Peer Review File

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Reviewer A

Comment 1: I would advise to review the parts that I evidences in blue. Some figures, like the ratio of dyspnea, need to be reviewed since.

Reply 1: We have reviewed and revised your suggestions. However, some issues have not been modified such as inclusion criteria (Page 6, line 1-12).

Changes in the text:

Page 2, line 13-17: Dyspnea was the most reported symptom of suffering (81.08%), followed by fatigue, constipation, and pain (41.89%, 35.14%, and 25.34%, respectively). All cases experienced fatigue, depression, and anxiety received pharmacological treatment. Dyspnea, pain, sleep/wake disturbance, nausea/vomiting, delirium, and malignant bowel obstruction were treated in at least 80% of the cases experiencing suffering.

Page 7, line 10-11: There was a typo error. It has been corrected to "The majority of patients were male (55%), with an average age of 67.69 (14.77) years.".

Page 8, line 2-4: Dyspnea, pain, nausea/vomiting, delirium and malignant bowel obstruction were treated in at least 80% of each symptom. Remaining suffering symptoms, including constipation, diarrhea, anorexia/cachexia, and sedation, were treated in at least 50% of cases.

Page 8, line 6-8: Of these, 104 admissions (43.51%) received treatment for underlying conditions contributing to dyspnea, such as respiratory tract infection, congestive heart failure, ascites, and acute exacerbation of chronic obstructive pulmonary disease.

Page 9, line 1-4: Regarding constipation, it was found that 36 out of 104 cases (34.6%) were caused by opioid use (opioid-induced constipation, OIC). Among these, 80% (32 out of 36) received laxatives, predominantly sennosides, magnesium sulfate, and lactulose. Meanwhile, 8.3% (3 out of 36) received ispaghula husk, a bulk forming laxative.

Page 20, Table 2: All figures in Table 2 has been reviewed and revised.

Comment 2: I would also advise to keep pharmacological explanations shorter in the discussion. E.G., best treatment for refractory OIC cannot be necessary bulking forming agents.

Reply 2: We have revised this sentence according to your suggestion.

Changes in the text:

Page 12, line 17-19: As a result, stimulant laxatives and osmotic laxatives are typically recommended as the first line treatment for OIC. It is important to note that some of our patients received ispaghula husk, a bulk-forming laxative, is not effective for treating OIC.

Comment 3: One major point that authors need to amend is the idea of "palliative care diagnosis". PC is not a diagnosis, is a situation of multidimensional needs linked to presence of life threatening or progressive disease. Please review and amend this concept.
Reply 3: Intentionally, "time since palliative care diagnosis" means the time of palliative care service had been provided to patient.
Changes in the text: We have modified this term from "time since palliative care diagnosis" to "time since palliative care was provided" (Page 6, line 15), "… received their first diagnosis of palliative care …" to "… received palliative care …" (Page 9, line 22), "Intention of palliative care diagnosis" to "Intend to receive palliative care" (Page 19, Table 1)

Comment 4: The figure provided about the death rate and the length of PC assistance tell a lot about the very late referral, consistently with the idea of meeting those patients just when they reach the hospital for their final crises. The importance of this work is that it depicts the reality of many places where the idea of early PC is still a dream.
Reply 4: Thank you for your great suggestion. We have included this issue in the highlight box.
Changes in the text:
Page 4, line 11-12: There is an urgent need to heighten awareness and provide early palliative care to target patients in tertiary care hospitals to achieve better care outcomes.

Comment 5: There is a need of English professional review throughout the manuscript.
Reply 5: The manuscript has been proved and edited by native.
Changes in the text: All of content in this manuscript has been revised by native.

Reviewer B

Comment 1: Please have the manuscript be read and edited by a native speaker, there are too many grammatical mistakes in the English language at present.
Reply 1: The manuscript has been proved and edited by native.

Changes in the text: All of content in this manuscript has been revised by native.

Comment 2: under methods can you explain how it was determined if an opioid was given for dyspnea or pain, if a patient suffered from both symptoms?

Reply 2: Because the study was a retrospective review of medical charts, all prescribed medications and their indication (dyspnea, pain, or both) were recorded in the doctor's order sheet. However, if not stated in the doctor's order sheet, the indications could be found in the nurse' note.

Changes in the text:

Page 6, line 22-24: All prescribed medications and their indications for individual suffering symptoms were recorded in the doctor's order sheet. However, if not stated in the doctor's order sheet, the indications could be found in the nurse' note.

Comment 3: under results. you write that the duration of palliative care was 9 days on average, but it is unclear if that means those 9 days were the length of the hospital stay or the time until death. one could assume that if the patient left the hospital alive, palliative care could have continued by primary care givers. so this needs explaining (definition for duration of palliative care)

Reply 3: Duration of palliative care in this situation was started at time of palliative care was provided until finished that hospital admitted with any discharge status.

Changes in the text:

Page 7, line 15-17: The average hospital stay duration was 14.32±13.43 days, whereas the average duration of palliative care during admission was 9.00±10.54 days.

Comment 4: Around the clock iv morphine/fentanyl: is bolussing for breakthrough pain (or dyspnea worsening) allowed in your protocols?

Reply 4: Due to the retrospective design of the study, all medications were permitted for use. Subsequently, the authors categorized all prescribed medications into ATC regimen, or as-needed regimen as shown in Figure 1 and 2.

Changes in the text: -

Comment 5: Constipation is indeed a symptom one sees quite often, and therefore, several guidelines state that laxatives should be given from the start of treatment with long acting

opioids. it is not clear if this is also the practice in your institution, and this information should be added so that the reader can place the occurrence of constipation in context.

Reply 5: Due to the retrospective design of the study, this finding reflects actual clinical practice in our setting, despite all practice guidelines, including local guideline, recommending the prescription of laxatives for every patient receiving long-term opioid treatment.

Changes in the text:

Page 9, line 1-4: Regarding constipation, it was found that 36 out of 104 cases (34.6%) were caused by opioid use (opioid-induced constipation, OIC). Among these, 80% (32 out of 36) received laxatives, predominantly sennosides, magnesium sulfate, and lactulose. Meanwhile, 8.3% (3 out of 36) received ispaghula husk, a bulk forming laxative.

Page 12, line 24-25; Page 13, line 1-5: In addition, treatment for constipation was primarily provided when patients experienced symptoms (68 out of 69 cases received laxatives for symptomatic treatment). However, if the constipation was mild, the treatment did not be initiated even if the patient received opioid. This finding reflects actual clinical practice in our setting. Thus, healthcare providers should be mindful in treating and preventing constipation, especially when opioid have been prescribed.

Comment 6: You did not grade the severity of the symptoms. this is an important limitation to your study, and could be attributable to the fact that it was a retrospective chart study. however, the severity of the symptom (for example as classified via CTCAE) would most likely guide the pharmacological treatment. please comment on this aspect in the discussion.

Reply 6: We also addressed this issue and discussed how severity grading affects our study, particularly in relation to pain management, in the discussion part. (Page 12, line 7-13) However, this concern will be included in the limitations of our study.

Changes in the text:

Page 13, line 9-11: These data, especially severity of each suffering symptoms, could offer valuable insights into the medication patterns used to alleviate suffering symptoms in individual patients.

Comment 7: Many centers have nurses and or pharmacists that play a role in palliative care, for example in monitoring for symptoms, patient education on self management and proposals for specific treatments. you explain the need for multidisciplinary care in your discussion but you give no insight into how these professions are currently engaged in your hospital. kindly elaborate on this so that the reader understands the setting better.

Reply 7: We incorporated your suggestion into the discussion part. Additionally, this concern has been included in the limitations of our study. (Page 13, line 14-16)

Changes in the text:

Page 9, line 9-12: Since there are no palliative care specialist physicians or other healthcare professionals specialized in palliative care in our hospital, treatment related to suffering symptoms is managed by general physicians or specialists in other areas.

Reviewer C

Comment 1: I disagree with you conclusion and highlight box statements on the "inappropriate use of opioids"

- You state that the "inappropriate use of opioids for treating suffering symptoms, especially for dyspnea and pain, remain a significant concern." (conclusion) and "Nearly all patients experiencing pain or dyspnea received pharmacological treatment, but the prescription of opioids for managing these suffering symptoms was still inappropriate. (highlight box)

- However, I don't believe you have fully supported this statement as throughout your discussion you explicitly state on p. 6, line 32-39, you cannot determine appropriateness of opioids for individuals without first identifying their type of pain and assessing pain severity, to determine the dosage and/or interventions for effective symptom relief. But throughout your discussion, you are stating your observations study population level and making assumptions at the study population level. For example, in theory, although only half of your population received ATC opioid prescriptions for pain, it is possible that that was appropriate for each those individuals. You could amend the wording to state "potentially inappropriate use of opioids for treating..."

- Additionally, 'appropriateness' of medications must align with the patient's preferences. If patients refuse palliative care interventions, then giving them palliative care medications could be inappropriate for that individual.

- Through your discussion, you do refer that the dosage, route, regimen, to the fact that "appropriateness" is dependent on the individual

o P.6, lines 8-12 – the argument is that opioids should be used to treat dyspnea when dyspnea can't be corrected by treating underlying causes – so the use of opioids is 'appropriate for these cases'

o P. 6, lines 12-18 – the argument is that you can achieve effective symptom control with low-dose (30mg or oral), but higher doses (of IVIF) can be appropriate for those with advance stages of disease or those at the end-of-life – so the dosage and route of 'appropriate opioids' is dependent on disease progression for the individual

o P. 6, lines 40-48, is making the argument that ATC regimen should be the standard for opioids for this population, but only 50% of patients received this regimen in your setting

In relation to the "appropriateness" comments, I believe a finding you should emphasize in your conclusions and highlight box, is that the use of pain assessments should be [utilized more or standard practice], to inform pain management treatments.

- You note that not everyone experience pain received a pain assessment. Therefore, you can't make assumptions about the 'appropriateness' of these opioids: the reason (p.6, 8-12), dosage (p.6, lines 12-18), and regimen (p.6, 40-48).

Reply 1: We have removed these two statements under key findings in the highlight box, and revised to demonstrate our findings and limitations of the study. In addition, we have removed term "appropriateness" from our manuscript.

According to your recommendation, we realize the incompatibility of discussion and the point we attend to emphasize. Appropriateness of pharmacological treatment should be started from patients and then their assessment process is the keyword of satisfied outcome. Unavailable this step making it difficult to assume the appropriateness of some situation as your arguments. Thus, we hope that comprehensively the patient evaluation process could be clarified more and indicated the true problem in the treatment process.

Changes in the text:

Page 2, line 20-21: This statement has been removed.

Page 4, line 3-5 in highlight box: Our study revealed that suffering symptoms were routinely identified in hospitalized palliative care patients by non-palliative care specialists, but there was still a lack of comprehensive assessment of their severity.

Page 13, line 9-11: These data, especially severity of each suffering symptoms, could offer valuable insights into the medication patterns used to alleviate suffering symptoms in individual patients.

Page 13, line 13-15: This statement (However, our result …. Non-palliative care specialists.) has been removed.

Page 13, line 21-23: While more than 50% of all suffering symptoms received pharmacological treatment, the lack of comprehensive assessment of symptoms severity remained a significant concern.

Comment 2: Within the highlighted box, you state "Efforts should be directed towards improving the prescription practices for managing suffering symptoms comprehensively, beyond just pain and dyspnea". However, your results show and state "Pharmacological treatment of each suffering symptom was provided to more than 80% of hospitalized patients, except for constipation and anorexia/cachexia." Further, in the discussion you do not include any comments/elaboration about the symptoms beyond pain, dyspnea, and constipation (in relation to opioid use). Please remove the statement from the highlighted text box.
Reply 2: We have modified this statement to focus on the comprehensive assessment of dyspnea and pain.
Changes in the text:
Page 4, line 13-14 in highlight box: Efforts should be directed towards improving the assessment of dyspnea and pain severity for comprehensive management of suffering symptoms.

Comment 3: Within the highlight box, you state "There is limited data available regarding pharmacological treatment for each suffering symptom in patients received palliative care." However, this is not the case. Internationally, there are many studies that report pharmacologic treatments for symptoms. Please revise to make the statement accurate (e.g., "… received palliative care in Thailand.", etc) or remove the statement.
Reply 3: We have removed this statement and revised to highlight the role of treatment by non-palliative care specialist physicians in tertiary care hospitals.
Changes in the text:
Page 4, line 7-9 in highlight box: Suffering symptoms in patients received palliative care are well recognized and adequately managed with pharmacological treatment by non-palliative care specialist physicians in tertiary care hospitals.

Comment 4: - Methods, include 1-2 sentences of how you categorized "causative treatment" and "symptomatic treatment" for medications.
Reply 4: We have added your suggestion in the Methods part.
Changes in the text:

Page 6, line 24-25; Page 7, line 1-2: Treatment was categorized into two groups: causative treatment and symptomatic treatment. Causative treatment is defined as treatment focused on the underlying cause of each symptom. If the underlying cause could not be identified, the treatment was classified as symptomatic treatment.

Comment 5: - Methods, how were people that didn't want palliative care account for in the study. Were they excluded? If they were included, did you count their symptoms in the symptom counts?

Reply 5: All participants in this study had to receive palliative care as documented by physician in their medical charts. Therefore, individuals who didn't want palliative care were not included. (Page 5, line 24-25)

Changes in the text: -

Comment 6: - Results: If you have data on how often strong opioids were used in ATC regime for dyspnea, please include (related text: p 4, lines 33-35, "Strong opioids, including morphine intravenous infusion (IVIF) and fentanyl IVIF, were the most frequent treatments as part of the ATC regimen for dyspnea.")

Reply 6: We have included the frequency (percentage) of each medication in the text. Additionally, we have corrected some typos (changed fentanyl IVIF to midazolam IVIF).

Changes in the text:

Page 8, line 12-14: Strong opioids, including morphine intravenous infusion (IVIF, 61/135) and midazolam IVIF (21/135), were the most frequent treatments as part of the ATC regimen for dyspnea (45.12%, and 15.56%, respectively).

Comment 7: o Logic error, need to add yellow text: p.4, lines 22-25 "Dyspnea, pain, nausea/vomiting, delirium and malignant bowel obstruction were treated in over 80% of all admissions with reports of having that symptom. However, the remaining suffering symptoms, including constipation, diarrhea, anorexia/cachexia, and sedation, were treated in more than 50% of all admissions with reports of that symptom".

As you already say, only n=75, 25.34% of all admissions had pain. Of those 75 individuals, n=74 (98.67%) of individuals had a treatment for pain. Therefore, of all admission, only n=74/296 had a treatment for pain =/= >80% of all admissions.

Reply 7: Thank you for pointing this out. We have revised the term “of all admissions” to “of each symptoms”. Thus, the total number used to calculate the proportion should be the frequency of each symptom.

Changes in the text:

Page 8, line 2-4: Dyspnea, pain, nausea/vomiting, delirium and malignant bowel obstruction were treated in at least 80% of each symptom. Remaining suffering symptoms, including constipation, diarrhea, anorexia/cachexia, and sedation, were treated in at least 50% of cases.

Comment 8: Abstract: “Pharmacological treatment of each suffering symptom was provided to more than 80% of hospitalized patients, except for constipation and anorexia/cachexia”

But abstract states “Constipation, diarrhea, and anorexia/cachexia were treated in approximately 66.35%, 78.57% and 67.86 of cases, respectively.”

Reply 8: We have revised this issue in the highlight box to another statement according to Reviewer 3’s suggestion.

Changes in the text:

Page 4, line 3-5: Our study revealed that suffering symptoms were routinely identified in hospitalized palliative care patients by non-palliative care specialists, but there was still a lack of comprehensive assessment of their severity.

Comment 9: - P.6 line 4-5, “Concerning treatment of dyspnea, one patient in our study did not receive any treatment for dyspnea as they were denied all treatment.” Was it that the patient denied all treatment, or the providers denied the permission. If the former, remover “were” in the sentence. If the later, you need to expand to explain why this would happen in a hospital setting.

Reply 9: This was due to the patient’s refusal of all interventions.

Changes in the text:

Page 10, line 21-22: Concerning treatment of dyspnea, one patient in our study did not receive any treatment for dyspnea due to refusal of all interventions.

Comment 10: Finally, given you conducted medical chart reviews, I would strongly encourage you to also evaluate whether these treatments relieved the symptoms or not. Knowing what symptoms are and what is prescribed is reported throughout the literature in various settings (e.g., internationally and in various care settings (hospitals, hospices, community, nursing homes)) but there is less literature on whether what is prescribed relieves symptoms.

Reply 10: This suggestion is very valuable. However, clinical outcomes after receiving pharmacological treatments could not be evaluated due to incomplete and unsystematic records. We have included this statement in the limitations of our study.

Changes in the text:

Page 13, line 9-11: Additionally, clinical outcomes after receiving pharmacological treatments could not be evaluated due to incomplete and unsystematic records.

Comment 11: Minor typo:

- Small typo: p. 4, line 6, ..with an average age o3-5f 67.69
- Small typo: All cases [who or that] experienced fatigue, depression, and anxiety received appropriate pharmacological treatment.

Reply 11: We do the typing correction as your advice.

Changes in the text:

Page 7, line 10-11: The majority of patients were male (55%), with an average age of 67.69 (14.77) years.

Page 2, line 15-16: All cases experienced fatigue, depression, and anxiety received pharmacological treatment.