

Peer Review File

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Review Comments (Round 1)

Reviewer A

Abstract

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Comment 1: Line 31-Methods: Mention how many were 'all' admitted patients , like 'All (n=369?) admitted cancer patients to the Palliative care unit...."

Reply 1: Thank you for your advice. I have clarified the number of the patients (i.e., 369) , and that 10 patients were excluded from analyses due to missing data.

Changes in the text:

All 369 cancer patients admitted cancer patients to the palliative care unit of a 533-bed general hospital in Japan from October 2016 to October 2019 were enrolled. Lines 33–34

Among 369 cancer patients admitted to the PCU, we excluded 10 cases for whom a death location could not be identified. Among the remaining 359 patients, 180 were analyzed in the development phase and 179 in the validation phase. Lines 37–38

Comment 2: Line 34: what is 00 items ?, is that a typo and needed to be a complete number ?

Reply 2: Thank you for your advice. This was a typo, and we have collected this part.

Changes in the text: Attending physicians recorded 22 potential scale items ... Line 35

Manuscript

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Subjects

Comment 3:

Line 97: All '(n=369?)' consecutive admitted ...

Also clarify these were unique patients and not multiple admissions for same patient (if so). if there were multiple admissions for same patients please mention in discussion.

Reply 3: Thank you for your advice. We have clarified that we used the data from the first admission only.

Changes in the text: The data from the first admission for each patient were used for this study; rehospitalizations (e.g., second or subsequent hospitalizations) were excluded. Lines 84–85

Methods

Comment 4: Line 105: who are authors 5-10, 14-16

Reply 4: Thank you for your advice. This is typo: 5-10 and 14-16 were reference numbers; we have corrected this part.

Changes in the text: On the basis of the literature review (5–10, 14–16) and discussion among the authors, we measured 22 items as potential scale items available on the first day of PCU admission, ... Lines 84–85

Comment 5: Line 106: please clarify '00' items

Reply 5: Please see reply 2. (Revised text Line 35, Line 89)

Comment 6: Line 111: Clarify in methods how was the calorie count measured ? Was a nutritionist involved ? was food provided by hospital and labelled with calories and nurses recorded it ? and if family is allowed to bring in food, how were calories counted then ?

Reply 6: Thank you for your advice. We have clarified the way we calculated the calorie intake.

Changes in the text: Patients' caloric intake was calculated based on the designated calories of the meals provided by the hospital and the percentage of the food consumed (e.g., a patient offered a 1200 kcal meal who ate 20% of the meal was considered to have ingested 240 kcal). The caloric content of meals served in the hospital was routinely reported in the medical record by nutritionists. The percentages of the food consumed were also routinely recorded by ward nurses in 10% increments. Also, food from family members was allowed, and the number of calories eaten was reflected based on the nurse's report. Lines 107–111

Comment 7: line 116: please clarify/correct the word 'asitia'. Also bullet no. 5) is perhaps supposed to be 6).

Reply 7: Thank you for your advice. I fixed it following the reviewer's comment.

Changes in the text: “ ... anorexia), and 6) preferred ...” Line 97

Results

Comment 8: Line 171: median admission period 18.5 days (range 1-105). Please clarify, is this admission period counted from day 1 in hospital or counted from day when patient came to the Palliative unit?

Reply 8: Thank you for your advice. We have clarified the admission periods were calculated from the day when patient came to the PCU.

Changes in the text: The admission period was calculated from the day a patient came to the PCU. Lines 101

...the median PCU admission period was 18.5 days (range, 1–105)... Lines 153–154

Comment 9: In multi-variate analysis, was the effect of number of admitted days analyzed ? It would be good to know how the duration of admission contributed to the discharge ?

Reply 9: Thank you for your comment. We did not include the duration of admission into the prediction model because we intended to develop a predictive model to assess the possibility that a patient would discharge to home at the early phase of admission, i.e., admission duration was not available at the time of prediction in a clinical practice. We have added this rationale in the Method section and in the Abstract Methods subsection.

Changes in the text: we measured 22 potential scale items available on the first day of PCU admission Lines 89–90

...recorded 22 potential scale items at admission Line 35, Line 89

Reviewer B

Comment 10: Introduction: would add admission criteria to your Palliative Care unit. This may be very different from one institution/country to the other, and important to know in this context. Also indicate your average length of stay in the Palliative Care unit.

Reply 10: Thank you for your advice. We have added the general scope of PCUs in Japanese health care system.

Changes in the text: In the Japanese healthcare system, 459 certified palliative care units provide specialist palliative care for patients with advanced malignancies; this specialist care is fully covered by the national insurance. Each PCU has an average of 20 beds and at least one attending physician, and the PCU usually belongs to a general hospital. The PCU plays a major role in end-of-life care but must also facilitate smooth transitions to home care services if appropriate. Per unit, the average number of patients admitted and the number of patients who died at the PCU was 187 and 153, respectively. In 2016, the average length of stay of 32.2 days. Lines 76–80

Comment 11: Line 90: remove "concerning"

Reply 11: Thank you for your advice. I have removed the extra word. Line 70

Comment 12: Line 104: it is unclear to me what happens if you discharged the patient home and they get readmitted. Are you following those patients or are you assuming if they went home they are dying at home? If you didn't follow them after they went home, I would go back and review your data again and report the percentage that died at home. The ability to discharge home is not a great indicator for success. The ability to discharge home successfully and remain home for end of life is the ultimate goal so this needs to be clear in your analysis.

Reply 12: Thank you for your advice. We have clarified that we followed all patients after they went home and added data about home death. We believe the rate of home death was high enough compared with national average (13%), and discharge to home can be an appropriate

outcome in our analysis. We agree with the reviewer's comment about the limitation of using discharge home as an outcome, and we have added this limitation.

Changes in the text: The follow-up period was from the patients' admission to the PCU until their death, and the location of death was identified. Lines 87–88

Among 136 patients who were discharged home, a total of 67 (49.3%) died at home eventually. Line 149

Finally, although we adopted "home discharge" as an outcome, "length of stay at home" may be a more important outcome. The finding that the rate of home death was sufficiently high in our patients who had been discharged home (49% compared with the national average of 13%) provides some rationale indicating the value of this outcome. Future studies might explore "length of home stay" or "home death" as outcomes. Lines 212–216

Comment 13: Line 105-106: unclear to me who are authors 5-10, 14-16? and how many items were measured? Needs to be edited/clarified (say 00 right now, same in abstract)

Reply 13: Thank you for your advice. Please see Reply 4, this was an editing mistake. Line 88

Comment 14: Line 108: what exactly are you measuring when you say "spouse"

Reply 14: Thank you for pointing out the vagueness of this wording. We have clarified that the meaning as "the presence or absence of a spouse."

Changes in the text: ... the presence or absence of a spouse,... Line 91

Comment 15: Line 124-125: clarify what you mean by "reliability and validity of STAS were confirmed"? Did you do your own validation study on this?

Reply 15: Thank you for your advice. Inter-rater reliability and criterion-related validity of the STAS have been tested in previous study, not in this study. I have clarified this as follows.

Changes in the text: The reliability and validity of the Japanese version of the STAS were confirmed in a previous study (20). Line 112-113

Comment 16: Line 220-228: unclear despite the explanation why men would have older caregivers vs women have younger caregivers? Is marital status different?

Reply 16: Thank you for your advice. We mistakenly deleted the data referring to this analysis. We have added the data and modified the description of the discussion. Also, we agree with reviewer' comment that there might be a complex interaction among variables, and this has been included in the limitations.

Changes in the text: The percentage of the patients whose spouse was the primary caregiver was 77% (86/112) among males and 38% (26/68) among females. Lines 152–153

Fourth, although sex was identified as a predictive factor of home discharge, there might be a complex interaction among variables such as the patient's sex, their relationship to the primary caregiver (spouse or not), and the age of the primary caregiver. Lines 209–211

A possible reason women were more likely to be discharged home in this cohort is that less than 40% of the female patients reported their spouse as the primary caregiver compared with approximately 80% of the male patients. This marked difference may indicate that the caregivers for the female were younger people capable of caring for patients. For example, children often become the caregivers for their mothers when they are discharged and moved back to their homes. Lines 188–191

Comment 17: Line 257: Before "However", a "." is missing.

Reply 17: Thank you for your identifying this oversight. It has been corrected. Line 199

Reviewer C

Abstract

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Comment 18

Line 29-30: This could be worded to make the study design clearer

Reply 18: Following the reviewer's comment, we have simplified the description of the study design to make it easier to understand by adding a subheading "Study design" before the Methods" heading.

Changes in the text:

Study design. A single-center retrospective cohort study.

Methods. All 369 cancer patients admitted to ...

Comment 19

Line 34-35: 'Attending physicians recorded 00 items potentially consisting of scale at admission – reword this to make it clearer how the data was collected.

Reply 19: Please see reply 2, this was editing error; sorry for our mistake. We have included the correct details and revised the wording to clarify the data collection of potential scale items.

Changes to the text:

Attending physicians recorded 22 potential scale items at admission, including 1) demographic variables, 2) patient general conditions, 3) vital signs, 4) medications, and 5) patient symptoms.

Line 35–36

... we measured 22 potential scale items available on the first day of PCU admission, Lines 89–90

Comment 20

Line45: Please spell out what AUC means.

Reply 20: Following the reviewer's suggestion, we have added the spell-out of the AUC.

Changes in the text:

...the area under the curve (AUC) in the Abstract, Line 41-42, and in Subjects and Methods, Line 135

Subjects and methods

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Comment 21: Line89-90: More details about how the data was collected. Is all this data routinely collected on admission or was a specific clinical case report form designed? Is the data usually in an

electronic record or on paper?

Reply 21: Following the reviewer's suggestion, we have added details about how the data was collected.

Changes in the text:

The data were collected and reported in patients' electric medical records on admission as a part of routine practice. Line 72

Subjects

Comment 22: Line 97-100: What happened to patients who had multiple admissions were they considered multiple times or excluded after their initial admission?

Reply 22: We have clarified that we used the data from the first admission only.

Changes in the text: The data from the first admission for each patient were used for this study; rehospitalizations (e.g., second or subsequent hospitalizations) were excluded. Lines 84-85

Measurement outcomes

Comment 23: Line 105: Please use consistent formats for references. The references in this line do not have brackets.

Reply 23: Thank you for pointing out the inconsistency. We have corrected all citations and reference list items following the journal's guidelines and NLM uniform requirements.

Comment 24: Line 110: We suggest using the ECOG abbreviation after spelling it out at least once in the first instance. It would be helpful for some readers to know what the performance status levels mean, and not assume the readers know this in the methods section Please reference its validity/ original study.

Reply 24: Following the reviewer’s recommendation, we have added spell-out of the ECOG, and added explanation about ECOG PS with reference.

Changes in the text: According to the Eastern Cooperative Oncology Group [ECOG] performance status scale... Line 93

The admission period was calculated from the day a patient came to the PCU. The ECOG scale provides a consistent reference of measurement indicating the level of function of patients with cancer in terms of caring for themselves, their activities of daily living, and their physical abilities. The items are scored from “0” (fully active, able to carry on all pre-disease performance without restriction) to “4” (completely disabled; cannot carry on any self-care; totally confined to bed or chair) (19). Lines 101–105

Comment 25: Line 111: Definition/description of PPI and what briefly describe what high or low scores mean.

Reply 25: Following the reviewer’s recommendation, we have added explanation about PPI.

Changes in the text: The Palliative Prognostic Index measures a patient’s general conditions based on performance status and several symptoms, such as dyspnea, delirium, oral intake, and edema (20). Scores range from 0 to 15, with higher scores indicating poorer general condition. Lines 105–106

Comment 26: Line 111: Calories ingested on the first day: Who records and assesses this? Is this routinely recorded in Japanese hospital system. How is it recorded? Does it use pictures of food or a specific scale? Why is 520Kcal the cut off for calories? How did you determine this cut off?

Reply 26: Following the reviewer’s suggestion, we have improved the text by clarifying how we calculated calories ingested in this study. The cut-off points were determined ad-hoc in this study, and we have clarified this as a limitation. See also reply 6.

Changes in the text: Patients’ caloric intake was calculated based on the designated calories of the meals provided by the hospital and the percentage of the food consumed (e.g., a patient offered a 1200 kcal meal who ate 20% of the meal was considered to have ingested 240 kcal). The caloric content of meals served in the hospital was routinely reported in the medical record by nutritionists. The percentages of the food consumed were also routinely recorded by ward nurses in 10% increments. Also, food from family members was allowed, and the number of calories eaten was reflected based on the nurse’s report. Lines 107–111

We used ad-hoc cutoff points for all variables because there are no confirmed cutoff points relevant to this study’s aim. Lines 121–122

Comment 27: Line 119-122: Suggest rewording: “The primary cancer sites were divided into the following categories:...”

Reply 27: Thank you for your advice. I fixed it as follows.

Changes in the text: The primary cancer sites were divided into the following categories ...
Line 99

Statistical analyses

Comment 28: Line 151: There was no mention of area under the curve (AUC) calculation in the statistical analysis although this was reported in the results. It would help to say what number is considered a good test and reference if possible.

Reply 28: Thank you for pointing out the need for added details regarding the AUC calculation. Following the reviewer's suggestion, we have added the explanation of ROC and AUC analyses.

Changes in the text: An ROC curve is a statistical method used to analyze the usefulness of a diagnostic method. The curve is formed on the graphical plot by connecting them with a polygonal line. The area under the curve (AUC) is used to quantify the sensitivity and specificity. The AUC value approaches "1" if the diagnostic method has high discriminative power. Lines 133–136

Discussion

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Comment 29: Line 249-255: Consider acknowledging that this applies best to Japanese health care system and culture and may not be applicable in western society. For example the culture of looking after one's elderly family member may be more embedded in the Japanese culture, whilst some of these patients may end up residing in a nursing home in the Western culture.

Reply 29: Yes, we agree with the reviewer's comment, and we have added this as a limitation.

Changes in the text: Sixth, there would be cultural differences in interpreting the study results; for example, the culture of looking after one's elderly family member at home differs among countries. (Lines 211–212)

Comment 30: Line 240: Typo: However, there is conflicting evidence(Space)as ...

Reply 30: Thank you for your advice. I fixed it the spacing issue and checked for any other spacing errors (lack of a space or too many spaces) throughout the paper.

Table 1

Comment 31

Page number 11-12: Univariate analysis for the preferred place of care data is not included in table.

Reply 31: Sorry, this is an editing mistake. We have corrected the omission.

Comment 32: Please be consistent with the terminology: The readers may not understand what PPI or PS is.

Reply 32: Please see also **reply 24** and 25. We have added description of the ECOG PS and PPI in the text and added a footnote for Table 1.

Changes in the text: PS: Eastern Cooperative Oncology Group [ECOG] performance status. ECOG performance status measures a patient's level of functioning in terms of their ability to care for themselves, daily activity, and physical ability, ranging from 0 (fully active) to 4 (completely disabled) .

PPI: Palliative Prognostic Index measures patient general conditions based on performance status and symptoms. Higher score means poor general condition, ranging from 0 to 15.

Figure 1

Comment 33: Spelling mistake: Specificity

Reply 33: I apologize for this typo. I have corrected the spelling in all occurrences in the paper.

Changes in the text: Lines 43, 61, 132, 139, 141, 170, 175

Review Comments (Round 2)

Reviewer A

Thank you for the responses and revision in such a timely manner. One point of clarification. In your reply to my original comment.

'Results

In multi-variate analysis, was the effect of number of admitted days analyzed? It would be good to know how the duration of admission contributed to the discharge?'

You have appropriately mentioned it was not possible to estimate impact of duration of admission in the PCU on discharge outcome. However, my question was related to duration of admission 'in the hospital' prior to transfer to PCU. Were you able to analyze this effect, like, was there a difference in discharge outcome of a patient from PCU who remained admitted in hospital for longer duration before transfer to the PCU vs. shorter duration before transfer?

I feel this is an important variable to study, perhaps in future studies, since a longer duration of admission in the hospital (as compared to shorter) before transfer to PCU, potentially can have a negative effect on discharge outcome. Thank you for your efforts and contributions to this field.

Reply #1

We have now understood the comment of this reviewer in the first review. We agree that the inclusion of admission length before PCU transfer may be an important factor to predict the target outcome; however, we have no referred data in our current database, and thus we have

decided not to add this analysis for this time, instead we have added a limitation sentence that inclusion of admission length before PCU transfer may be important in future study.

Reviewer B

Thank you for responding to all the comments thoroughly and making appropriate edits.

In discussion: you list: First, ... then Second, ... then Third, ... then Finally, ... then Fourth, ... I would remove finally and re-number when you proof read the manuscript.

Reply #2

Following your suggestion, we have corrected this part.

Reviewer C

Congratulations on the amended manuscript. It is much clearer. There are minor changes to help make the article clearer.

Page 3 (Subjects and Methods, first paragraph): The data were collected and reported in patients' ELECTRONIC medical records as part of ... (rather than electric medical records, and rather than as A part of..).

Reply #3

Following your suggestion, we have corrected this part. (line 77)

Page 3 (Subjects and Methods, second paragraph): is the 187 and 153 deaths ANNUALLY? Please clarify this.

Reply #4

Following your suggestion, we have clarified the figures are per year (annually). (line 86)

Page 5 (Statistical analyses, first paragraph). Can the authors please clarify how the patients who were discharged to other hospitals were classified? Were they in the home discharge group or hospital death group?

Reply #5

Following your suggestion, we have clarified the patients who were discharged to other hospitals, we classified them into hospital death group because we followed all of them until death and confirmed that they died in hospitals. (line 125)

Table 2: Can the authors clarify if the symptoms of fatigue OR symptoms other than fatigue was analysed? To be made clearer which variable was significant.

Reply #6

Following your suggestion, we have clarified the symptoms of fatigue were analyzed. We have added a legend: Odds ratios were calculated to identify the patients who discharged to home, so that the Odds ratio of 6.928 means a patient without fatigue has 6.9 times likelihood for home discharge compared with a patient with fatigue. At the same time, we have modified some sentences in text related to this revision for clarification.