

Peer Review File

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Review Comments A

Comment 1: The authors fail to indicate how this variation in vital signs will have an implication on clinical practice. They state in the introduction that they wanted to check whether this variation is predictive of impending death in order to provide appropriate care at the end of life. It is unclear however how would they want that to change care at the end of life? Is it by initiating an end of life discussion earlier?

Reply 1: A detailed understanding of changes in the vital signs of non-cancer patients in the last days of life will provide important insights into the prediction of impending death in non-cancer patients in the dying phase. The purpose of the present study was to investigate whether the vital signs of non-cancer patients change in the last days of life, and not to clarify whether these variations are predictive of impending death in these patients. To date, few studies have focused on “non-cancer patients” in the dying phase of life; therefore, we herein examined whether vital signs changed.

We significantly changed the structure of the “Introduction” session so that the implications for clinical practice were easy to understand as follows:

Changes in the text:

End-of-life care, particularly within 3 days of death, is important for patients and their families (1, 2). The findings of a nationwide survey of bereaved families of terminal cancer patients in palliative care units in Japan revealed that more than 90% of family members wanted to be present at the moment of death (3). Furthermore, previous studies suggested that care in the dying phase may affect the psychological prognosis of bereaved families (4)(5). Medical professionals have to make many important decisions for patients and their families in the last days of life, including the discontinuation of invasive treatments and informing family members and close friends in time (6)(7). (Page 4, Line 42-49)

A detailed understanding of the clinical course of non-cancer patients in the dying phase is critical for the provision of appropriate care in the last days of life (7). A number of symptoms, signs, and changes in vital signs occur in the last three days of life of cancer patients (8), based on which many

prognostic models have been developed (9)(10). Routine measurements of vital signs are conducted in daily clinical settings, and previous studies reported changes in these signs in cancer patients immediately before death (11)(12)(13). Although non-cancer patients appear to have a similar clinical course in the last days of life as advanced cancer patients, there is currently no information on changes in the vital signs of non-cancer patients before death. If similar changes in vital signs in last days of life occur in non-cancer patients and terminal cancer patients, the same indicators of prognosis used for cancer patients in the dying phase may be applied to non-cancer patients. (Page 4, Line 50-page 5, Line 61)

Comment 2: These patients are non-terminal cancer patients and not all variation in vital signs will necessarily translate into impending death and the authors do not control for any confounding factors and there is no control group as the selection criteria required for death to occur.

As mentioned in Reply 1, the present study was solely intended to investigate the presence or absence of changes in vital signs in non-cancer patients who died at a hospital. We did not think there was a need for a control group because we used a linear mixed model to clarify whether the gradient of the line across the time variable significantly differed from zero.

On the other hand, following Reviewer A's suggestion, we reconsidered potential confounding factors and changed the text as follows:

Changes in the text:

Furthermore, subjects in the present study were acutely ill, and many had received medications that may have affected their vital signs and survival times, including fluid therapy, antipsychotic medication, antiarrhythmic drugs, and steroids.(page 9, Line 137-140).

Comment 3: The clinical implication of this study is unclear and the conclusion of this study cannot be generalized even to the theoretical study population of non-cancer patients.

As mentioned in the Reply, clarifying changes in the vital signs of non-cancer patients in the dying phase will contribute to the development of tools to predict impending death in non-cancer patients in the last days of life.

As Reviewer A pointed out, this was a single-center study with a small sample size.

Referring to comment 5 from Reviewer C, we changed "Limitations" accordingly as follows:

Changes in the text:

This was a single-center study with a small sample size. We used the Shapiro-Wilk test to confirm the normal distribution of each vital sign, and confirmed that the distributions of vital signs were generally normal. However, this is not a fatal issue in an exploratory study. Further studies are needed to establish whether the changes observed in vital signs in the dying phase are similar in other settings with a large sample. (Page 9, Line 132-137)

Review Comments B

Comment 1: Figure 2 and its description are inconsistent. Please see the legend of Figure 2. For example, is it right " $P < 0.001$ (days before death > -3)" ?

Reply 1: As Reviewer B pointed out, Figure 2 may be misleading; therefore, we changed the wording to “Day-7 to -3.5” and “Day-3 to death” in Figure 2.

Comment 2: One important concern is whether the study is reproducible. First, there are small sized subjects. The normality distribution should be assumed for the T test. For example, it is necessary to clarify whether the distribution of blood pressure was normal.

Reply 2: We used the Shapiro-Wilk test to confirm the normal distribution of each vital sign. For example, regarding systolic blood pressure (-7.0, -3.0, -0.5 days), probability (P) values were 0.533, 0.35, and 0.052, respectively. P values for heart rate were 0.85, 0.097, and 0.602, respectively. Although we tested other vital signs and confirmed generally normal distributions, the distribution of some vital signs was not normal. However, this is not a fatal issue because this was an exploratory study. Thus, further studies are needed to confirm whether changes in vital signs in the dying phase are similar with a large sample.

We changed the Discussion as follows:

Changes in the text:

This was a single-center study with a small sample size. We used the Shapiro-Wilk test to confirm the normal distribution of each vital sign, and confirmed that the distributions of vital signs were generally normal. However, this is not a fatal issue in an exploratory study. Further studies are needed to establish whether the changes observed in vital signs in the dying phase are similar in other settings with a large sample. (Page 9, Line 132-137)

Comment 3: This manuscript was written in the same way as the study published by Bruera et al (Reference 11) and the results are similar. Originality seems to be low. It is need to check up plagiarism using identified program.

Reply 3: The present results are significant because non-cancer patients may show the same changes in vital signs as cancer patients in the dying phase. Although Bruera et al. limited their study population to terminal cancer patients who were admitted to the Acute Palliative Care Unit in the United States, the present study only targeted non-cancer patients.

We also checked for plagiarism using an identified program (iThenticate) and the text match rate was 4%.

Review Comments C

Comment 1: This is a secondary analysis of a retrospective study to examine survival after decreased oral intake in “terminally ill noncancer patients”. The objective, sample size, and study design for the main retrospective study need to be clearly outlined.

Reply 1: The purpose of the main study was to examine the development of a markedly reduced oral intake and investigate factors related to subsequent survival times in non-cancer patients. We included patients who were older than 20 years old and had died between April 2017 and April 2018. We excluded patients who were diagnosed with cancer, received tube feeding or central venous nutrition, or were on a ventilator during hospitalization, and who died within three days of admission. We included eighty-two patients who died in the hospital during the study period.

We changed the text as follows for clarity and to describe the methodology of the main retrospective research.

Changes in the text:

The main retrospective study was a medical chart review of non-cancer patients admitted to the General Medicine Ward of Kamisu Saiseikai Hospital, Ibaraki, Japan. (Page 5, Line 70)

Comment 2: How was “terminally ill” defined?

In the present study and main retrospective study, we examined the data of non-cancer patients who

had died. We used the expression “terminal” patient to indicate a patient in the dying phase, particularly within 3-7 days before death.

We changed the word “terminally-ill” in the Abstract and text as follows to prevent any misunderstanding.

Changes in the text:

Furthermore, although vital signs are routinely measured in clinical practice, changes in vital signs in the dying phase in non-cancer patients have not yet been elucidated in detail (Abstract, Page 2, Line 19).

End-of-life care, particularly within 3 days of death, is important for patients and their families (1, 2) (Page 4, Line 42)

The present study involved a secondary analysis of a retrospective study performed to examine survival times following marked decreases in oral intake in non-cancer patients in the dying phase (Page 5, Line 68).

Comment 3: It is a bit confusing that this study included patients who died between April 2017 and April 2018, but the investigators posted Information about the study “on a notice board in the hospital, to provide an opportunity for the study subjects to refuse to participate”.

We provided information on the research content on a notice board in the hospital before the start of this study, and then collected and analyzed data. According to this comment, we changed the text as follows,

Changes in the text:

The need for informed consent from family members was waived by the Institutional Review Board of Kamisu Saiseikai Hospital because this study only involved a retrospective chart review. Information on the study content was presented on a notice board in the hospital before its initiation. (Page 6, Line 78-81)

Comment 4: Please clarify the proportion of patients with missing data in regard to vital signs.

Reply 4: There were no missing data because vital signs were routinely measured at this hospital and there were no omissions in the medical records. On the other hand, the number of data points at

each time differed because the length of hospital stays varied between patients. We added table 2.

Comment 5: The sample size was very small and this needs to be justified and explained as a limitation.

Reply 5: We have added the following sentences to the text.

Changes in the text:

This was a single-center study with a small sample size. We used the Shapiro-Wilk test to confirm the normal distribution of each vital sign, and confirmed that the distributions of vital signs were generally normal. However, this is not a fatal issue in an exploratory study. Further studies are needed to establish whether the changes observed in vital signs in the dying phase are similar in other settings with a large sample. (Page 9, Line 132-137)

Comment 6: The underlying disease in Table 1 is not well characterized. Did these patients have advanced illness (e.g. end stage liver failure, stage IV chronic kidney disease) or did they just have a diagnosis of liver disease (regardless of stage). The main underlying disease contributing to death (e.g. stage IV heart failure) should be clearly stated along with any acute complications (e.g. myocardial infarction).

Reply 6: Following this comment, we modified Table 1 (Page 16).

Comment 7: This is a very mixed population of patients and this needs to be discussed. 15 (31%) had “others” and this should be better described.

Reply 7: The other causes of death were as follows: dementia in seven patients, septic shock in five, and gastrointestinal bleeding in three. We modified Table 1 accordingly.

Comment 8: In the results section, it would be helpful to describe the absolute values of vital signs as well as actual magnitude of change.

Reply 8: According to this advice, we added the absolute values of vital signs as Table 2 (Page 17). The actual magnitude of changes in vital signs was not necessary because changes in vital signs were observed in each section (Day -7 to -3.5, and Day-3 to death) using a linear mixed model.

Comment 9. Please clarify if patients were on supplemental oxygen.

Reply 9: We added the following sentence to the text.

Changes in the text:

Vital signs were collected from medical records for up to seven days before the date of death, and included systolic and diastolic blood pressure, heart rate, body temperature, and oxygen saturation (Patients received supplemental oxygen depending on their conditions), which were routinely documented at this hospital. (Page 6, Line 89-92)

Comment 10. Typo “Bruela” vs. Bruera in discussion 2nd paragraph.

Reply 10: We changed the relevant parts in the text.

Changes in the text:

Bruera et al. also found significant decreases in blood pressure and oxygen saturation in the three days before death in terminal cancer patients (Page 8, Line 123).