

## Peer Review File

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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 STOPP version 2. 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

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

10  
11 **Comment 3:** The authors often wrote how many PIM changes were implemented by the  
12 physicians based on the pharmacist’s recommendations. This is totally confusing because  
13 the physicians could not know about all PIM found in the retrospective chart review. They  
14 could only know of the few changes already suggested to them by pharmacists during the  
15 hospitalization of patients and of whom most were already dead the second PIM  
16 assessment was done.

17  
18 **Reply 3:** PIMs were assessed only once when the patient was admitted to the palliative  
19 care unit. It was not assessed twice. The pharmacist assessed the medications that the  
20 patient was taking at the time of admission using the STOPP version 2 criteria. If the  
21 pharmacist thought that the PIM detected at the time of admission should be changed,  
22 they would recommend a prescription change to the physician. Conversely, if the  
23 pharmacist thought that the detected PIM was difficult to change, they would not  
24 recommend anything to the physician. We have added text to the Methods to make it  
25 easier to understand the research methods. Please refer to reply 2 for changes in the text.

26  
27 **Comment 4:** Page 6, sensitivity analysis: Actually it makes no sense to me to include 81  
28 study participants in this study at all when there are 3 who did not get an initial PIM  
29 assessment. I would like to encourage the authors to do all analyses with n=78 as main  
30 analysis and drop the sensitivity analysis. In the end there should be 3 and not 5 tables.

31  
32 **Reply 4:** Based on your comment, we have removed the description of sensitivity analysis  
33 from this manuscript.

34  
35 **Changes in the text:** We have deleted the following from the Methods section:

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

4  
5 Furthermore, we have also deleted the following from the Results section:

6  
7 “Sensitivity Analysis

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

14  
15 “Furthermore, the results of the sensitivity analysis indicated that the main result of this  
16 study was robust. This was because the main results were the same — regardless of  
17 whether the PIMs prescribed to patients whose PIMs were not assessed at the time of  
18 hospitalization from October 9, 2020, to February 28, 2021 — were assumed to have been  
19 changed based on pharmacists’ recommendations.”

20  
21 In addition, we have deleted tables 4 and 5.

22  
23 **Comment 5:** Table 2: Please add a column for „PIM changes by pharmacists at palliative care  
24 ward admission”. I think these numbers are more relevant to understand the column “Changed  
25 PIMs” than the column “Detected PIMs at retrospective chart review”, which I would name this  
26 way to make it more understandable that there were 2 times of PIM assessments.

27  
28 **Reply 5:** We are concerned that you misunderstood that we assessed PIM twice in this  
29 study. In this study, we only assessed PIM once, at the time of admission. We believe that  
30 the reason for your confusion is the inadequate description in the Methods and Results  
31 sections of this article. Based on your comment and the comment of Reviewer B ("The  
32 sample size is rather low to allow sound conclusions in respect to the research question"),  
33 and the comments of Reviewer C ("Methods; difficult to follow and make sense of Study  
34 design needs to be elaborated on" and "A univariate analysis showed that 2 the rate of  
35 change in medications in our palliative unit was significantly lower than in 3 previous  
36 studies (Table 3) not a valid comparison"), we have substantially modified the study.

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

10  
11 **Changes in the text:** We have changed Table 2 (page 21, line 1 to page 23, line 1) from:

12  
13 “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.

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

1 PIMs, potentially inappropriate medications “

2

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

7

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

15

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

17

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

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

3  
4 **RESPONSES TO REVIEWER B'S COMMENTS:**

5  
6 **Comment 1:** The authors present a cross-sectional single center cohort-study to assess  
7 the prevalence of potentially inappropriate medications (PIMs) in advanced cancer  
8 patients.

9 **Strengths:**

10 The research question is of relevance for clinicians and policy makers and the chosen  
11 research method adequate. The manuscript is written very well (but please notice that I  
12 am not a native speaker) and well structured. The discussion, noted limitations and  
13 conclusions are sound. The same applies to tables and figures.

14  
15 **Reply 1:** Thank you for your appreciation of our manuscript. We corrected the manuscript  
16 in accordance with your comments.

17  
18 **Comment 2:** The sample size is rather low to allow sound conclusions in respect to the  
19 research question.

20  
21 **Reply 2:** Based on your comment and the comments of Reviewer C ("Methods; difficult  
22 to follow and make sense of Study design needs to be elaborated on" and "A univariate  
23 analysis showed that 2 the rate of change in medications in our palliative unit was  
24 significantly lower than in 3 previous studies (Table 3) not a valid comparison"), we have  
25 substantially modified this study.

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

35  
36 **Changes in the text:** We have changed the following text (page 3, line 15 to page 4, line



1 4) from:

2  
3 “Results: A total of 71 potentially inappropriate medications were detected in 475  
4 medications administered to 81 patients. Of these, 18 medications were changed based  
5 on the recommendation of pharmacists (rate of change of medications: 25.4%). The  
6 univariate analysis results showed that this rate of change of medications was  
7 significantly lower than previous reports intended for non-cancer patients (47.7%). The  
8 rate of change of medications for benzodiazepines was extremely low, but for other drugs  
9 it was almost the same as in previous reports.”

10  
11 to

12  
13 “Results: A total of 218 potentially inappropriate medications were detected in 1261  
14 medications administered to 220 patients. Of these, 61 medications were discontinued or  
15 changed based on the recommendation of pharmacists (rate of discontinuation/change of  
16 medications: 28.0%). The univariate analysis results showed that this rate of  
17 discontinuation or change of medications was significantly lower than that of the previous  
18 report intended for non-cancer patients (40.6%). The rate of discontinuation/change of  
19 medications for benzodiazepines was extremely low, but for other drugs it was almost the  
20 same as in the previous report.”

21  
22 Furthermore, we have changed the following text (page 7, line 18 to page 8, line 11) from:

23  
24 “Sample Size Calculation

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

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

3  
4 to

#### 5 6 “Sample Size Calculation

7 To compare the PIMs' discontinued/changed rate in this study with that in the most recent  
8 previous study in which pharmacists reduced PIMs through intervention using the STOPP  
9 2Criterion, we examined the sample size calculation. Before the main study, we  
10 conducted a preliminary study to calculate the sample size. The preliminary study was  
11 conducted on patients hospitalized in the palliative care unit from January 1 to February  
12 28, 2021, and the medical records at the time of admission were reviewed to investigate  
13 PIMs' discontinued/changed rate. The PIMs' discontinued/changed rate was 31.0%.  
14 Based on the results of this preliminary study, the sample size required to compare the  
15 PIMs' discontinued/changed rate in this study with the PIMs discontinued/changed rate  
16 in the most recent previous study was 220. The  $\alpha$  risk and  $\beta$  risk were set at 0.05 and 0.80,  
17 respectively.”

18  
19 Furthermore, we have changed the following text (page 10, line 1 to page 11, line 2) from:

#### 20 21 “Incidence of PIMs

22 Eighty-one consecutive patients were enrolled retrospectively from February 28, 2021,  
23 resulting in the enrollment of patients admitted between October 9, 2020, and February  
24 28, 2021. All the patients were Japanese. Seventy-five of these patients had already died,  
25 and the survival time after evaluation for the presence of PIMs was  $20.8 \pm 20.9$  days  
26 (mean  $\pm$  SD). The remaining six patients were confirmed to be alive as of June 1, 2021.  
27 Table 1 shows the characteristics of the 81 patients. One or more PIMs were found in 40  
28 of the 81 target patients (49.9%). Four hundred seventy-five medications were prescribed  
29 to them and using STOPP, 71 were determined to be PIMs. The classification of the  
30 detected PIMs is shown in Table 2.

#### 31 32 Pharmacists' Recommendations and Changes in Medications

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

36 The rate of change in medications was 25.4% (18/71). A univariate analysis showed that

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

3  
4 to

#### 5 6 “Incidence of PIMs

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

11 One or more PIMs were found in 112 of the 220 target patients (50.9%). Regarding the  
12 medication, 1261 were prescribed to them, and using STOPP2, 218 were determined to  
13 be PIMs. The classification of the detected PIMs is shown in Table 1.

#### 14 15 Pharmacists’ Recommendations and Discontinuation/Changes in Medications

16 The pharmacists recommended physicians to discontinue or change 65 PIMs. The  
17 physician accepted the recommendations and discontinued/changed the prescription for  
18 61 PIMs. Conversely, the physicians did not discontinue or change four PIMs, despite the  
19 recommendation of pharmacists. Table 2 shows the classification of the PIMs that were  
20 discontinued or changed based on pharmacists’ recommendations.

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

25  
26 Furthermore, we have changed the following text (page 11, line 8 to page 13, line 2) from:

27  
28 “STOPP classifies PIMs into 13 types (7), and we detected several PIMs in Section A  
29 (Indication of medications), Section D (Central nervous system and psychotropic drugs),  
30 and Section K (Drugs that predictably increase the risk of falls in older people) in this  
31 study. The same pattern was observed in two previous studies used for comparative  
32 purposes (3, 4). However, the rate of change in medications per section seems to differ  
33 from this study. First, in Section A, 6 of 11 medications were changed in this study (rate  
34 of change of medications: 54.5%), while 56 of 113 medications were changed in the  
35 previous studies (rate of change of medications: 49.6%). Most of the PIMs classified as  
36 Section A were duplications of drugs, and our results showed no significant difference in

1 the possibility of correcting duplications of drugs, even for patients with end-stage cancer.  
2 However, in Section D, one out of ten medications were changed in this study (rate of  
3 change of medications: 10.0%), while 106 of 286 medications were changed in the  
4 previous studies (rate of change of medications: 37.1%). In Section K, one of 23  
5 medications was changed in this study (rate of change of medications: 4.3%), while 51 of  
6 113 medications were changed in the previous studies (rate of change of medications:  
7 45.1%). The risk of falling was low, because the end-stage cancer patients hospitalized in  
8 the palliative care unit could not stand. Therefore, changing or stopping the administration  
9 of PIMs of Section K, that included medications that increased the risk of falling in elderly  
10 patients, was unnecessary.

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

21  
22 to

23  
24 “STOPP2 classifies PIMs into 13 types (16), and we detected several PIMs in Section A  
25 (Indication of medications), Section D (Central nervous system and psychotropic drugs),  
26 and Section K (Drugs that predictably increase the risk of falls in older people) in this  
27 study. The same pattern was observed in two previous studies used for comparative  
28 purposes (3, 4). However, the rate of discontinuation or change in medications per section  
29 seems to differ from this study. First, in Section A, 16 of 30 medications were  
30 discontinued or changed in this study (rate of discontinuation or change of medications:  
31 53.3%), while 11 of 22 medications were changed in the previous studies (rate of  
32 discontinuation or change of medications: 50.0%). Most of the PIMs classified as Section  
33 A were duplications of drugs, and our results showed no significant difference in the  
34 possibility of correcting duplications of drugs, even for patients with end-stage cancer.  
35 However, in Section D, 4 of 38 medications were discontinued or changed in this study  
36 (rate of discontinuation or change of medications: 10.5%), while 25 of 64 medications

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

20  
21 **Comment 3:** Some paragraphs are not in the correct place. For example, much of what is  
22 reported under "power calculation" are rather results.

23  
24 **Reply 3:** Based on your comment, we have restructured the Methods. Please see reply 2  
25 for the text changes.

26  
27 **Comment 4:** Moreover, much of the STROBE list should be revisited. Already the first  
28 item is not correctly respected, as the title does not convey the research method. Instead,  
29 findings are already reported in the title. I recommend thorough and detailed revision.

30  
31 **Reply 4:** Based on your comment, we have changed the title of this manuscript and  
32 revised the STROBE checklist thoroughly.

33  
34 **Changes in the text :** We have changed the following text (page 1, line 2 to line 5) from:  
35  
36 “Potentially inappropriate medications for end-stage cancer patients are more difficult to

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

3  
4 to

5  
6 “Potentially inappropriate medications discontinued or changed based on pharmacists’  
7 recommendations in older end-stage cancer patients receiving palliative care: a cross-  
8 sectional study”

9  
10 **Comment 5:** Also, I recommend some more literature research to discuss and reference the most  
11 relevant literature.

12  
13 **Reply 5:** Based on your comment and the comment of reviewers C and D, we have added  
14 11 references and revised the Introduction significantly. In addition, we have removed  
15 references by Thomas et al. that we consider less important to the revised Introduction,  
16 and renumbered the references.

17  
18 **Changes in the text:** We have changed the following text (page 4, line 16 to page 6, line  
19 9), from:

20  
21 “Introduction

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

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

8  
9 to

## 11 “Introduction

12 Recently, potentially inappropriate medications (PIMs) in older cancer patients have  
13 become a growing serious clinical problem, especially after Chen et al. and Mostafa et al.  
14 reported that reducing PIMs can reduce adverse events and prevent premature death in  
15 elderly cancer patients (1, 2). To reduce PIMs, it has been reported that not only  
16 physicians, who prescribe, but also pharmacists, who detect PIMs and recommend to the  
17 physicians to discontinue or change the prescription, are important (3–5). Furthermore,  
18 many researchers have reported that pharmacists can reduce PIMs for older cancer  
19 patients as well, highlighting the role of these professionals in the field of cancer medicine  
20 (6–9). However, all these studies were conducted in cancer patients receiving anticancer  
21 therapy, and there have been no reports of pharmacists contributing to the reduction of  
22 PIMs in older cancer patients hospitalized in the palliative care unit. Therefore, we  
23 designed this study to investigate whether pharmacists contribute to PIMs reduction in  
24 older cancer patients hospitalized in the palliative care unit.

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

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

5  
6 Furthermore, we have added the following references and renumbered them (page 18,  
7 line 2 to page 19, line 17):

8  
9 “6. Choukroun C, Leguelinel-Blache G, Roux-Marson C, et al. Impact of a  
10 pharmacist and geriatrician medication review on drug-related problems in older  
11 outpatients with cancer. *J Geriatr Oncol* 2021;12(1):57-63.

12 7. van Loveren FMAM, van Berlo-van de Laar IRF, Imholz ALT, et al. Prevalence  
13 and follow-up of potentially inappropriate medication and potentially omitted medication  
14 in older patients with cancer - The PIM POM study. *J Geriatr Oncol* 2021;12(1):80-84.

15 8. Whitman A, DeGregory K, Morris A, et al. Pharmacist-led medication  
16 assessment and deprescribing intervention for older adults with cancer and  
17 polypharmacy: a pilot study. *Support Care Cancer* 2018;26(12):4105-4113.

18 9. Nipp RD, Ruddy M, Fuh CX, Zangardi ML, et al. Pilot Randomized Trial of a  
19 Pharmacy Intervention for Older Adults with Cancer. *Oncologist* 2019;24(2):211-218.

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21 Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in  
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27 oncological palliative care deprescribing guideline: the 'OncPal deprescribing guideline'.  
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29 13. Gallagher P, Ryan C, Byrne S, et al. STOPP (Screening Tool of Older Person's  
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31 Consensus validation. *Int J Clin Pharmacol Ther* 2008;46(2):72-83.

32 14. Lavan AH, Gallagher P, Parsons C, et al. STOPPFrail (Screening Tool of Older  
33 Persons Prescriptions in Frail adults with limited life expectancy): consensus validation.  
34 *Age Ageing* 2017;46(4):600-607.

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36 end-of-life: development and validation of STOPPFrail version 2. *Age Ageing*



1 2021;50(2):465-471.

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

4  
5 Furthermore, we have deleted following references:

6  
7 “1. Thomas R E, Thomas B C. A systematic review of studies of the STOPP/START  
8 2015 and American Geriatric Society Beers 2015 criteria in patients  $\geq$  65 Years. Curr  
9 Aging Sci 2019;12(2):121-54.”

10  
11  
12 **RESPONSES TO REVIEWER C’S COMMENTS:**

13  
14 **Comment 1:** This manuscript has potential but the current presentation and comparisons  
15 with prior research raise concerns regarding rigour and validity of the claims being made

16  
17 **Reply 1:** Thank you for your appreciation of our manuscript. We corrected the manuscript  
18 in accordance with your comments.

19  
20 **Comment 2:** Title: a more succinct, objective study title required that makes reference to  
21 aim and design without summarising main findings

22  
23 **Reply 2:** Based on your comment, we have changed the title of this manuscript.

24  
25 **Changes in the text:** We have changed the title (page 1, line 2 to line 4) from:

26  
27 “Potentially inappropriate medications for end-stage cancer patients are more difficult to  
28 curtail on the basis of pharmacists’ recommendations, than for elderly patients  
29 hospitalized for other illnesses”

30  
31 to

32  
33 “Potentially inappropriate medications discontinued or changed based on pharmacists’  
34 recommendations in older end-stage cancer patients receiving palliative care: a cross-  
35 sectional study.”

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

2

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

5

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

8

9 “Abstract

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

16 Methods: Patients brought their medications with them upon admission to the hospital.  
17 These medications were examined by pharmacists and deemed inappropriate based on  
18 the Screening Tool of Older Persons’ Prescriptions (STOPP) version 2. In this study, these  
19 81 patients were surveyed, and the percentage of medications that were changed based  
20 on pharmacists’ recommendations was compared with the previously published results of  
21 similar studies on elderly non-cancer inpatients, using univariate analysis.

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

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

35

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

1 aged persons' prescriptions criteria version 2; Benzodiazepines; Elderly patients”

2  
3 to

4  
5 “Abstract

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

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

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

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

34  
35 Keywords: End-stage cancer; Potentially inappropriate medications; Screening tool of  
36 aged persons' prescriptions criteria version 2; Benzodiazepines; **Older** patients”

1  
2 Furthermore, we have changed the following text (page 11, line 4 to page 13, line 7) from:

3  
4 “Discussion

5 The results of this study indicate that it is more difficult to reduce the prescription of PIMs  
6 in cancer patients hospitalized in palliative care units, than in patients hospitalized with  
7 other diseases. Moreover, 75 of the 81 patients in the study were dead by June 1, 2021,  
8 when the medical files were examined. As these 75 patients died an average of 20.8 days  
9 after the date of detection of PIMs, most of the subjects were likely to have been end-  
10 stage cancer patients. In addition, the fact that they were admitted to our palliative care  
11 unit, suggests that they required intensive palliative care. Therefore, the results of this  
12 study indicate that it is more difficult to reduce PIMs in hospitalized end-stage cancer  
13 patients receiving intensive palliative care. Furthermore, the results of the sensitivity  
14 analysis indicated that the main result of this study was robust. This was because the main  
15 results were the same — regardless of whether the PIMs prescribed to patients whose  
16 PIMs were not assessed at the time of hospitalization from October 9, 2020, to February  
17 28, 2021 — were assumed to have been changed based on pharmacists’ recommendations.  
18 STOPP classifies PIMs into 13 types (7), and we detected several PIMs in Section A  
19 (Indication of medications), Section D (Central nervous system and psychotropic drugs),  
20 and Section K (Drugs that predictably increase the risk of falls in older people) in this  
21 study. The same pattern was observed in two previous studies used for comparative  
22 purposes (3, 4). However, the rate of change in medications per section seems to differ  
23 from this study. First, in Section A, 6 of 11 medications were changed in this study (rate  
24 of change of medications: 54.5%), while 56 of 113 medications were changed in the  
25 previous studies (rate of change of medications: 49.6%). Most of the PIMs classified as  
26 Section A were duplications of drugs, and our results showed no significant difference in  
27 the possibility of correcting duplications of drugs, even for patients with end-stage cancer.  
28 However, in Section D, one out of ten medications were changed in this study (rate of  
29 change of medications: 10.0%), while 106 of 286 medications were changed in the  
30 previous studies (rate of change of medications: 37.1%). In Section K, one of 23  
31 medications was changed in this study (rate of change of medications: 4.3%), while 51 of  
32 113 medications were changed in the previous studies (rate of change of medications:  
33 45.1%). The risk of falling was low, because the end-stage cancer patients hospitalized in  
34 the palliative care unit could not stand. Therefore, changing or stopping the administration  
35 of PIMs of Section K, that included medications that increased the risk of falling in elderly  
36 patients, was unnecessary.

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

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

16  
17 to

## 18 19 “Discussion

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

1 this study (rate of discontinuation/change of medications: 10.3%), while 6 of 14  
2 medications were discontinued or changed in the previous studies (rate of  
3 discontinue/change of medications: 42.9%). The risk of falling was low, because the end-  
4 stage cancer patients hospitalized in the palliative care unit could not stand up. Therefore,  
5 changing or stopping the administration of PIMs of Section K, which included  
6 medications that increased the risk of falling in older patients, was unnecessary.

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

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

23  
24 Furthermore, we have changed the following text (page 14, line 3 to line 10) from:

25  
26 “Nevertheless, this cross-sectional study has some limitations. First, all the study  
27 participants were recruited from a single center; thus, they did not represent the general  
28 population of end-stage cancer patients. Second, all the participants were recruited from  
29 the patients hospitalized in the palliative care unit; thus, they did not represent the general  
30 population of end-stage cancer patients, including home patients and outpatients. Finally,  
31 neither this study, nor the previous studies used for comparison, are representative of the  
32 general population of elderly patients, as they were conducted on Japanese subjects.  
33 Therefore, the results must be interpreted whilst considering these limitations.”

34  
35 to

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

9  
10 Furthermore, we have changed the following text (page 12, line 14 to line 18) from:

11  
12 “Conclusion

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

19  
20 to

21  
22 “Conclusion

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

29  
30  
31 **Comment 4:** Introduction: lacks proper structure and flow; need to make better use of  
32 paragraphs to introduce the clinical area of relevant to this study, the role of pharmacists and  
33 then the particular gap in the literature that this study plans to address – at present all of this is  
34 squashed into the opening paragraph  
35 Describing reference 1 as recent in opening statement is not accurate (it was published in 2015)  
36 “However, to our knowledge, studies have not examined the extent to which pharmacists’

1 recommendations can play a role in the reduction of the prescription of PIMs, in elderly cancer  
2 patients receiving palliative care.” It would be nice to see a statement like this backed up by a  
3 review as opposed to the authors’ knowledge which could be prone to bias. See recent scoping  
4 review interventions to optimise medication prescribing and adherence in older adults with  
5 cancer by Murphy et al (Res Social Adm Pharm. 2021 Apr 17;S1551-7411(21)00134-0. doi:  
6 10.1016/j.sapharm.2021.04.011) which shows that pharmacists were involved in various  
7 interventions but none of the included studies referred to patients receiving palliative care.  
8 The appropriateness of STOPP criteria to a palliative population needs to be discussed  
9 I don’t follow the reference to Kimura et al. and its relevance to this study and why the results are  
10 being compared against it – this does not seem like a valid comparison  
11

12 **Reply 4:**

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

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

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



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

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

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

26  
27 **Changes in the text:** we have changed the following text (page 3, line 1 to page 4, line  
28 11) from:

29  
30 “Abstract

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

1 Methods: Patients brought their medications with them upon admission to the hospital.  
2 These medications were examined by pharmacists and deemed inappropriate based on  
3 the Screening Tool of Older Persons' Prescriptions (STOPP) version 2. In this study, these  
4 81 patients were surveyed, and the percentage of medications that were changed based  
5 on pharmacists' recommendations was compared with the previously published results of  
6 similar studies on elderly non-cancer inpatients, using univariate analysis.

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

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

21  
22 to

23  
24 “Abstract

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

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

1 univariate analysis.

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

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

17  
18 Furthermore, we have changed the following text (page 4, line 16 to page 6, line 9) from:

19  
20 “Introduction

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

36 Kimura et al. reported how the prescription of several PIMs, based on STOPP, could have

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

7  
8 to

## 9 10 “Introduction

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

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

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

4  
5 Furthermore, we have changed the following text (page 7, line 18 to page 8, line 11) from:

6  
7 “Sample Size Calculation

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

22  
23 to

24  
25 “Sample Size Calculation

26 To compare the PIMs' discontinued/changed rate in this study with that in the most recent  
27 previous study, in which pharmacists reduced PIMs through intervention using the  
28 STOPP2 criterion, we examined the sample size calculation. Before the main study, we  
29 conducted a preliminary study to calculate the sample size. The preliminary study was  
30 conducted on patients hospitalized in the palliative care unit from January 1 to February  
31 28, 2021, and the medical records at the time of admission were reviewed to investigate  
32 PIMs' discontinued/changed rate. The PIMs' discontinued/changed rate was 31.0%.  
33 Based on the results of this preliminary study, the sample size required to compare the  
34 PIMs' discontinued/changed rate in this study with the PIMs discontinued/changed rate  
35 in the most recent previous study was 220. The  $\alpha$  risk and  $\beta$  risk were set at 0.05 and 0.80,  
36 respectively.”

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

3  
4 “Results

5 Incidence of PIMs

6 Eighty-one consecutive patients were enrolled retrospectively from February 28, 2021,  
7 resulting in the enrollment of patients admitted between October 9, 2020, and February  
8 28, 2021. All the patients were Japanese. Seventy-five of these patients had already died,  
9 and the survival time after evaluation for the presence of PIMs was  $20.8 \pm 20.9$  days  
10 (mean  $\pm$  SD). The remaining six patients were confirmed to be alive as of June 1, 2021.  
11 Table 1 shows the characteristics of the 81 patients. One or more PIMs were found in 40  
12 of the 81 target patients (49.9%). Four hundred seventy-five medications were prescribed  
13 to them and using STOPP, 71 were determined to be PIMs. The classification of the  
14 detected PIMs is shown in Table 2.

15  
16 Pharmacists’ Recommendations and Changes in Medications

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

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

23  
24 Sensitivity Analysis

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

31  
32 to

33  
34 “Results

35 Incidence of PIMs

36 All patients enrolled in this study were Japanese. Participants’ age was  $79.5 \pm 7.4$  years old

1 (mean±SD), and 131 were males and 89 were females. The most common type of cancer  
2 was gastric cancer, with 35 cases. This was followed by colorectal cancer with 32 cases  
3 and lung cancer with 29 cases.

4 One or more PIMs were found in 112 of the 220 target patients (50.9%). Regarding the  
5 medication, 1261 were prescribed to them, and using STOPP2, 218 were determined to  
6 be PIMs. The classification of the detected PIMs is shown in Table 1.

#### 7 8 Pharmacists' Recommendations and Discontinuation/Changes in Medications

9 The pharmacists recommended physicians to discontinue or change 65 PIMs. The  
10 physicians accepted the recommendations and discontinued/changed the prescription for  
11 61 PIMs. Conversely, the physicians did not discontinue or change four PIMs, despite the  
12 recommendation of pharmacists. Table 2 shows the classification of the PIMs that were  
13 discontinued or changed based on pharmacists' recommendations.

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

18  
19 Furthermore, we have changed the following text (page 11, line 4 to page 13, line 7) from:

#### 20 21 “Discussion

22 The results of this study indicate that it is more difficult to reduce the prescription of PIMs  
23 in cancer patients hospitalized in palliative care units, than in patients hospitalized with  
24 other diseases. Moreover, 75 of the 81 patients in the study were dead by June 1, 2021,  
25 when the medical files were examined. As these 75 patients died an average of 20.8 days  
26 after the date of detection of PIMs, most of the subjects were likely to have been end-  
27 stage cancer patients. In addition, the fact that they were admitted to our palliative care  
28 unit, suggests that they required intensive palliative care. Therefore, the results of this  
29 study indicate that it is more difficult to reduce PIMs in hospitalized end-stage cancer  
30 patients receiving intensive palliative care. Furthermore, the results of the sensitivity  
31 analysis indicated that the main result of this study was robust. This was because the main  
32 results were the same — regardless of whether the PIMs prescribed to patients whose  
33 PIMs were not assessed at the time of hospitalization from October 9, 2020, to February  
34 28, 2021 — were assumed to have been changed based on pharmacists' recommendations.  
35 STOPP classifies PIMs into 13 types (7), and we detected several PIMs in Section A  
36 (Indication of medications), Section D (Central nervous system and psychotropic drugs),

1 and Section K (Drugs that predictably increase the risk of falls in older people) in this  
2 study. The same pattern was observed in two previous studies used for comparative  
3 purposes (3, 4). However, the rate of change in medications per section seems to differ  
4 from this study. First, in Section A, 6 of 11 medications were changed in this study (rate  
5 of change of medications: 54.5%), while 56 of 113 medications were changed in the  
6 previous studies (rate of change of medications: 49.6%). Most of the PIMs classified as  
7 Section A were duplications of drugs, and our results showed no significant difference in  
8 the possibility of correcting duplications of drugs, even for patients with end-stage cancer.  
9 However, in Section D, one out of ten medications were changed in this study (rate of  
10 change of medications: 10.0%), while 106 of 286 medications were changed in the  
11 previous studies (rate of change of medications: 37.1%). In Section K, one of 23  
12 medications was changed in this study (rate of change of medications: 4.3%), while 51 of  
13 113 medications were changed in the previous studies (rate of change of medications:  
14 45.1%). The risk of falling was low, because the end-stage cancer patients hospitalized in  
15 the palliative care unit could not stand. Therefore, changing or stopping the administration  
16 of PIMs of Section K, that included medications that increased the risk of falling in elderly  
17 patients, was unnecessary.

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

28  
29 to

### 31 “Discussion

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



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

30

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

33

34 “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	0	0

drug burden

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
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Section B: Cardiovascular system	6	3	3
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Section	C:	9	3	3
Antiplatelet/Anticoagulant drugs				
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:	4	3	2
Antimuscarinic/Anticholinergic				

drug burden

1 PIMs, potentially inappropriate medications “

2

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

5

6 “Table 3. Results of the univariate analysis of the rates of change in PIMs in our palliative

7 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			

8 95%CI: 95% confidence interval

9 \*P<0.05 was considered significant”

10

11 to

12

13 “Table 2. Results of the univariate analysis of the rates of discontinuation/change in PIMs

14 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	

1 95%CI, 95% confidence interval; PIMs, potentially inappropriate medications

2 \*P<0.05 was considered significant”

3

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

6

7 6. “Choukroun C, Leguelinel-Blache G, Roux-Marson C, et al. Impact of a  
8 pharmacist and geriatrician medication review on drug-related problems in older  
9 outpatients with cancer. J Geriatr Oncol 2021;12(1):57-63.

10 7. van Loveren FMAM, van Berlo-van de Laar IRF, Imholz ALT, et al. Prevalence  
11 and follow-up of potentially inappropriate medication and potentially omitted  
12 medication in older patients with cancer - The PIM POM study. J Geriatr Oncol  
13 2021;12(1):80-4.

14 8. Whitman A, DeGregory K, Morris A, et al. Pharmacist-led medication assessment  
15 and deprescribing intervention for older adults with cancer and polypharmacy: a  
16 pilot study. Support Care Cancer 2018;26(12):4105-13.

17 9. Nipp RD, Ruddy M, Fuh CX, Zangardi ML, et al. Pilot randomized trial of a  
18 pharmacy intervention for older adults with cancer. Oncologist 2019;24(2):211-  
19 18.

20 10. American Geriatrics Society 2012 Beers Criteria Update Expert Panel. American  
21 Geriatrics Society updated Beers Criteria for potentially inappropriate medication  
22 use in older adults. J Am Geriatr Soc. 2012; 60(4):616–31.

23 11. The 2019 American Geriatrics Society Beers Criteria® Update Expert Panel.  
24 American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially  
25 Inappropriate Medication Use in Older Adults. J Am Geriatr Soc.  
26 2019;67(4):674–94.

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

16  
17 Furthermore, we have deleted following references:

18  
19 “1. Thomas R E, Thomas B C. A systematic review of studies of the STOPP/START  
20 2015 and American Geriatric Society Beers 2015 criteria in patients  $\geq$  65 Years. Curr  
21 Aging Sci 2019;12(2):121-54.”

22  
23 **Comment 5:** Reference to STROBE should appear in methods as opposed to introduction

24  
25 **Reply 5:** Based on your comment, we have moved the reference to STROBE from the  
26 Introduction to the Methods.

27  
28 **Changes in the text:** We have deleted the following text from the Introduction:

29  
30 “We present this article following The Strengthening the Reporting of Observational  
31 Studies in Epidemiology (STROBE) reporting checklist.”

32  
33 Furthermore, we have added the following text (page 6, line 13 to line 14):

34  
35 “We present this article following the Strengthening the Reporting of Observational  
36 Studies in Epidemiology (STROBE) reporting checklist.”

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**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



1 the medical records on the day of hospitalization in this study.”

2  
3 Furthermore, we have changed the following text (page 3, line 1 to page 4, line 11) from:

4  
5 “Abstract

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

12 Methods: Patients brought their medications with them upon admission to the hospital.  
13 These medications were examined by pharmacists and deemed inappropriate based on  
14 the Screening Tool of Older Persons’ Prescriptions (STOPP) version 2. In this study, these  
15 81 patients were surveyed, and the percentage of medications that were changed based  
16 on pharmacists’ recommendations was compared with the previously published results of  
17 similar studies on elderly non-cancer inpatients, using univariate analysis.

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

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

32  
33 to

34  
35 “Abstract

36 Background: Avoiding potentially inappropriate medications can reduce adverse events

1 in older cancer patients receiving palliative care. However, studies have not examined the  
2 extent to which pharmacists' recommendations reduce the prescription of potentially  
3 inappropriate medications. Therefore, we designed a cross-sectional study to determine  
4 the extent to which their recommendations play a role in reducing the prescription of  
5 potentially inappropriate medications for older cancer patients receiving palliative care.

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

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

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

28  
29 Furthermore, we have changed the following text (page 10, line 11) from:

30  
31 “Pharmacists' Recommendations and Changes in Medications”

32  
33 to

34  
35 “Pharmacists' Recommendations and Discontinuation/Changes in Medications”

36

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

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

7  
8 to

9  
10 “The rate of **discontinuation/change** in medications was 28.0% (61/218). A univariate  
11 analysis showed that the rate of **discontinuation or change** in medications in our palliative  
12 unit was significantly lower than that in the most recent previous study (rate of  
13 **discontinuation/change** of medications: 40.6%) (Table 2).”

14  
15 Furthermore, we have changed the following text (page 11, line 4 to page 13, line 7) from:

16  
17 “Discussion

18 The results of this study indicate that it is more difficult to reduce the prescription of PIMs  
19 in cancer patients hospitalized in palliative care units, than in patients hospitalized with  
20 other diseases. Moreover, 75 of the 81 patients in the study were dead by June 1, 2021,  
21 when the medical files were examined. As these 75 patients died an average of 20.8 days  
22 after the date of detection of PIMs, most of the subjects were likely to have been end-  
23 stage cancer patients. In addition, the fact that they were admitted to our palliative care  
24 unit, suggests that they required intensive palliative care. Therefore, the results of this  
25 study indicate that it is more difficult to reduce PIMs in hospitalized end-stage cancer  
26 patients receiving intensive palliative care. Furthermore, the results of the sensitivity  
27 analysis indicated that the main result of this study was robust. This was because the main  
28 results were the same — regardless of whether the PIMs prescribed to patients whose  
29 PIMs were not assessed at the time of hospitalization from October 9, 2020, to February  
30 28, 2021 — were assumed to have been changed based on pharmacists’ recommendations.  
31 STOPP classifies PIMs into 13 types (7), and we detected several PIMs in Section A  
32 (Indication of medications), Section D (Central nervous system and psychotropic drugs),  
33 and Section K (Drugs that predictably increase the risk of falls in older people) in this  
34 study. The same pattern was observed in two previous studies used for comparative  
35 purposes (3, 4). However, the rate of change in medications per section seems to differ  
36 from this study. First, in Section A, 6 of 11 medications were changed in this study (rate

1 of change of medications: 54.5%), while 56 of 113 medications were changed in the  
2 previous studies (rate of change of medications: 49.6%). Most of the PIMs classified as  
3 Section A were duplications of drugs, and our results showed no significant difference in  
4 the possibility of correcting duplications of drugs, even for patients with end-stage cancer.  
5 However, in Section D, one out of ten medications were changed in this study (rate of  
6 change of medications: 10.0%), while 106 of 286 medications were changed in the  
7 previous studies (rate of change of medications: 37.1%). In Section K, one of 23  
8 medications was changed in this study (rate of change of medications: 4.3%), while 51 of  
9 113 medications were changed in the previous studies (rate of change of medications:  
10 45.1%). The risk of falling was low, because the end-stage cancer patients hospitalized in  
11 the palliative care unit could not stand. Therefore, changing or stopping the administration  
12 of PIMs of Section K, that included medications that increased the risk of falling in elderly  
13 patients, was unnecessary.

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

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

29

30 to

31

32 “Discussion

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

1 psychotropic drugs), and Section K (Drugs that predictably increase the risk of falls in  
2 older people) in this study. The same pattern was observed in two previous studies used  
3 for comparative purposes (3, 4). However, the rate of discontinuation or change in  
4 medications per section seems to differ from this study. First, in Section A, 16 of 30  
5 medications were discontinued or changed in this study (rate of discontinuation or change  
6 of medications: 53.3%), while 11 of 22 medications were changed in the previous study  
7 (rate of discontinuation or change of medications: 50.0%). Most of the PIMs classified as  
8 Section A were duplications of drugs, and our results showed no significant difference in  
9 the possibility of correcting duplications of drugs, even for patients with end-stage cancer.  
10 However, in Section D, 4 of 38 medications were discontinued or changed in this study  
11 (rate of discontinuation or change of medications: 10.5%), while 25 of 64 medications  
12 were discontinued or changed in the previous study (rate of discontinuation/change of  
13 medications: 26.6%). In Section K, 7 of 68 medications were discontinued or changed in  
14 this study (rate of discontinuation/change of medications: 10.3%), while 6 of 14  
15 medications were discontinued or changed in the previous studies (rate of  
16 discontinuation/change of medications: 42.9%). The risk of falling was low, because the  
17 end-stage cancer patients hospitalized in the palliative care unit could not stand up.  
18 Therefore, changing or stopping the administration of PIMs of Section K, which included  
19 medications that increased the risk of falling in older patients, was unnecessary.  
20 Furthermore, most of the drugs classified in Sections D and K were benzodiazepines. The  
21 benzodiazepines used to treat patients with end-stage delirium could not be discontinued  
22 when patients were already experiencing delirium (19). Discontinuation of regularly used  
23 benzodiazepines would generate withdrawal phenomena and cause unnecessary suffering  
24 in patients at the end of their lives (20). These reasons might have contributed to the lower  
25 rate of discontinuation or change of medications in this study. If we exclude PIMs  
26 classified in Sections D and K and compare the rates of discontinuation/change of PIMs  
27 of this study with those of previous studies, 50 of 112 PIMs were discontinued or changed  
28 in this study, while 23 of 55 PIMs were discontinued or changed in the previous studies.  
29 The rate of reductions in prescribed PIMs, in sections other than D and K, was  
30 approximately the same.  
31 However, the rate of discontinuation or change in medications for PIMs in sections other  
32 than D and K, may not differ for terminal cancer patients hospitalized in the palliative  
33 care unit, compared to other patients. This suggests that even end-stage cancer patients  
34 hospitalized in the palliative care unit, may benefit from efforts to detect and reduce the  
35 prescription of PIMs using STOPP2.”

36

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

3  
4 **Reply 8:** The patients who were included in the preliminary study were included in the  
5 final analysis. Please refer to the reply 4 to your comment 4 for changes in the text.

6  
7 **Comment 9:** Statement on ethics could be more concise

8  
9 **Reply 9:** Based on your comment, we have simplified the statement on ethics.

10  
11 **Changes in the text:** We have deleted the following text from the Methods section:

12  
13 “The institutional ethics board waived the requirement of informed consent.”

14  
15 **Comment 10:** The statistical analysis section is unclear (e.g. what does “using EZR in  
16 R commander version 1.37” mean?)

17  
18 **Reply 10:** Based on your comment, we have revised the Statistical Analysis significantly.

19  
20 **Changes in the text:** We have changed the following text (page 9, line 13 to line 17)  
21 from:

22  
23 “Statistical Analysis

24 A univariate analysis was performed using EZR in R commander version 1.37 (8). All  
25 analyses were two-sided, and the statistical significance was set at 0.05. This cross-  
26 sectional study extracted data from the medical records of patients already out of the  
27 hospital. Therefore, some patients could not be enrolled in the study, because PIMs were  
28 not assessed despite their hospitalization during the enrollment for this study (October 9,  
29 2020, to February 28, 2021). As a sensitivity analysis, we performed a univariate analysis  
30 identical to the main analysis, assuming that PIMs were detected in these cases on the day  
31 of hospitalization and were either changed or not changed based on pharmacists’  
32 recommendations.”

33  
34 to

35  
36 “Statistical Analysis

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

8  
9 **Comment 11:** “Therefore, some patients could not be enrolled in the study, because  
10 PIMs were 12 not assessed despite their hospitalization during the enrollment for this  
11 study” – I don't understand this and it doesn't seem directly relevant to statistical  
12 analysis

13  
14 **Reply 11:** The text you indicated as unnecessary describes the PIMs detected for the  
15 sensitivity analysis. We believe that your comment implies that sensitivity analysis is not  
16 necessary for this study. The same suggestion has been given to us by Reviewer A. Based  
17 on your comment and Reviewer A's comment, we have removed the description of  
18 sensitivity analysis from this manuscript.

19  
20 **Changes in the text:** We have deleted the following text from the Methods section:

21  
22 As a sensitivity analysis, we performed a univariate analysis identical to the main analysis,  
23 assuming that PIMs were detected in these cases on the day of hospitalization and were  
24 either changed or not changed based on pharmacists' recommendations.

25  
26 Furthermore, we have also deleted the following text from the Results section:

27  
28 Sensitivity Analysis

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

35  
36 In addition, we have also deleted the following text from the Discussion section:

1  
2 Furthermore, the results of the sensitivity analysis indicated that the main result of this  
3 study was robust. This was because the main results were the same — regardless of  
4 whether the PIMs prescribed to patients whose PIMs were not assessed at the time of  
5 hospitalization from October 9, 2020, to February 28, 2021 — were assumed to have been  
6 changed based on pharmacists' recommendations.

7  
8 Lastly, we have also deleted tables 4 and 5.

9  
10 **Comment 12: Results**

11 “Seventy-five of these patients had already died, 23 and the survival time after  
12 evaluation for the presence of PIMs was  $20.8 \pm 20.9$  days 24 (mean  $\pm$  SD)”; don't see  
13 the relevance of this

14  
15 **Reply 12:** Based on your comment, we thought it was unnecessary to mention the patient's  
16 prognosis. We have deleted the text related to this.

17  
18 **Changes in the text:** We have deleted the following text:

19  
20 “Eighty-one consecutive patients were enrolled retrospectively from February 28, 2021,  
21 resulting in the enrollment of patients admitted between October 9, 2020, and February  
22 28, 2021. All the patients were Japanese. Seventy-five of these patients had already died,  
23 and the survival time after evaluation for the presence of PIMs was  $20.8 \pm 20.9$  days  
24 (mean  $\pm$  SD). The remaining six patients were confirmed to be alive as of June 1, 2021.”

25  
26 Furthermore, we have deleted the following text:

27  
28 “Moreover, 75 of the 81 patients in the study were dead by June 1, 2021, when the medical  
29 files were examined. As these 75 patients died an average of 20.8 days after the date of  
30 detection of PIMs, most of the subjects were likely to have been end-stage cancer patients.  
31 In addition, the fact that they were admitted to our palliative care unit, suggests that they  
32 required intensive palliative care. Therefore, the results of this study indicate that it is  
33 more difficult to reduce PIMs in hospitalized end-stage cancer patients receiving intensive  
34 palliative care. Furthermore, the results of the sensitivity analysis indicated that the main  
35 result of this study was robust. This was because the main results were the same —  
36 regardless of whether the PIMs prescribed to patients whose PIMs were not assessed at



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

3  
4 **Comment 13:** “Pharmacists' Recommendations and Changes in Medication” not  
5 outlined in methods

6  
7 **Reply 13:** Based on your comment, we have included details of the pharmacist's  
8 recommendations in our Methods section.

9  
10 **Changes in the text:** We have added the following text (page 6, line 16 to page 7, line  
11 16):

12  
13 “PIMs detection, Pharmacists' Recommendations and Discontinuation/Changes in  
14 Medications

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

32  
33 **Comment 14:** “A univariate analysis showed that 2 the rate of change in medications in  
34 our palliative unit was significantly lower than in 3 previous studies (Table 3” not a valid  
35 comparison

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

5  
6 **Comment 15:** “Sensitivity Analysis” – I don’t follow this section; it also appears to be  
7 heavily reliant on assumptions

8  
9 **Reply 15:** Based on your comment, we have removed the description of sensitivity  
10 analysis from this manuscript. Please refer to the reply 11 to your comment 11 for changes  
11 in the text.

12  
13 **Comment 16:** Table 1: not terribly informative; could be presented as written text;  
14 detailed breakdown of all cancer types not necessary

15  
16 **Reply 16:** Based on your comment, we have deleted Table 1 and incorporated the data in  
17 the text.

18  
19 **Changes in the text:** We have deleted Table 1.

20  
21 Furthermore, we have added the following text (page 10, line 3 to line 6):

22  
23 “All patients enrolled in this study were Japanese. Participants’ age was  $79.5 \pm 7.4$  years  
24 old (mean $\pm$ SD), and 131 were males and 89 were females. The most common type of  
25 cancer was gastric cancer, with 35 cases. This was followed by colorectal cancer with 32  
26 cases and lung cancer with 29 cases.”

27  
28 **Comment 17:** Table 2: gives no proper insight into the actual PIMs identified

29  
30 **Reply 17:** Based on your comment, we have substantially revised Table 2. Please refer to  
31 the reply 14 to your comment 14 for changes in the text.

32  
33 **Comment 18:** Table 3+4 not valid comparisons

34  
35 **Reply 18:** Based on your comment, we have substantially restructured Table 3 and deleted  
36 Table 4. Please refer to replies 14 and 15 to your comments 14 and 15 for changes in the

1 text.

2  
3 **Comment 19:** Needs to be revised as direct comparisons with other study are not valid

4  
5 **Reply 19:** Based on your comment, we have restructured the comparison with other  
6 studies. Please refer to the reply 14 to your comment 14 for changes in the text.

7  
8 **Comment 20:** Why was STOPP chose as opposed to OncPal or even STOPPFrail?

9  
10 **Reply 20:** Based on your comment, we have added descriptions of OncPal and  
11 STOPPFrail to the Discussion.

12  
13 **Changes in the text:** We have added the following text (page 13, line 8 to page 14, line  
14 2):

15  
16 “STOPP2 is a criterion that can more accurately detect PIMs using blood test results as a  
17 reference (16). Furthermore, it is so easy to use that a trained pharmacist can complete  
18 the assessment in a few minutes (5, 17). Therefore, we used STOPP2 to detect PIMs in  
19 our daily practice, and we used the medical records containing its results in this study.  
20 However, STOPP, an older version of STOPP2, has been shown to significantly improve  
21 medication appropriateness during hospitalization for acute illness in older patients, and  
22 its effects can be maintained for 6 months after intervention. STOPP2, like STOPP, is  
23 supposed to be applied during hospitalization for acute illness in older patients, so  
24 STOPP2 might not be optimal for end-stage cancer patients hospitalized in the palliative  
25 care unit. Better evidence might be obtained through a similar study performed using  
26 OncPal, a criterion developed to detect PIMs in cancer patients receiving end-of-life care,  
27 or STOPPFrail, a criterion developed to detect PIMs in frail patients with limited life  
28 expectancy.”

29  
30 **RESPONSES TO REVIEWER D’S COMMENTS:**

31  
32 **Comment 1:** This study aimed to determine the extent to which their recommendations  
33 play a role in reducing the prescription of potentially inappropriate medications for  
34 elderly cancer patients receiving palliative care.

35 The subject is important to be addressed.

36

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

3  
4 **Comment 2:** However, I have some concerns.

5  
6 **Reply 2:** Based on your comments, we have revised our manuscript.

7  
8 **Comment 3:** Main Issues

9 Authors used the STOPP2 criteria for identifying PIMs in patients receiving palliative  
10 care and their survival might be less than 6 months.

11 The population with limited life expectancy receiving palliative care is different from  
12 older adults with long life expectancy, therefore the criteria for general older adults may  
13 not be optimal for this population.

14 Explicit tool, STOPPFrail, to assist clinicians with deprescribing medications in frailer  
15 older adults with limited life expectancy in all healthcare settings has been first developed  
16 in 2017 and recently updated. Also, oncological palliative care deprescribing guideline,  
17 the ‘OncPal deprescribing guideline has been already developed.

18 These guidelines may be more appropriate for this population.

19 These issues need to be explained.

20  
21 **Reply 3:** STOPP2 is a criterion that can more accurately detect PIMs using blood test  
22 results as a reference. Furthermore, it is so easy to use that a trained pharmacist can  
23 complete the assessment in a few minutes. Therefore, we selected STOPP2 to detect PIMs  
24 in our daily practice, and we used the medical records containing its results in this study.  
25 However, as you mentioned, it may not have been optimal to use the STOPP 2 criteria in  
26 a population with limited life expectancy receiving palliative care, as this is different from  
27 the elderly who have a longer life expectancy. Based on your comments and reviewer C's  
28 comments, we have mentioned the reason for using STOPP 2 for this study and mentioned  
29 STOPPPFrail and OncPal in the text.

30  
31 **Changes in the text:** We have changed following text (page 4, line 16 to page 6, line 9)  
32 from:

33  
34 “Introduction

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

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

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

21  
22 to

## 23 24 “Introduction

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

1 patients hospitalized in the palliative care unit.

2 **Criteria such as Beers Criteria, OncPal, Screening Tool of Older Persons' Prescriptions**  
3 **(STOPP), Screening Tool of Older Persons' Prescriptions in Frail adults with limited life**  
4 **expectancy (STOPPFrail), among others, have been proposed to detect PIMs (10–15).**

5 The most recent version of STOPP, STOPP version 2 (STOPP2), provides more detailed  
6 criteria for determining PIMs, including the use of blood test results (16). It is also a  
7 simple and practical criterion that can be evaluated in a few minutes by trained  
8 pharmacists (5, 17). In our palliative care unit, we use STOPP2 among other criteria for  
9 detecting PIMs, because blood tests are basically performed upon admission. In our daily  
10 clinical practice, pharmacists detect PIMs when a patient is hospitalized in the palliative  
11 care unit and recommend to the physician to discontinue or change the prescriptions to  
12 reduce PIMs. In this study, we retrospectively reviewed the patients' medical records and  
13 evaluated the PIMs' discontinuation/change rates at our palliative care unit. Furthermore,  
14 by comparing our PIMs' discontinuation/change rates with those of a previous study, in  
15 which pharmacists reduced PIMs by intervening using the STOPP2 criterion, we  
16 investigated whether pharmacists contribute to reducing PIMs in older cancer patients  
17 hospitalized in the palliative care unit.”

18  
19 Furthermore, we have added the following text (page 13, line 8 to page 14, line 2):

20  
21 “STOPP2 is a criterion that can more accurately detect PIMs using blood test results as a  
22 reference (16). Furthermore, it is so easy to use that a trained pharmacist can complete  
23 the assessment in a few minutes (5, 17). Therefore, we used STOPP2 to detect PIMs in  
24 our daily practice, and we used the medical records containing its results in this study.  
25 However, STOPP, an older version of STOPP2, has been shown to significantly improve  
26 medication appropriateness during hospitalization for acute illness in older patients, and  
27 its effects can be maintained for 6 months after intervention. STOPP2, like STOPP, is  
28 supposed to be applied during hospitalization for acute illness in older patients, so  
29 STOPP2 might not be optimal for end-stage cancer patients hospitalized in the palliative  
30 care unit. Better evidence might be obtained through a similar study performed using  
31 OncPal, a criterion developed to detect PIMs in cancer patients receiving end-of-life care,  
32 or STOPPFrail, a criterion developed to detect PIMs in frail patients with limited life  
33 expectancy.”

34  
35 **Comment 4:** So, conclusion that it was more difficult to change PIMS detected by  
36 STOPP in patients with limited expectancy compared with general older population may

1 not be inappropriate.

2  
3 **Reply 4:** Based on your comment, we did not make any significant changes to our  
4 conclusions. However, based on the comment of Reviewer C, we have changed "elderly"  
5 to "older" throughout the manuscript.

6  
7 **Changes in the text:** We have changed following text (page 12, line 14 to line 18) from:

8  
9 “Conclusion

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

16  
17 to

18  
19 “Conclusion

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