomas et al. that we considered less important to the revised Introduction and renumbered the references.

The two papers reported by Kimura et al., taken as previous studies in this manuscript, are a retrospective investigation of their routine practice, as shown below. First, they detected PIMs by pharmacists using the STOPP2 criteria from medications brought by patients admitted to a ward that mainly treats cardiovascular diseases. Then, the pharmacists reviewed the detected PIMs to see if they could be discontinued/changed. Subsequently, if the pharmacist determined that the PIMs could be discontinued or changed, they would recommend to the physicians that the PIMs should be discontinued or changed. Then, if the physicians judged that the pharmacists' recommendation was correct, the physicians would discontinue or change the PIMs; however, if the pharmacists' recommendation was wrong, the physicians would not discontinue/change the PIMs. They conducted a retrospective survey of such daily practice and calculated the prescription change rate using the number of PIMs detected by pharmacists as the denominator and the number of PIMs discontinued/changed by physicians as the numerator, and reported it in their paper. The first report was published in 2017 and the second report in 2019. In the conclusion of these papers, Kimura et al. state that it is important to detect PIMs using the STOPP2 criteria in hospitalized patients. In addition, the role of the pharmacist in determining whether PIMs can be discontinued/changed based on the patient's situation is important, rather than simply detecting PIMs and suspending/changing the PIMs.

Now, as part of our daily practice, pharmacists detect PIMs using the STOPP2 criteria

from medications brought by patients admitted to the palliative care unit. The pharmacists detect PIMs using the STOPP2 criteria. Then, the pharmacists consider whether the detected PIMs can be discontinued/changed by the pharmacists. Then, if the pharmacists determine that the PIMs can be discontinued or changed, they recommend to the physician that the PIMs should be discontinued or changed. Subsequently, if the physician determines that the pharmacists' recommendation is correct, the physician discontinues or changes the PIMs; however, if the pharmacists' decision is wrong, the physician does not discontinue/change the PIMs. In other words, Kimura et al.'s daily practice and our daily practice are almost the same, only the wards are different. Therefore, we designed this study to investigate whether it is important for pharmacists to detect PIMs in the palliative care unit and to recommend that physicians discontinue or change medications by comparing our PIM discontinuation/change rate with that reported by Kimura et al.

To compare our PIM discontinuation/modification rate with Kimura et al.'s report, we first need to perform a sample size calculation to determine how many patients records we need to examine retrospectively. The preliminary study was conducted with this purpose.

Now, based on your comment 4 and 6, we thought that if the preliminary study was conducted on a small number of cases, the sample size calculation should also be done on a small number of cases. So, we narrowed down the number of previous studies to compare with our study from two to one. Then, we re-calculated the sample size. The result of the sample size calculation was 220 cases. Subsequently, based on the result of the sample size calculation, we collected additional patient data and performed a univariate analysis again. Although the number of cases increased, the results did not change significantly. However, as mention above, we have restructured our study, so we have changed many text of this manuscript.

Changes in the text: we have changed the following text (page 3, line 1 to page 4, line 11) from:

“Abstract

Background: Avoiding potentially inappropriate medications can reduce adverse events in aged cancer patients receiving palliative care. However, studies have not examined the extent to which pharmacists’ recommendations reduce the prescription of potentially inappropriate medications. Therefore, we designed a cross-sectional study to determine the extent to which their recommendations play a role in reducing the prescription of potentially inappropriate medications for elderly cancer patients receiving palliative care.

Methods: Patients brought their medications with them upon admission to the hospital. These medications were examined by pharmacists and deemed inappropriate based on the Screening Tool of Older Persons' Prescriptions (STOPP) version 2. In this study, these 81 patients were surveyed, and the percentage of medications that were changed based on pharmacists' recommendations was compared with the previously published results of similar studies on elderly non-cancer inpatients, using univariate analysis.

Results: A total of 71 potentially inappropriate medications were detected in 475 medications administered to 81 patients. Of these, 18 medications were changed based on the recommendation of pharmacists (rate of change of medications: 25.4%). The univariate analysis results showed that this rate of change of medications was significantly lower than previous reports intended for non-cancer patients (47.7%). The rate of change of medications for benzodiazepines was extremely low, but for other drugs it was almost the same as in previous reports.

Conclusions: In the case of elderly end-stage cancer patients receiving palliative care, compared with elderly patients hospitalized for other diseases — it was more difficult to, on pharmacists' recommendations — change potentially inappropriate medications detected by STOPP. The low significance of discontinuing or changing benzodiazepines in subjects was a major reason it was difficult to reduce the prescription and, eventually, administer potentially inappropriate medications based on pharmacists' recommendations."

to

"Abstract

Background: Avoiding potentially inappropriate medications can reduce adverse events in older cancer patients receiving palliative care. However, studies have not examined the extent to which pharmacists' recommendations reduce the prescription of potentially inappropriate medications. Therefore, we designed a cross-sectional study to determine the extent to which their recommendations play a role in reducing the prescription of potentially inappropriate medications for older cancer patients receiving palliative care.

Methods: Patients brought their medications with them upon admission to the hospital. These medications were examined by pharmacists and deemed inappropriate based on the Screening Tool of Older Persons' Prescriptions version 2 (STOPP2). In this study, these 220 patients were surveyed, and the percentage of medications that were discontinued or changed based on pharmacists' recommendations was compared with previously published results of similar studies on older non-cancer inpatients, using

univariate analysis.
Results: A total of 218 potentially inappropriate medications were detected in 1261 medications administered to 220 patients. Of these, 61 medications were discontinued or changed based on the recommendation of pharmacists (rate of discontinuation/change of medications: 28.0%). The univariate analysis results showed that this rate of discontinuation or change of medications was significantly lower than that of a previous report intended for non-cancer patients (40.6%). The rate of discontinuation/change of medications for benzodiazepines was extremely low, but for other drugs it was almost the same as in the previous report.
Conclusions: In the case of older end-stage cancer patients receiving palliative care, compared with older patients hospitalized for other diseases, it was more difficult, on pharmacists' recommendations, to discontinue or change potentially inappropriate medications detected by STOPP2. The low significance of discontinuing or changing benzodiazepines in subjects was a major reason it was difficult to reduce the prescription and, eventually, administer potentially inappropriate medications based on pharmacists' recommendations."

Furthermore, we have changed the following text (page 4, line 16 to page 6, line 9) from:

"Introduction
Recently, it was reported that potentially inappropriate medications (PIMs) were associated with higher rates of hospitalization and increased the cost of health care in the elderly (1). It was also reported that pharmacists could reduce instances of prescribing PIMs for outpatients and inpatients, and their role has been emphasized (2–4). The role of pharmacists was also examined in the field of palliative care, as avoiding PIMs has been reported to reduce adverse events and fight untimely death in elderly cancer patients receiving palliative care (5, 6). However, to our knowledge, studies have not examined the extent to which pharmacists' recommendations can play a role in the reduction of the prescription of PIMs, in elderly cancer patients receiving palliative care. In the palliative care unit where this study was conducted, pharmacists routinely detect PIMs based on the Screening Tool of Older Persons' Prescriptions (STOPP) version 2, by examining the medications bought by patients on admission, and recommending physicians to change medications (7). Therefore, we designed a cross-sectional study to determine the extent to which pharmacists' recommendations can reduce the prescription of PIMs in elderly cancer patients receiving palliative care.
Kimura et al. reported how the prescription of several PIMs, based on STOPP, could have

been avoided for elderly Japanese patients hospitalized for non-cancer diseases through pharmacists' recommendations (3, 4). By comparing the results of these studies with those conducted in our daily practice, we examined the extent to which pharmacists' recommendations can decrease the prescription of PIMs in elderly cancer patients receiving palliative care. We present this article following The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting checklist."

to

"Introduction

Recently, potentially inappropriate medications (PIMs) in older cancer patients have become a growing serious clinical problem, especially after Chen et al. and Mostafa et al. reported that reducing PIMs can reduce adverse events and prevent premature death in older cancer patients (1, 2). To reduce PIMs, it has been reported that not only physicians, who prescribe, but also pharmacists, who detect PIMs and recommend to physicians to discontinue or change the prescription, are important (3–5). Furthermore, many researchers have reported that pharmacists can reduce PIMs for older cancer patients as well, highlighting the role of these professionals in the field of cancer medicine (6–9). However, all these studies were conducted in cancer patients receiving anticancer therapy, and there have been no reports of pharmacists contributing to the reduction of PIMs in older cancer patients hospitalized in the palliative care unit. Therefore, we designed this study to investigate whether pharmacists contribute to PIMs reduction in older cancer patients hospitalized in the palliative care unit.

Criteria such as Beers Criteria, OncPal, Screening Tool of Older Persons' Prescriptions (STOPP), Screening Tool of Older Persons Prescriptions in Frail adults with limited life expectancy (STOPPFrail), among others, have been proposed to detect PIMs (10–15). The most recent version of STOPP, STOPP version 2 (STOPP2), provides more detailed criteria for determining PIMs, including the use of blood test results (16). It is also a simple and practical criterion that can be evaluated in a few minutes by trained pharmacists (5, 17). In our palliative care unit, we use STOPP2 among other criteria for detecting PIMs, because blood tests are basically performed upon admission. In our daily clinical practice, pharmacists detect PIMs when a patient is hospitalized in the palliative care unit and recommend to the physician to discontinue or change the prescriptions to reduce PIMs. In this study, we retrospectively reviewed the patients' medical records and evaluated the PIMs' discontinuation/change rates at our palliative care unit. Furthermore, by comparing our PIMs' discontinuation/change rates with those of a previous study, in

which pharmacists reduced PIMs by intervening using the STOPP2 criterion, we investigated whether pharmacists contribute to reducing PIMs in older cancer patients hospitalized in the palliative care unit."

Furthermore, we have changed the following text (page 7, line 18 to page 8, line 11) from:

"Sample Size Calculation
Before the main study, a preliminary study was conducted on February 28, 2021. Thirty-eight patients, from the total number of patients admitted to our palliative care unit from January 1 to February 28, 2021, were included in the preliminary study. Among the subjects, 32 patients were aged 65 years or older. We extracted data related to STOPP, from the medical records of these patients on the day of admission, and found records related to STOPP in the case of 30 patients. PIMs were detected in medications brought by 16 of the 30 patients upon admission, and the total number of PIMs we detected was 29. Nine of the detected PIMs had been changed or discontinued by physicians on the recommendation of pharmacists. In similar studies by Kimura et al. (2017, 2019), 726 PIMs were detected in a total of 1,052 hospitalized patients. Of these PIMs, pharmacists recommended that 371 medications be discontinued or changed, and physicians subsequently changed 346 medications. We set αrisk to 0.05 and βrisk to 0.80 and calculated the sample size; 81 participants were needed to compare the rate of change of medications in the previous studies with our rate of change of medications."

to

"Sample Size Calculation
To compare the PIMs' discontinued/changed rate in this study with that in the most recent previous study, in which pharmacists reduced PIMs through intervention using the STOPP2 criterion, we examined the sample size calculation. Before the main study, we conducted a preliminary study to calculate the sample size. The preliminary study was conducted on patients hospitalized in the palliative care unit from January 1 to February 28, 2021, and the medical records at the time of admission were reviewed to investigate PIMs' discontinued/changed rate. The PIMs' discontinued/changed rate was 31.0%. Based on the results of this preliminary study, the sample size required to compare the PIMs' discontinued/changed rate in this study with the PIMs discontinued/changed rate in the most recent previous study was 220. The α risk and β risk were set at 0.05 and 0.80, respectively."

Furthermore, we have changed the following text (page 10, line 1 to page 11, line 2) from:

"Results

Incidence of PIMs

Eighty-one consecutive patients were enrolled retrospectively from February 28, 2021, resulting in the enrollment of patients admitted between October 9, 2020, and February 28, 2021. All the patients were Japanese. Seventy-five of these patients had already died, and the survival time after evaluation for the presence of PIMs was 20.8 ± 20.9 days (mean ± SD). The remaining six patients were confirmed to be alive as of June 1, 2021. Table 1 shows the characteristics of the 81 patients. One or more PIMs were found in 40 of the 81 target patients (49.9%). Four hundred seventy-five medications were prescribed to them and using STOPP, 71 were determined to be PIMs. The classification of the detected PIMs is shown in Table 2.

Pharmacists' Recommendations and Changes in Medications

Pharmacists recommended changes in 18 PIMs to physicians, which were implemented. Table 2 shows the classification of the PIMs that were changed based on pharmacists' recommendations.

The rate of change in medications was 25.4% (18/71). A univariate analysis showed that the rate of change in medications in our palliative unit was significantly lower than in previous studies (Table 3).

Sensitivity Analysis

From October 9, 2020, to February 28, 2021, three patients aged 65 years or older were not assessed for PIMs while hospitalized. Three PIMs were detected in the case of two of these three patients. Assuming that these three PIMs were changed based on pharmacists' recommendations, the results were consistent with the main result (Table 4). Furthermore, assuming that these three PIMs were not changed, the results were consistent with the main result (Table 5)."

to

"Results

Incidence of PIMs

All patients enrolled in this study were Japanese. Participants' age was 79.5±7.4 years old

(mean±SD), and 131 were males and 89 were females. The most common type of cancer was gastric cancer, with 35 cases. This was followed by colorectal cancer with 32 cases and lung cancer with 29 cases.
One or more PIMs were found in 112 of the 220 target patients (50.9%). Regarding the medication, 1261 were prescribed to them, and using STOPP2, 218 were determined to be PIMs. The classification of the detected PIMs is shown in Table 1.

Pharmacists' Recommendations and Discontinuation/Changes in Medications
The pharmacists recommended physicians to discontinue or change 65 PIMs. The physicians accepted the recommendations and discontinued/changed the prescription for 61 PIMs. Conversely, the physicians did not discontinue or change four PIMs, despite the recommendation of pharmacists. Table 2 shows the classification of the PIMs that were discontinued or changed based on pharmacists' recommendations.
The rate of discontinuation/change in medications was 28.0% (61/218). A univariate analysis showed that the rate of discontinuation or change in medications in our palliative unit was significantly lower than that in the most recent previous study (rate of discontinuation/change of medications: 40.6%) (Table 2)."

Furthermore, we have changed the following text (page 11, line 4 to page 13, line 7) from:

"Discussion
The results of this study indicate that it is more difficult to reduce the prescription of PIMs in cancer patients hospitalized in palliative care units, than in patients hospitalized with other diseases. Moreover, 75 of the 81 patients in the study were dead by June 1, 2021, when the medical files were examined. As these 75 patients died an average of 20.8 days after the date of detection of PIMs, most of the subjects were likely to have been end-stage cancer patients. In addition, the fact that they were admitted to our palliative care unit, suggests that they required intensive palliative care. Therefore, the results of this study indicate that it is more difficult to reduce PIMs in hospitalized end-stage cancer patients receiving intensive palliative care. Furthermore, the results of the sensitivity analysis indicated that the main result of this study was robust. This was because the main results were the same — regardless of whether the PIMs prescribed to patients whose PIMs were not assessed at the time of hospitalization from October 9, 2020, to February 28, 2021 — were assumed to have been changed based on pharmacists' recommendations.
STOPP classifies PIMs into 13 types (7), and we detected several PIMs in Section A (Indication of medications), Section D (Central nervous system and psychotropic drugs),

and Section K (Drugs that predictably increase the risk of falls in older people) in this study. The same pattern was observed in two previous studies used for comparative purposes (3, 4). However, the rate of change in medications per section seems to differ from this study. First, in Section A, 6 of 11 medications were changed in this study (rate of change of medications: 54.5%), while 56 of 113 medications were changed in the previous studies (rate of change of medications: 49.6%). Most of the PIMs classified as Section A were duplications of drugs, and our results showed no significant difference in the possibility of correcting duplications of drugs, even for patients with end-stage cancer. However, in Section D, one out of ten medications were changed in this study (rate of change of medications: 10.0%), while 106 of 286 medications were changed in the previous studies (rate of change of medications: 37.1%). In Section K, one of 23 medications was changed in this study (rate of change of medications: 4.3%), while 51 of 113 medications were changed in the previous studies (rate of change of medications: 45.1%). The risk of falling was low, because the end-stage cancer patients hospitalized in the palliative care unit could not stand. Therefore, changing or stopping the administration of PIMs of Section K, that included medications that increased the risk of falling in elderly patients, was unnecessary.

Furthermore, most of the drugs classified in Sections D and K were benzodiazepines. The benzodiazepines used to treat patients with end-stage delirium could not be discontinued when patients were already experiencing delirium (9). Discontinuation of regularly used benzodiazepines would generate withdrawal phenomena, and cause unnecessary suffering in patients at the end of their lives (10). These reasons might have contributed to the lower rate of change of medications in this study. If we exclude PIMs classified in Sections D and K, and compare the rates of change of PIMs of this study with previous studies, 16 of 38 PIMs were changed in this study, while 189 of 385 PIMs were changed in the previous studies. The rate of reductions in prescribed PIMs, in sections other than D and K, was approximately the same."

to

"Discussion

The results of this study show that older cancer patients hospitalized in palliative care units have more difficulty reducing PIM detected by STOPP2 than patients admitted for other diseases. STOPP2 classifies PIMs into 13 types (16), and we detected several PIMs in Section A (Indication of medications), Section D (Central nervous system and psychotropic drugs), and Section K (Drugs that predictably increase the risk of falls in

older people) in this study. The same pattern was observed in two previous studies used for comparative purposes (3, 4). However, the rate of discontinuation or change in medications per section seems to differ from this study. First, in Section A, 16 of 30 medications were discontinued or changed in this study (rate of discontinuation or change of medications: 53.3%), while 11 of 22 medications were changed in the previous study (rate of discontinuation or change of medications: 50.0%). Most of the PIMs classified as Section A were duplications of drugs, and our results showed no significant difference in the possibility of correcting duplications of drugs, even for patients with end-stage cancer. However, in Section D, 4 of 38 medications were discontinued or changed in this study (rate of discontinuation or change of medications: 10.5%), while 25 of 64 medications were discontinued or changed in the previous study (rate of discontinuation/change of medications: 26.6%). In Section K, 7 of 68 medications were discontinued or changed in this study (rate of discontinuation/change of medications: 10.3%), while 6 of 14 medications were discontinued or changed in the previous studies (rate of discontinuation/change of medications: 42.9%). The risk of falling was low, because the end-stage cancer patients hospitalized in the palliative care unit could not stand up. Therefore, changing or stopping the administration of PIMs of Section K, which included medications that increased the risk of falling in older patients, was unnecessary.
Furthermore, most of the drugs classified in Sections D and K were benzodiazepines. The benzodiazepines used to treat patients with end-stage delirium could not be discontinued when patients were already experiencing delirium (19). Discontinuation of regularly used benzodiazepines would generate withdrawal phenomena and cause unnecessary suffering in patients at the end of their lives (20). These reasons might have contributed to the lower rate of discontinuation or change of medications in this study. If we exclude PIMs classified in Sections D and K and compare the rates of discontinuation/change of PIMs of this study with those of previous studies, 50 of 112 PIMs were discontinued or changed in this study, while 23 of 55 PIMs were discontinued or changed in the previous studies. The rate of reductions in prescribed PIMs, in sections other than D and K, was approximately the same.

Furthermore, we have changed and renumbered the following table (page 21, line 1 to page 23, line 1) from:

"Table 2. The classification of detected and changed PIMs.

Pharmacological classes	Detected PIMs	Changed PIMs
Total	71	18
Section A: Indication of medications	11	6
Section B: Cardiovascular system	4	2
Section C: Antiplatelet/Anticoagulant drugs	4	1
Section D: Central nervous system and psychotropic drugs	10	1
Section E: Renal system	8	1
Section F: Gastrointestinal system	4	2
Section G: Respiratory system	0	0
Section H: Musculoskeletal system	2	0
Section I: Urogenital system	0	0
Section J. Endocrine system	0	0
Section K: Drugs that predictably increase the risk of falls in older people	23	1

Section L: Analgesic drugs	5	5
Section N: Antimuscarinic/Anticholinergic drug burden	0	0

1 “

2

3 to

4

5 “Table 1. The classification of detected and discontinued/changed PIMs.

Pharmacological classes	Number of Detected PIMs by pharmacists	Number of recommendations for prescription discontinued or changed by pharmacists	Number of prescriptions discontinued or changed by physicians
Total	218	65	61
Section A: Indication of medications	30	16	16
Section B: Cardiovascular system	6	3	3

Section C: Antiplatelet/Anticoagulant drugs	9	3	3
Section D: Central nervous system and psychotropic drugs	38	4	4
Section E: Renal system	21	1	1
Section F: Gastrointestinal system	9	2	1
Section G: Respiratory system	0	0	0
Section H: Musculoskeletal system	6	1	0
Section I: Urogenital system	3	1	0
Section J: Endocrine system	1	1	1
Section K: Drugs that predictably increase the risk of falls in older people	68	7	7
Section L: Analgesic drugs	23	23	23
Section N: Antimuscarinic/Anticholinergic	4	3	2

drug burden

PIMs, potentially inappropriate medications “

Furthermore, we have changed and renumbered the following table (page 24, line 1 to line 4) from:

“Table 3. Results of the univariate analysis of the rates of change in PIMs in our palliative care unit compared with previous report.

	Change in medications		Odd ratio	95%CI	P value
	Yes	No			
Our hospital	18	53	0.373	0.202–0.663	P<0.01*
Previous study	346	380			

95%CI: 95% confidence interval

*P<0.05 was considered significant”

to

“Table 2. Results of the univariate analysis of the rates of discontinuation/change in PIMs in our palliative care unit compared with previous report.

		Discontinuation or change in medication		Odd ratio	
		Yes	No		
Studies	Our study	61	157	0.569	
	Previous study (4)	54	79		

95%CI, 95% confidence interval; PIMs, potentially inappropriate medications

*P<0.05 was considered significant"

Furthermore, we have added following references and renumbered (page 18, line 2 to page 19, line 17):

6. "Choukroun C, Leguelinel-Blache G, Roux-Marson C, et al. Impact of a pharmacist and geriatrician medication review on drug-related problems in older outpatients with cancer. J Geriatr Oncol 2021;12(1):57-63.
7. van Loveren FMAM, van Berlo-van de Laar IRF, Imholz ALT, et al. Prevalence and follow-up of potentially inappropriate medication and potentially omitted medication in older patients with cancer - The PIM POM study. J Geriatr Oncol 2021;12(1):80-4.
8. Whitman A, DeGregory K, Morris A, et al. Pharmacist-led medication assessment and deprescribing intervention for older adults with cancer and polypharmacy: a pilot study. Support Care Cancer 2018;26(12):4105-13.
9. Nipp RD, Ruddy M, Fuh CX, Zangardi ML, et al. Pilot randomized trial of a pharmacy intervention for older adults with cancer. Oncologist 2019;24(2):211-18.
10. American Geriatrics Society 2012 Beers Criteria Update Expert Panel. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2012; 60(4):616–31.
11. The 2019 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc. 2019;67(4):674–94.

12. Lindsay J, Dooley M, Martin J, et al. The development and evaluation of an oncological palliative care deprescribing guideline: the 'OncPal deprescribing guideline'. Support Care Cancer 2015;23(1):71-8.
13. Gallagher P, Ryan C, Byrne S, et al. STOPP (screening tool of older person's prescriptions) and START (screening tool to alert doctors to right treatment): consensus validation. Int J Clin Pharmacol Ther 2008;46(2):72-83.
14. Lavan AH, Gallagher P, Parsons C, et al. STOPPFrail (screening tool of older persons prescriptions in frail adults with limited life expectancy): consensus validation. Age Ageing 2017;46(4):600-7.
15. Curtin D, Gallagher P, O'Mahony D. Deprescribing in older people approaching end-of-life: development and validation of STOPPFrail version 2. Age Ageing 2021;50(2):465-71.
17. Ryan C, O'Mahony D, Kennedy J, et al. Potentially inappropriate prescribing in an Irish elderly population in primary care. Br J Clin Pharmacol 2009;68(6):936-47."

Furthermore, we have deleted following references:

"1. Thomas R E, Thomas B C. A systematic review of studies of the STOPP/START 2015 and American Geriatric Society Beers 2015 criteria in patients ≥ 65 Years. Curr Aging Sci 2019;12(2):121-54."

Comment 5: Reference to STROBE should appear in methods as opposed to introduction

Reply 5: Based on your comment, we have moved the reference to STOBE from the Introduction to the Methods.

Changes in the text: We have deleted the following text from the Introduction:

"We present this article following The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting checklist."

Furthermore, we have added the following text (page 6, line 13 to line 14):

"We present this article following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting checklist."

Comment 6: Aim and objectives need to be clearer

Reply 6: Based on your comment, we have revised the Introduction significantly. Please refer to reply 4 for changes in the text.

Comment 7: Methods; difficult to follow and make sense of
Study design needs to be elaborated on
The process of how PIMs were screened for is not clear; there is no mention of how recommendations were made and if changes were instigated

Reply 7: Based on your comment, we have added the process of how PIMs were detected. Moreover, to convey more accurately the pharmacists' recommendations, "change (in medications)" was changed to "discontinuation or change (in medications)".

Changes in the text: We have added the following text (page 6, line 16 to page 7, line 16):

"PIMs detection, Pharmacists' Recommendations and Discontinuation/Changes in Medication
In our palliative care unit, the following tasks have been carried out as part of our daily work since 2019. First, when a patient was admitted, the pharmacists detected the PIMs of the medications the patient was taking using STOPP2 criteria and recorded the details of PIMs in the medical record. Next, the pharmacists considered whether the detected PIMs should be discontinued, changed, or maintained. The pharmacists did not recommend the physician to discontinue or change the prescription if: (1) the detected PIMs were not very harmful medications, considering the overall condition of the patient; (2) the detected PIMs were important drugs for palliative care; and (3) the patient refused to discontinue or change the medication due to psychological or emotional problems. In all other cases, pharmacists would recommend physicians to discontinue or change the medication. Then, after receiving the recommendation from the pharmacists, the physician decided whether the recommendation was reasonable or not. If the recommendation was considered to be reasonable, the prescription was discontinued or changed. And finally, details of this process were documented in the patient's medical record on the day of admission. In this study, we accessed the medical records of these patients retrospectively and collected demographic data and descriptions of PIMs from

the medical records on the day of hospitalization in this study."

Furthermore, we have changed the following text (page 3, line 1 to page 4, line 11) from:

"Abstract
Background: Avoiding potentially inappropriate medications can reduce adverse events in aged cancer patients receiving palliative care. However, studies have not examined the extent to which pharmacists' recommendations reduce the prescription of potentially inappropriate medications. Therefore, we designed a cross-sectional study to determine the extent to which their recommendations play a role in reducing the prescription of potentially inappropriate medications for elderly cancer patients receiving palliative care.
Methods: Patients brought their medications with them upon admission to the hospital. These medications were examined by pharmacists and deemed inappropriate based on the Screening Tool of Older Persons' Prescriptions (STOPP) version 2. In this study, these 81 patients were surveyed, and the percentage of medications that were changed based on pharmacists' recommendations was compared with the previously published results of similar studies on elderly non-cancer inpatients, using univariate analysis.
Results: A total of 71 potentially inappropriate medications were detected in 475 medications administered to 81 patients. Of these, 18 medications were changed based on the recommendation of pharmacists (rate of change of medications: 25.4%). The univariate analysis results showed that this rate of change of medications was significantly lower than previous reports intended for non-cancer patients (47.7%). The rate of change of medications for benzodiazepines was extremely low, but for other drugs it was almost the same as in previous reports.
Conclusions: In the case of elderly end-stage cancer patients receiving palliative care, compared with elderly patients hospitalized for other diseases — it was more difficult to, on pharmacists' recommendations — change potentially inappropriate medications detected by STOPP. The low significance of discontinuing or changing benzodiazepines in subjects was a major reason it was difficult to reduce the prescription and, eventually, administer potentially inappropriate medications based on pharmacists' recommendations."

to

"Abstract
Background: Avoiding potentially inappropriate medications can reduce adverse events

in older cancer patients receiving palliative care. However, studies have not examined the extent to which pharmacists' recommendations reduce the prescription of potentially inappropriate medications. Therefore, we designed a cross-sectional study to determine the extent to which their recommendations play a role in reducing the prescription of potentially inappropriate medications for older cancer patients receiving palliative care.
Methods: Patients brought their medications with them upon admission to the hospital. These medications were examined by pharmacists and deemed inappropriate based on the Screening Tool of Older Persons' Prescriptions version 2 (STOPP2). In this study, these 220 patients were surveyed, and the percentage of medications that were discontinued or changed based on pharmacists' recommendations was compared with previously published results of similar studies on older non-cancer inpatients, using univariate analysis.
Results: A total of 218 potentially inappropriate medications were detected in 1261 medications administered to 220 patients. Of these, 61 medications were discontinued or changed based on the recommendation of pharmacists (rate of discontinuation/change of medications: 28.0%). The univariate analysis results showed that this rate of discontinuation or change of medications was significantly lower than that of a previous report intended for non-cancer patients (40.6%). The rate of discontinuation/change of medications for benzodiazepines was extremely low, but for other drugs it was almost the same as in the previous report.
Conclusions: In the case of older end-stage cancer patients receiving palliative care, compared with older patients hospitalized for other diseases, it was more difficult, on pharmacists' recommendations, to discontinue or change potentially inappropriate medications detected by STOPP2. The low significance of discontinuing or changing benzodiazepines in subjects was a major reason it was difficult to reduce the prescription and, eventually, administer potentially inappropriate medications based on pharmacists' recommendations."

Furthermore, we have changed the following text (page 10, line 11) from:

"Pharmacists' Recommendations and Changes in Medications"

to

"Pharmacists' Recommendations and Discontinuation/Changes in Medications"

Furthermore, we have changed the following text (page 10, line 17 to page 11, line 2) from:

"The rate of change in medications was 25.4% (18/71). A univariate analysis showed that the rate of change in medications in our palliative unit was significantly lower than in previous studies (Table 3)."

to

"The rate of discontinuation/change in medications was 28.0% (61/218). A univariate analysis showed that the rate of discontinuation or change in medications in our palliative unit was significantly lower than that in the most recent previous study (rate of discontinuation/change of medications: 40.6%) (Table 2)."

Furthermore, we have changed the following text (page 11, line 4 to page 13, line 7) from:

"Discussion

The results of this study indicate that it is more difficult to reduce the prescription of PIMs in cancer patients hospitalized in palliative care units, than in patients hospitalized with other diseases. Moreover, 75 of the 81 patients in the study were dead by June 1, 2021, when the medical files were examined. As these 75 patients died an average of 20.8 days after the date of detection of PIMs, most of the subjects were likely to have been end-stage cancer patients. In addition, the fact that they were admitted to our palliative care unit, suggests that they required intensive palliative care. Therefore, the results of this study indicate that it is more difficult to reduce PIMs in hospitalized end-stage cancer patients receiving intensive palliative care. Furthermore, the results of the sensitivity analysis indicated that the main result of this study was robust. This was because the main results were the same — regardless of whether the PIMs prescribed to patients whose PIMs were not assessed at the time of hospitalization from October 9, 2020, to February 28, 2021 — were assumed to have been changed based on pharmacists' recommendations. STOPP classifies PIMs into 13 types (7), and we detected several PIMs in Section A (Indication of medications), Section D (Central nervous system and psychotropic drugs), and Section K (Drugs that predictably increase the risk of falls in older people) in this study. The same pattern was observed in two previous studies used for comparative purposes (3, 4). However, the rate of change in medications per section seems to differ from this study. First, in Section A, 6 of 11 medications were changed in this study (rate

of change of medications: 54.5%), while 56 of 113 medications were changed in the previous studies (rate of change of medications: 49.6%). Most of the PIMs classified as Section A were duplications of drugs, and our results showed no significant difference in the possibility of correcting duplications of drugs, even for patients with end-stage cancer. However, in Section D, one out of ten medications were changed in this study (rate of change of medications: 10.0%), while 106 of 286 medications were changed in the previous studies (rate of change of medications: 37.1%). In Section K, one of 23 medications was changed in this study (rate of change of medications: 4.3%), while 51 of 113 medications were changed in the previous studies (rate of change of medications: 45.1%). The risk of falling was low, because the end-stage cancer patients hospitalized in the palliative care unit could not stand. Therefore, changing or stopping the administration of PIMs of Section K, that included medications that increased the risk of falling in elderly patients, was unnecessary.

Furthermore, most of the drugs classified in Sections D and K were benzodiazepines. The benzodiazepines used to treat patients with end-stage delirium could not be discontinued when patients were already experiencing delirium (9). Discontinuation of regularly used benzodiazepines would generate withdrawal phenomena, and cause unnecessary suffering in patients at the end of their lives (10). These reasons might have contributed to the lower rate of change of medications in this study. If we exclude PIMs classified in Sections D and K, and compare the rates of change of PIMs of this study with previous studies, 16 of 38 PIMs were changed in this study, while 189 of 385 PIMs were changed in the previous studies. The rate of reductions in prescribed PIMs, in sections other than D and K, was approximately the same.

However, the rate of change in medications for PIMs in sections other than D and K, may not differ for terminal cancer patients hospitalized in the palliative care unit, compared to other patients. This suggests that even end-stage cancer patients hospitalized in the palliative care unit, may benefit from efforts to detect and reduce the prescription of PIMs using STOPP."

to

"Discussion

The results of this study show that older cancer patients hospitalized in palliative care units have more difficulty reducing PIM detected by STOPP2 than patients admitted for other diseases. STOPP2 classifies PIMs into 13 types (16), and we detected several PIMs in Section A (Indication of medications), Section D (Central nervous system and

psychotropic drugs), and Section K (Drugs that predictably increase the risk of falls in older people) in this study. The same pattern was observed in two previous studies used for comparative purposes (3, 4). However, the rate of discontinuation or change in medications per section seems to differ from this study. First, in Section A, 16 of 30 medications were discontinued or changed in this study (rate of discontinuation or change of medications: 53.3%), while 11 of 22 medications were changed in the previous study (rate of discontinuation or change of medications: 50.0%). Most of the PIMs classified as Section A were duplications of drugs, and our results showed no significant difference in the possibility of correcting duplications of drugs, even for patients with end-stage cancer. However, in Section D, 4 of 38 medications were discontinued or changed in this study (rate of discontinuation or change of medications: 10.5%), while 25 of 64 medications were discontinued or changed in the previous study (rate of discontinuation/change of medications: 26.6%). In Section K, 7 of 68 medications were discontinued or changed in this study (rate of discontinuation/change of medications: 10.3%), while 6 of 14 medications were discontinued or changed in the previous studies (rate of discontinuation/change of medications: 42.9%). The risk of falling was low, because the end-stage cancer patients hospitalized in the palliative care unit could not stand up. Therefore, changing or stopping the administration of PIMs of Section K, which included medications that increased the risk of falling in older patients, was unnecessary.

Furthermore, most of the drugs classified in Sections D and K were benzodiazepines. The benzodiazepines used to treat patients with end-stage delirium could not be discontinued when patients were already experiencing delirium (19). Discontinuation of regularly used benzodiazepines would generate withdrawal phenomena and cause unnecessary suffering in patients at the end of their lives (20). These reasons might have contributed to the lower rate of discontinuation or change of medications in this study. If we exclude PIMs classified in Sections D and K and compare the rates of discontinuation/change of PIMs of this study with those of previous studies, 50 of 112 PIMs were discontinued or changed in this study, while 23 of 55 PIMs were discontinued or changed in the previous studies. The rate of reductions in prescribed PIMs, in sections other than D and K, was approximately the same.

However, the rate of discontinuation or change in medications for PIMs in sections other than D and K, may not differ for terminal cancer patients hospitalized in the palliative care unit, compared to other patients. This suggests that even end-stage cancer patients hospitalized in the palliative care unit, may benefit from efforts to detect and reduce the prescription of PIMs using STOPP2."

Comment 8: I don't understand the point of the preliminary study; were these patients included in the final analysis

Reply 8: The patients who were included in the preliminary study were included in the final analysis. Please refer to the reply 4 to your comment 4 for changes in the text.

Comment 9: Statement on ethics could be more concise

Reply 9: Based on your comment, we have simplified the statement on ethics.

Changes in the text: We have deleted the following text from the Methods section:

"The institutional ethics board waived the requirement of informed consent."

Comment 10: The statistical analysis section is unclear (e.g. what does "using EZR in R commander version 1.37" mean?)

Reply 10: Based on your comment, we have revised the Statistical Analysis significantly.

Changes in the text: We have changed the following text (page 9, line 13 to line 17) from:

"Statistical Analysis
A univariate analysis was performed using EZR in R commander version 1.37 (8). All analyses were two-sided, and the statistical significance was set at 0.05. This cross-sectional study extracted data from the medical records of patients already out of the hospital. Therefore, some patients could not be enrolled in the study, because PIMs were not assessed despite their hospitalization during the enrollment for this study (October 9, 2020, to February 28, 2021). As a sensitivity analysis, we performed a univariate analysis identical to the main analysis, assuming that PIMs were detected in these cases on the day of hospitalization and were either changed or not changed based on pharmacists' recommendations."

to

"Statistical Analysis

A univariate analysis was performed to compare the PIMs' discontinued/changed rate of subjects in this study with those in the most recent previous study. All analyses were two-sided, and the statistical significance was set at 0.05. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics (18).”

Comment 11: “Therefore, some patients could not be enrolled in the study, because PIMs were 12 not assessed despite their hospitalization during the enrollment for this study” – I don't understand this and it doesn't seem directly relevant to statistical analysis

Reply 11: The text you indicated as unnecessary describes the PIMs detected for the sensitivity analysis. We believe that your comment implies that sensitivity analysis is not necessary for this study. The same suggestion has been given to us by Reviewer A. Based on your comment and Reviewer A's comment, we have removed the description of sensitivity analysis from this manuscript.

Changes in the text: We have deleted the following text from the Methods section:

As a sensitivity analysis, we performed a univariate analysis identical to the main analysis, assuming that PIMs were detected in these cases on the day of hospitalization and were either changed or not changed based on pharmacists' recommendations.

Furthermore, we have also deleted the following text from the Results section:

Sensitivity Analysis
From October 9, 2020, to February 28, 2021, three patients aged 65 years or older were not assessed for PIMs while hospitalized. Three PIMs were detected in the case of two of these three patients. Assuming that these three PIMs were changed based on pharmacists' recommendations, the results were consistent with the main result (Table 4). Furthermore, assuming that these three PIMs were not changed, the results were consistent with the main result (Table 5).

In addition, we have also deleted the following text from the Discussion section:

Furthermore, the results of the sensitivity analysis indicated that the main result of this study was robust. This was because the main results were the same — regardless of whether the PIMs prescribed to patients whose PIMs were not assessed at the time of hospitalization from October 9, 2020, to February 28, 2021 — were assumed to have been changed based on pharmacists' recommendations.

Lastly, we have also deleted tables 4 and 5.

Comment 12: Results
"Seventy-five of these patients had already died, 23 and the survival time after evaluation for the presence of PIMs was 20.8 ± 20.9 days 24 (mean ± SD)"; don't see the relevance of this

Reply 12: Based on your comment, we thought it was unnecessary to mention the patient's prognosis. We have deleted the text related to this.

Changes in the text: We have deleted the following text:

"Eighty-one consecutive patients were enrolled retrospectively from February 28, 2021, resulting in the enrollment of patients admitted between October 9, 2020, and February 28, 2021. All the patients were Japanese. Seventy-five of these patients had already died, and the survival time after evaluation for the presence of PIMs was 20.8 ± 20.9 days (mean ± SD). The remaining six patients were confirmed to be alive as of June 1, 2021."

Furthermore, we have deleted the following text:

"Moreover, 75 of the 81 patients in the study were dead by June 1, 2021, when the medical files were examined. As these 75 patients died an average of 20.8 days after the date of detection of PIMs, most of the subjects were likely to have been end-stage cancer patients. In addition, the fact that they were admitted to our palliative care unit, suggests that they required intensive palliative care. Therefore, the results of this study indicate that it is more difficult to reduce PIMs in hospitalized end-stage cancer patients receiving intensive palliative care. Furthermore, the results of the sensitivity analysis indicated that the main result of this study was robust. This was because the main results were the same — regardless of whether the PIMs prescribed to patients whose PIMs were not assessed at

the time of hospitalization from October 9, 2020, to February 28, 2021 — were assumed to have been changed based on pharmacists' recommendations."

Comment 13: "Pharmacists' Recommendations and Changes in Medication" not outlined in methods

Reply 13: Based on your comment, we have included details of the pharmacist's recommendations in our Methods section.

Changes in the text: We have added the following text (page 6, line 16 to page 7, line 16):

"PIMs detection, Pharmacists' Recommendations and Discontinuation/Changes in Medications
In our palliative care unit, the following tasks have been carried out as part of our daily work since 2019. First, when a patient was admitted, the pharmacists detected the PIMs of the medications the patient was taking using STOPP2 criteria and recorded the details of PIMs in the medical record. Next, the pharmacists considered whether the detected PIMs should be discontinued, changed, or maintained. The pharmacists did not recommend the physician to discontinue or change the prescription if: (1) the detected PIMs were not very harmful medications, considering the overall condition of the patient; (2) the detected PIMs were important drugs for palliative care; and (3) the patient refused to discontinue or change the medication due to psychological or emotional problems. In all other cases, pharmacists would recommend physicians to discontinue or change the medication. Then, after receiving the recommendation from the pharmacists, the physician decided whether the recommendation was reasonable or not. If the recommendation was considered to be reasonable, the prescription was discontinued or changed. And finally, details of this process were documented in the patient's medical record on the day of admission. In this study, we accessed the medical records of these patients retrospectively and collected demographic data and descriptions of PIMs from the medical records on the day of hospitalization in this study."

Comment 14: "A univariate analysis showed that 2 the rate of change in medications in our palliative unit was significantly lower than in 3 previous studies (Table 3" not a valid comparison

Reply 14: Based on your comment, we have limited the number of previous studies that compare the PIMs detected in this study to the most recent one previous study. We then restructured the study. Please refer to the reply 4 to your comment 4 for changes in the text.

Comment 15: "Sensitivity Analysis" – I don't follow this section; it also appears to be heavily reliant on assumptions

Reply 15: Based on your comment, we have removed the description of sensitivity analysis from this manuscript. Please refer to the reply 11 to your comment 11 for changes in the text.

Comment 16: Table 1: not terribly informative; could be presented as written text; detailed breakdown of all cancer types not necessary

Reply 16: Based on your comment, we have deleted Table 1 and incorporated the data in the text.

Changes in the text: We have deleted Table 1.

Furthermore, we have added the following text (page 10, line 3 to line 6):

"All patients enrolled in this study were Japanese. Participants' age was 79.5±7.4 years old (mean±SD), and 131 were males and 89 were females. The most common type of cancer was gastric cancer, with 35 cases. This was followed by colorectal cancer with 32 cases and lung cancer with 29 cases."

Comment 17: Table 2: gives no proper insight into the actual PIMs identified

Reply 17: Based on your comment, we have substantially revised Table 2. Please refer to the reply 14 to your comment 14 for changes in the text.

Comment 18: Table 3+4 not valid comparisons

Reply 18: Based on your comment, we have substantially restructured Table 3 and deleted Table 4. Please refer to replies 14 and 15 to your comments 14 and 15 for changes in the

text.

Comment 19: Needs to be revised as direct comparisons with other study are not valid

Reply 19: Based on your comment, we have restructured the comparison with other studies. Please refer to the reply 14 to your comment 14 for changes in the text.

Comment 20: Why was STOPP chose as opposed to OncPal or even STOPPFrail?

Reply 20: Based on your comment, we have added descriptions of OncPal and STOPPFrail to the Discussion.

Changes in the text: We have added the following text (page 13, line 8 to page 14, line 2):

"STOPP2 is a criterion that can more accurately detect PIMs using blood test results as a reference (16). Furthermore, it is so easy to use that a trained pharmacist can complete the assessment in a few minutes (5, 17). Therefore, we used STOPP2 to detect PIMs in our daily practice, and we used the medical records containing its results in this study. However, STOPP, an older version of STOPP2, has been shown to significantly improve medication appropriateness during hospitalization for acute illness in older patients, and its effects can be maintained for 6 months after intervention. STOPP2, like STOPP, is supposed to be applied during hospitalization for acute illness in older patients, so STOPP2 might not be optimal for end-stage cancer patients hospitalized in the palliative care unit. Better evidence might be obtained through a similar study performed using OncPal, a criterion developed to detect PIMs in cancer patients receiving end-of-life care, or STOPPFrail, a criterion developed to detect PIMs in frail patients with limited life expectancy."

RESPONSES TO REVIEWER D'S COMMENTS:

Comment 1: This study aimed to determine the extent to which their recommendations play a role in reducing the prescription of potentially inappropriate medications for elderly cancer patients receiving palliative care.
The subject is important to be addressed.

Reply 1: Thank you for your appreciation of our manuscript. We corrected the manuscript in accordance with your comments.

Comment 2: However, I have some concerns.

Reply 2: Based on your comments, we have revised our manuscript.

Comment 3: Main Issues
Authors used the STOPP2 criteria for identifying PIMs in patients receiving palliative care and their survival might be less than 6 months.
The population with limited life expectancy receiving palliative care is different from older adults with long life expectancy, therefore the criteria for general older adults may not be optimal for this population.
Explicit tool, STOPPFrail, to assist clinicians with deprescribing medications in frailer older adults with limited life expectancy in all healthcare settings has been first developed in 2017 and recently updated. Also, oncological palliative care deprescribing guideline, the 'OncPal deprescribing guideline has been already developed.
These guidelines may be more appropriate for this population.
These issues need to be explained.

Reply 3: STOPP2 is a criterion that can more accurately detect PIMs using blood test results as a reference. Furthermore, it is so easy to use that a trained pharmacist can complete the assessment in a few minutes. Therefore, we selected STOPP2 to detect PIMs in our daily practice, and we used the medical records containing its results in this study. However, as you mentioned, it may not have been optimal to use the STOPP 2 criteria in a population with limited life expectancy receiving palliative care, as this is different from the elderly who have a longer life expectancy. Based on your comments and reviewer C's comments, we have mentioned the reason for using STOPP 2 for this study and mentioned STOPPPFrail and OncPal in the text.

Changes in the text: We have changed following text (page 4, line 16 to page 6, line 9) from:

"Introduction
Recently, it was reported that potentially inappropriate medications (PIMs) were associated with higher rates of hospitalization and increased the cost of health care in the

elderly (1). It was also reported that pharmacists could reduce instances of prescribing PIMs for outpatients and inpatients, and their role has been emphasized (2–4). The role of pharmacists was also examined in the field of palliative care, as avoiding PIMs has been reported to reduce adverse events and fight untimely death in elderly cancer patients receiving palliative care (5, 6). However, to our knowledge, studies have not examined the extent to which pharmacists' recommendations can play a role in the reduction of the prescription of PIMs, in elderly cancer patients receiving palliative care. In the palliative care unit where this study was conducted, pharmacists routinely detect PIMs based on the Screening Tool of Older Persons' Prescriptions (STOPP) version 2, by examining the medications bought by patients on admission, and recommending physicians to change medications (7). Therefore, we designed a cross-sectional study to determine the extent to which pharmacists' recommendations can reduce the prescription of PIMs in elderly cancer patients receiving palliative care.

Kimura et al. reported how the prescription of several PIMs, based on STOPP, could have been avoided for elderly Japanese patients hospitalized for non-cancer diseases through pharmacists' recommendations (3, 4). By comparing the results of these studies with those conducted in our daily practice, we examined the extent to which pharmacists' recommendations can decrease the prescription of PIMs in elderly cancer patients receiving palliative care. We present this article following The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting checklist."

to

"Introduction

Recently, potentially inappropriate medications (PIMs) in older cancer patients have become a growing serious clinical problem, especially after Chen et al. and Mostafa et al. reported that reducing PIMs can reduce adverse events and prevent premature death in older cancer patients (1, 2). To reduce PIMs, it has been reported that not only physicians, who prescribe, but also pharmacists, who detect PIMs and recommend to physicians to discontinue or change the prescription, are important (3–5). Furthermore, many researchers have reported that pharmacists can reduce PIMs for older cancer patients as well, highlighting the role of these professionals in the field of cancer medicine (6–9). However, all these studies were conducted in cancer patients receiving anticancer therapy, and there have been no reports of pharmacists contributing to the reduction of PIMs in older cancer patients hospitalized in the palliative care unit. Therefore, we designed this study to investigate whether pharmacists contribute to PIMs reduction in older cancer

patients hospitalized in the palliative care unit.
Criteria such as Beers Criteria, OncPal, Screening Tool of Older Persons' Prescriptions (STOPP), Screening Tool of Older Persons' Prescriptions in Frail adults with limited life expectancy (STOPPFrail), among others, have been proposed to detect PIMs (10–15). The most recent version of STOPP, STOPP version 2 (STOPP2), provides more detailed criteria for determining PIMs, including the use of blood test results (16). It is also a simple and practical criterion that can be evaluated in a few minutes by trained pharmacists (5, 17). In our palliative care unit, we use STOPP2 among other criteria for detecting PIMs, because blood tests are basically performed upon admission. In our daily clinical practice, pharmacists detect PIMs when a patient is hospitalized in the palliative care unit and recommend to the physician to discontinue or change the prescriptions to reduce PIMs. In this study, we retrospectively reviewed the patients' medical records and evaluated the PIMs' discontinuation/change rates at our palliative care unit. Furthermore, by comparing our PIMs' discontinuation/change rates with those of a previous study, in which pharmacists reduced PIMs by intervening using the STOPP2 criterion, we investigated whether pharmacists contribute to reducing PIMs in older cancer patients hospitalized in the palliative care unit."

Furthermore, we have added he following text (page 13, line 8 to page 14, line 2):

"STOPP2 is a criterion that can more accurately detect PIMs using blood test results as a reference (16). Furthermore, it is so easy to use that a trained pharmacist can complete the assessment in a few minutes (5, 17). Therefore, we used STOPP2 to detect PIMs in our daily practice, and we used the medical records containing its results in this study. However, STOPP, an older version of STOPP2, has been shown to significantly improve medication appropriateness during hospitalization for acute illness in older patients, and its effects can be maintained for 6 months after intervention. STOPP2, like STOPP, is supposed to be applied during hospitalization for acute illness in older patients, so STOPP2 might not be optimal for end-stage cancer patients hospitalized in the palliative care unit. Better evidence might be obtained through a similar study performed using OncPal, a criterion developed to detect PIMs in cancer patients receiving end-of-life care, or STOPPFrail, a criterion developed to detect PIMs in frail patients with limited life expectancy."

Comment 4: So, conclusion that it was more difficult to change PIMS detected by STOPP in patients with limited expectancy compared with general older population may

not be inappropriate.

Reply 4: Based on your comment, we did not make any significant changes to our conclusions. However, based on the comment of Reviewer C, we have changed "elderly" to "older" throughout the manuscript.

Changes in the text: We have changed following text (page 12, line 14 to line 18) from:

"Conclusion
In the records of elderly patients hospitalized with end-stage cancer and receiving palliative care, compared with those of elderly patients hospitalized for other diseases, PIMs detected by STOPP were more difficult to reduce based on pharmacists' recommendations. The low significance of discontinuing or changing benzodiazepines in subjects, was a major reason for the difficulty in reducing the prescription of PIMs based on pharmacists' recommendations."

to

"Conclusion
In the records of older patients hospitalized with end-stage cancer and receiving palliative care, compared with those of older patients hospitalized for other diseases, PIMs detected by STOPP were more difficult to reduce based on pharmacists' recommendations. The low significance of discontinuing or changing benzodiazepines in subjects, was a major reason for the difficulty in reducing the prescription of PIMs based on pharmacists' recommendations."