Peer Review File

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Reviewer A

This is a retrospective cross-sectional study trying to explore how cancer type affects opioid dose, which sounds like an interesting but unanswered topic in the oncological world. It also tries to examine the effect of adjuvant analgesics on opioid dose.

Listed below are some comments and questions.

Introduction

1. What is the rationale behind the decision of focussing on "slow release" opioid only, instead of including all patients on regular strong opioids?

Reply: All patients on regular strong opioids were included in the study. Patients not taking slow release opioids who were only taking immediate release opioids on an as-required basis were excluded, as those patients do not represent the chronic cancer pain cohort that this study aimed to examine. For those patients on slow release opioids, slow release opioid data was used to represent a stable baseline daily opioid requirement to allow comparison between patient groups. Additional immediate release opioids taken varied from day to day and was difficult to properly quantify in our study which looked at dose on discharge from hospital as an indicator of reasonable stable adequate opioid dose at that timepoint to control pain. Thus this immediate release opioid dosing is not seen as a reliable source of stable opioid requirement that would allow a just comparison between groups.

Changes in the text: In order to capture an equal timepoint reflecting pain control for all patients, patient records were audited on day of hospital discharge to represent stable regular opioid dose as a measure of sufficiently controlled pain. . Immediate release opioids were excluded on the basis that day-to-day dosing was highly variable, thus not being a reliable indicator of stable opioid requirement that would allow a just comparison between groups, in addition to being the minority opioid requirement.
(Methods, lines 72-78)

2. What is rationale behind setting up a study to investigate whether there is any association between opioid dose and cancer type? With this primary objective, the research question seems to be looking at whether a specific cancer type predicts a poor pain control. What is the biological plausibility of a certain cancer type leading to poorer control?

Reply: The biological plausibility here refers to the various likely pain syndromes experienced according to primary site and likely metastatic site. An example in the introduction (lines 48-50) refers to head and neck cancers, which have a greater likelihood of presenting with neuropathic pain from its primary, where neuropathic pain is known to be less responsive to

opioids, requires higher opioid doses, and has poorer outcomes. Pain from primary or secondary brain tumours result from peritumoural oedema and can be associated with nausea and vomiting, which is most effectively managed using corticosteroids, with opioid having an adjunctive analgesic role instead.

There is limited data to further reference this because this is understudied, hence the motivation to conduct such a study.

Changes in the text: Pain from primary or secondary brain tumours result from peritumoural oedema and can be associated with nausea and vomiting, which is most effectively managed using corticosteroids, with opioid having an adjunctive analgesic role instead[10,11]. (Introduction, lines 51-53)

3. "The prescription of adjuvant analgesics by cancer type and their effect on opioid requirements in cancer pain were examined as a secondary outcome" - Was the study looking for a causal relationship (as opposed to association) between adjuvant analgesics and opioid dose?

Reply: The study was looking to examine any associations within the data between prescription of adjuvant analgesics and slow release opioid dose.

Changes in the text: The secondary objective was to examine for any associations between SR opioid dose and adjuvant analgesic type and dose. (Introduction, lines 60-61)

4. Are there any other secondary outcomes apart from the use of adjuvant analgesics? If not, how was this secondary outcome selected? Is this defined a priori?

Reply: Yes, this was defined a priori. The text has been modified to provide further clarification on this.

Changes in the text: The secondary objective was to examine for any associations between SR opioid dose and adjuvant analgesic type and dose. (Introduction, lines 60-61)

Methods

1. What is the rationale of focussing on hospitalised patients, rather than including both in-patients and out-patients? This probably limits the generalisability of the study results, as hospitalised patients may not represent the general population of cancer patients.

Reply: We agree that inclusion of both inpatients and outpatients could have improved generalisability, however this would also mean a more varied cohort. Mixing inpatients and outpatients would also be tricky and introduce groups of confounders. The inclusion of only inpatients on discharge was done to represent a cohort with chronic cancer pain, and at a timepoint where their pain was satisfactorily controlled to the point of being discharged from hospital (patients with poorly controlled pain are not discharged). Outpatients are inevitably

at various levels of pain (e.g. uncontrolled pain requiring or declining an inpatient admission vs controlled pain post recent discharge). In order to include outpatients and compare both groups equally, one would need to identify outpatients with satisfactorily controlled pain and at an equal timepoint. These were outside the scope of our study.

Although this study only includes inpatients, these were the aims at the outset and these limitations are discussed in the paper, however this limitation now been made more clear.

Changes in the text:
Outpatients were not included as they form a different heterogenous group with various pain levels, hence the opioid dose used is not always a reflection of sufficient opioid dose required to achieve satisfactory pain control, and thus cannot be treated the same as the opioid dose of an inpatient at discharge timepoint. (Methods, lines 76-78)

The study was performed in an inpatient cohort within a large quarternary cancer centre, thus may have included patients who had more complex pain. The inclusion of outpatients however would have included a varied cohort of patients, ranging from poorly controlled to well controlled pain, hence the opioid doses would not have been able to be equally treated..(Limitations, lines 215-218)

2. How did you decide on the 12 distinct cancer types? Is this according to some standard classification?

Reply: 12 cancer types were chosen to include representation of as many cancer types as possible. The classifications were chosen based on the World Health Organisation classification of cancer types. Some cancer types were combined due to limited representation to the health service.

Changes in the text:
The classifications were chosen based on the World Health Organisation classification of cancer types. Certain cancer types have been grouped to anatomical location (e.g. kidney/bladder, oesophageal/gastric) due to relative limited representation to the health service. (Methods, lines 68-69)

3. “Patients were dichotomised into those that had been prescribed SR opioids at discharge and those who had not” - Are those patients who had not been prescribed SR opioids at discharge not on opioids at all?

Reply: That is correct.

4. Is it on some basis that the capping for each cancer type is at 20? Has there been a consideration on the statistical power to differentiate differences between the various cancer types?

Reply: This was based on convenience sampling. There were no previous relevant similar studies conducted to calculate statistical power. Please see answer to next question for further

details.

5. It was recorded that 151 discharges were excluded on the basis of exceeding 20 patients per cancer type. What are the inclusion and exclusion criteria to decide which discharges are included or excluded when the number exceeds 20 for a certain cancer type? Are they randomly selected? How did you avoid or minimise selection bias?

Reply: Patient records were examined sequentially for cancer type. For the SR opioid group, recruitment for each of the 12 distinct cancer types was intended to be capped at twenty patients. This was chosen for convenience sampling, and to limit bias against certain cancer types being disproportionately represented, allowing for meaningful comparison between all included cancer types (irrespective of differing cancer prevalences). This is already included in the text (Methods, lines 83-86).

6. Which opioid drug were the patients prescribed with? How was that converted to oMEDD? It probably would be better to specify the conversion ratio.

Reply: Information on the various opioids prescribed is described, however now updated for clarity.

For standardization of data analysis, SR opioid dose was converted to oral morphine equivalent daily dose (oMEDD) using a standardised evidence-based calculation(12). (this is already included in the text; Methods, lines 95-96). This conversion ratio references a contemporary evidenced-based Opioid Dose Equivalence Calculation Table published by the Australian and New Zealand College of Anaesthetists; 2021.

Changes in the text:

For standardization of data analysis, SR opioid dose was converted to oral morphine equivalent daily dose (oMEDD) using a standardised evidence-based calculation which varied between opioids according to contemporary evidenced-based opioid dose equivalence calculation table(12). (Methods, lines 95-97)

The commonest SR opioid prescribed was oxycodone (57%, n=123) followed by morphine (21%, n=45). (Results, line 128)

Added Table 2: **Median oral morphine equivalent daily dose according to opioid type**

Statistical analysis

1. “Participants with missing data were excluded” - What kind of data were missing? How many patients were excluded due to missing data? Which cancer type did they belong to?

Reply: There was 1 melanoma patient without opioid type information. This has now been clarified in the text.

Changes in the text:

Participants with missing data were excluded (1 patient with melanoma without opioid type). (Statistical analysis, lines 112-113)

2. Would you consider to include in Figure 1 the fact that some patients were excluded due to missing data?

Reply: This has now been included in Figure 1.

Results

1. Do we know more details about the disease pattern apart from the primary cancer type, e.g. the presence or absence of metastases, sites of metastases and number of metastatic sites? These are perhaps more important factors than the primary cancer type in contributing to pain.

Reply: All patients were incurable (Stage IV or locally advanced unresectable cancer), and intent of opioid use was for palliative management of cancer pain (see Methods, line 67-68 and Figure 1). Sites and number of metastatic sites were not included, and are not normally included in similar literature.

2. Slow release opioids are usually available in certain defined dosage strengths. How did the dosing for the slow release opioids look like? - As the oMEDD could also be limited by the dosing of the slow release opioids, and this might in turn affect whether differences in median oMEDD could be detected among different cancer types.

Reply: It is unlikely that clinicians would prescribe vastly different opioid doses simply based on available opioid dose preparations. Morphine and oxycodone comprised of 78% of the opioids prescribed. We have added Table 2 to provide more information on opioid dose by opioid type.

3. Did all the included patients have cancer pain? What was the nature and the sites of the pain?

Reply: Yes, all patients had cancer pain as specified in the study objectives (see Introduction, line 61). The exact nature and site of pain can only be determined using a prospective data collection method which was outside the scope of this study, and is recognised as a limitation (see Limitations, lines 218-219).

4. How was the pain control of the included patients? As we all know, opioid dose is only a surrogate marker for pain control, the median oMEDD among different cancer type groups can only be compared when the patients have comparable pain control. Without proper pain assessment outcomes, comparison of oMEDD would not be meaningful.

Reply: Although pain scores at specific timepoints are unable to be determined in a retrospective dataset, the best surrogate for opioid dose reflecting controlled pain is at the hospital discharge timepoint, which was the timepoint used in this study. This is recognized and mentioned in the methods and limitations sections. Other studies examining similar outcomes did not attempt to collect their data at timepoints reflecting controlled pain, nor did they collect data on pain control, hence we deem our study more considered in this matter.

5. How do you define adjuvant analgesics? Paracetamol may not be commonly considered as adjuvant analgesics.

Reply: Adjuvant analgesics are co-analgesics often utilised with opioids to achieve control of cancer pain through multimodal analgesic action(5) and may reduce opioid dose and adverse effects by potentiating analgesic effects through non-opioid pathways(6, 7). (see introduction, lines 43-44).

Paracetamol is considered an adjuvant analgesic based on recent studies that refer to paracetamol as such below. This has been clarified in the methods section.
(1) Wheeler KE, et al. Adjuvant Analgesic Use in the Critically Ill: A Systematic Review and Meta-Analysis. Crit Care Explor. 2020 Jul 6;2(7):e0157.;
(2) vLeiva-Vásquez O, Pérez-Cruz P. Paracetamol as an adjuvant to opioids for cancer pain management. Rev Med Chil. 2021 Jun;149(6):899-905.

Changes in the text:
This study included paracetamol as an adjuvant analgesic. (Methods, lines 93-94)

6. Were paracetamol, pregabalin and steroids the only adjuvant analgesics that have been prescribed? If not, what was the rationale of selecting only the top three prescribed adjuvant analgesics for analysis of the secondary outcome?

Changes in the text:
All patients were prescribed either paracetamol, pregabalin, or steroids. A minority of patients were also co-prescribed non-steroidal anti-inflammatory drugs (n=5), Serotonin and norepinephrine reuptake inhibitors (e.g. desvenlafaxine, duloxetine) (n=6), and tricyclic antidepressants (e.g. nortriptyline, amitriptyline) (n=6). (Results, lines 146-148)

7. Were steroids prescribed specifically for pain control in all the 61 patients? Or were they prescribed for other indications in some of the patients, e.g. spinal cord compression, brain metastases and intestinal obstruction?

Reply: The indication for steroid prescription were specifically for pain control.
Changes in the text:
Steroid use was only recorded if its documented use was for pain control. (Methods, line 94)

8. In table 2, it was said that “patients prescribed pregabalin had significantly higher oMEDD doses than patients not prescribed pregabalin”. For “patients not prescribed pregabalin”, have they been prescribed with other adjuvant analgesics? Similar query for the paracetamol and steroids groups.

Reply: Usual pain management in cancer requires the prescription of multiple analgesics. To find patients who were either only on adjuvant pregabalin, or only on steroids, or only on paracetamol would be difficult to attain in the real world.

Discussion

1. An American paper with a larger cohort of 750 patients was quoted, which has not found any statistically significant difference in median oMEDD requirement across six cancer types. What is the rational behind repeating a study to answer the same research question

with a smaller cohort of 215 patients?

Reply: The American paper referenced performed a subgroup analysis to determine this result from their paper which originally aimed to examine prescription trends over a time period. They included only outpatients at point of referral to palliative care. There was no information about metastasis site, nor pain scores. Unlike our paper which treated point of discharge as surrogate for controlled cancer pain, their paper did not include pain scores nor surrogate markers for pain control, hence it is assumed that patients were censored at various levels of pain and even less accurate than reported here, despite their greater sample size.

Changes in the text:

However, this study included only outpatients at point of referral to palliative care, and pain scores were not included to indicate whether pain was controlled or not at the censored timepoint. (Discussion, lines 159-160)

2. In short, I think this article should be rejected. There are major flaws in the study design and details are lacking in quite a number of aspects of the data and results. This is not adding value to current knowledge.

Reply: We have attempted to provide clarification based on the feedback and have changed the text to reflect suggestions. We hope that these explanations will help make the paper clearer and acceptable for publication.

Reviewer B

The authors present a notable cohort study examining the opioid dose of patients in different cancer types. The manuscript is well written, concise and easy to follow. Relevant literature is discussed and limitations are stated. The methodology is sound, I really appreciated that the authors use an a priori cap of 20 patients per group, Ethic approval was obtained. Language editing is not necessary. I do have minor remarks:

1. The title does not fulfil publication guidelines (equator network). It should contain the method used (retrospective cohort study).

Changes in text:

Title: **Does cancer type and adjuvant analgesic prescribing influence opioid dose? A retrospective cohort study**

2. Line 150: The authors state that "patients with brain and colorectal cancers had far lower median". Please omit "far", because just as you argue in the next sentence, the difference is clinically irrelavant.

Reply: Thank you, this has now been modified.

3. Conclusion: The first sentence is a bit "thick" and also not the main conclusion. I would suggest to delete this: "Our findings represent a starting point for the potential further stratification of cancer pain management"

Reply: Thank you, this has now been deleted.

4. Table 1: Check formatting of percentage numbers. There a no decimals (good), but in the line: "ECOG not recordet" it is ".3". Please revise to 0% or 0.3%

Reply: Thank you, this has now been recalculated as 0.5% and changed accordingly.

Reviewer C

1. I enjoyed reading it very much and I only had two questions. By using the date of discharge, you were assuming the patient's pain was at goal?

Reply: Yes, that is correct. This is clarified further in the text:

Changes in the text:

In order to capture an equal timepoint reflecting pain control for all patients, patient records were audited on day of hospital discharge to represent stable regular opioid dose as a measure of sufficiently controlled pain. Methods (lines 74-76):

2. Second, were there patients in your cohort who were discharged on methadone or buprenorphine? Those are tricky conversions to OME. Last, would it be useful to have a table on the opioids used in the cohort, along with mean, and median doses by opioid? Nice job!

Reply: Added Table 2: **Median oral morphine equivalent daily dose according to opioid type**

Reviewer D

The topic of this article is attractive as the idea of whether certain cancer pathologies influence opioid use and adjuvants is exciting. However, the article itself suffers from many imprecisions and shortcuts.

Introduction

1. L87 -88 : You do not have to develop elements of methodology section in the introduction

Reply: L87-88 in the original manuscript contains information about methodology because it is listed under the “Methods” section. Nonetheless, we have checked the introduction for elements of methodology.

Methodology

First the methodology is very controversial

2. You only include inpatients with opioids at discharge , but we don’t know the reason that lead to hospitalization. Moreover , we don’t understand why you cape to 20 patients per etiology , probably the inclusion of these patients would changed your statistics

Reply: The inclusion of only inpatients on discharge was done to represent a cohort with chronic cancer pain, and at a timepoint where their pain was satisfactorily controlled to the point of being discharged from hospital (patients with poorly controlled pain are not discharged). The reason for hospitalization is not relevant, as the presence of cancer pain and

opioid requirement is not dependent on reason for hospitalization.

For the SR opioid group, recruitment for each of the 12 distinct cancer types was intended to be capped at twenty patients. This was chosen for convenience sampling, and to limit bias against certain cancer types being disproportionately represented, allowing for meaningful comparison between all included cancer types (irrespective of differing cancer prevalences). This is already included in the text (Methods, lines 86-89)

3. You exclude Opioids immediate release . why?

Reply: For those patients on slow release opioids, slow release opioid data was used to represent a stable baseline daily opioid requirement to allow comparison between patient groups. The dose and frequency of immediate release opioids that were taken by the patient varied from day to day and was difficult to properly quantify in our study which looked at dose on discharge from hospital as an indicator of reasonable stable adequate opioid dose at that timepoint to control pain. Thus this immediate release opioid dosing is not seen as a reliable source of stable opioid requirement that would allow a just comparison between groups.

Changes in the text: SR opioid data was used to represent a stable baseline daily opioid requirement. Immediate release opioids were excluded, as their dose and frequency varies from day-to-day, and thus not as a reliable source of stable opioid requirement that would allow a just comparison between groups, in addition to being the minority opioid requirement. (Methods, lines 94-95)

4. L99 – 100 : must be in Results section

Reply: It is not clear whether this refers to L99-100 in the original manuscript, which reads: "Analysis of median oMEDD considered against the top three most prescribed adjuvant analgesics in the patient cohort as an independent variable was performed using a Kruskal-Wallis test, where the p-value represented the null hypothesis, with $p<0.05$ considered statistically significant."

We believe that this is a key section of the methods performed, however this can be moved to the final paragraph of the results section if deemed fit by the editor.

Statistical analysis

5. You need to provide the Software name and version you used for this analysis

Changes in text:

All analyses were performed using Stata version 15.1 (Stata Corp, College Station, Texas, United States of America). (Methods, lines 122-123)

Discussion

6. This section must be completely rebuilt

It seems challenging to think that with this kind of methodology you can answer on opioid

use by type of cancer. your outcomes do not correspond to the published data. Moreover you should refer to the studies that evaluate the most painful cancers like that of H. Breivik in 2009 (European Pain In Cancer study)

Reply: We have indeed referenced the work of Breivik et al. This is a general comment, and further clarification is welcome.

Adjuvants

7. You should refer to the recent recommendations of the WHO (2019) which does not recommend Gabapentinoides and other adjuvants in neuropathic cancer pain

Reply: We disagree with this statement, as gabapentinoids and adjuvant analgesics are widely used in neuropathic cancer pain management.

We have referenced the WHO guidelines for the pharmacological and radiotherapeutic management of cancer pain in adults and adolescents. Geneva: World Health Organisation; 2018.

Contrary to the reviewer's suggestion, it is untrue that "the WHO does not recommend gabapentinoids and other adjuvants for neuropathic cancer pain". On page 40 of the document, it states "WHO makes no recommendation for or against the use of anti-epileptics/anticonvulsants for the treatment of cancer-related neuropathic pain."
The document then explains this further to reference fraudulent data called into question, thus limiting the ability to provide recommendation. It does acknowledge, however, that "Certain anti-epileptics have been reported to be effective for treatment of neuropathic pain (see Fallon, 2013 (100) for review), including gabapentin, pregabalin, carbamazepine and valproate."

Two peak bodies, the European Society of Medical Oncology (ESMO) and European Association of Palliative Care (EAPC) both separately do recommend the use of adjuvant analgesics, including gabapentinoids, for neuropathic cancer pain. See references below:

Fallon M, et al. ESMO Guidelines Committee. Management of cancer pain in adult patients: ESMO Clinical Practice Guidelines. Ann Oncol. 2018 Oct 1;29(Suppl 4):iv166-iv191. doi: 10.1093/annonc/mdy152. PMID: 30052758.

Caraceni A et al. European Palliative Care Research Collaborative (EPCRC); European Association for Palliative Care (EAPC). Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. Lancet Oncol. 2012 Feb;13(2):e58-68. doi: 10.1016/S1470-2045(12)70040-2. PMID: 22300860.

8. This study is too limited, the methodology has too much bias, no useful information can be reached by the data collected so the discussion is light and not useful. The paper must be completely rebuilt

Reply: We have responded and amended the paper where specific comments have been made.

Reviewer E

1. Congratulations on a thoughtfully designed and well-written paper. Your points were clear and concise. You acknowledged the limitations of your study, and the conclusions drawn were commensurate with the intention of the study and available data.

Reply: Thank you for your kind comments.