

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	End-of-life outcomes with or without early palliative care: A propensity-score matched, population-based cancer cohort study
AUTHORS	Seow, Hsien; Sutradhar, Rinku; Burge, Fred; McGrail, Kimberlyn; Guthrie, Dawn; Lawson, Beverley; Oz, Urun Erbas; Chan, Kelvin; Peacock, Stuart; Barbera, Lisa

VERSION 1 – REVIEW

REVIEWER	<p>Aynharan Sinnarajah University of Calgary, Canada</p> <p>I've led a grant submission this year with some of the authors of this paper (Seow, McGrail, Chan, Peacock, Barbera).</p> <p>I've been a co-investigator on submitted grants with some of the authors who are Principal Investigators (Seow, Guthrie).</p> <p>I'm on an expert panel advising 1 of Guthrie's project.</p> <p>Barbera is one of my mentors starting this year.</p>
REVIEW RETURNED	08-Aug-2020

GENERAL COMMENTS	<p>End-of-life outcomes with or without early palliative care: A propensity-score matched, population-based cancer cohort study BMJ Open Seow et al.</p> <p>Thank you for the opportunity to review this study. This is an important topic to explore the end of life (EOL) outcomes with or without early palliative care (PC) for patients living and dying with cancer. What is novel in this study is the addition of patient reported outcomes to the model to adjust for some factors that predict receipt of early palliative care. The comments below are meant to be constructive and help the readers better appreciate the significance of the findings.</p> <p>1. Introduction: In the first paragraph, the 3rd sentence reads as: "Palliative care is often applied". And the 4th sentence reads as "Palliative care is used". These read awkwardly as one doesn't often think of palliative care as being applied or used (e.g. we wouldn't say 'Cardiology is applied' or 'Cardiology is used'). A palliative care service might be used, or a palliative approach to care might be used. Suggest rephrasing.</p> <p>2. Study design:</p> <p>a. Why was early palliative care measurement stopped at <12 months? What if they receive palliative care >12 months? There is more evidence that some cancer patients are now receiving very early PC (>12 months before death). Might these be miscounted as 'not-early PC'? Please comment on rationale for this.</p>
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	<p>b. Why was physician consult narrowly defined to only include outpatient clinic or home visit? What about those physician consults for palliative care occurring in inpatients or long term care sites? Reference #3 employed a more comprehensive measurement of palliative care including all of these settings. It looks like those were excluded from this study. Please comment on rationale or mention in limitations.</p> <p>c. How were patients living in Continuing Care sites handled? Were they less likely to receive the Home Care RAI and less likely to receive Supportive Home Care (one of outcomes)? And does living in Continuing Care also predict different hospital based care?</p> <p>d. Since this is one of the few studies that also adjusted for patient specific variables around function, cognition, pain, depression and caregiver, it would be good to see the distribution of all of the values of each field in each group (prior to propensity score matching). i.e. expand on the bottom of Appendix S1. This will allow for interested readers to see what possible gaps in access to Early PC might be.</p> <p>e. Similarly, please list all variables included in propensity score matching in Appendix S1. e.g. I don't see 'prior hospital utilisation 24-12 months before death', nor 'year of death' etc.. Similar to above, the distribution of the population used in this model is of interest to readers to see how this might apply to their jurisdictions.</p> <p>f. Please comment on why radiation or cancer surgery was included in the model. It's not a variable that one often sees in these EOL prediction models related to PC. Ref #22 also doesn't mention these 2 variables.</p> <p>g. Disease duration is sometimes employed in these models as it can independently predict EOL outcomes as well as PC access. e.g. those diagnosed < 6 months before death, by definition, will never be eligible for Early PC. I don't see where this variable is included during propensity score matching. Please explain how this was accounted for, or if not, provide rationale or mention in limitations</p> <p>h. Sensitivity analysis: I'm unclear on why this is being conducted. Rationale for this perhaps is best mentioned here rather than later in Results.</p> <p>3. Results:</p> <p>a. Patients section, 3rd para: The first sentence refers to 'homecare but without end-of-life intent'. What group does this reference specifically? In Methods, there is mention of 'long stay home care'. Is this the same group that is being referenced? Please clarify.</p> <p>b. Sensitivity analysis: I have not seen evidence nor see a reference for this hypothesis. i.e. Late sub-group were willing to receive palliative care early but offered late. And never sub-group were more likely to refuse palliative care. Please provide evidence for this hypothesis. I can think of alternative, equally plausible hypotheses: a) Individual provider preferences leads to patients with those providers receiving later Palliative care; b) Certain tumor groups (e.g. Hematology) traditionally receive late PC because of higher chances of 'curative intent' treatments (e.g. bone marrow transplant); c) Late cancer diagnoses groups more likely to receive late PC (e.g. lung, pancreatic)</p> <p>i. Therefore, if no evidence for this hypothesis, and I'm not sure this is clinically valid, suggest there's no need for this sensitivity analysis.</p> <p>4. Limitations:</p>
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	<p>a. There are more limitations than outlined here including Disease duration, provider preferences etc. Please expand.</p> <p>5. Tripod Checklist: Why was the Prediction Model Development checklist used for this study? This is not a prediction model study. I'm not sure whether there's an accepted checklist for propensity score instead that can be used. It also seems that a STROBE list is more suitable (if no other list is available)?</p> <p>a. A quick literature scan showed: Yao et al. JNCI. Reporting and Guidelines in Propensity Score Analysis: A Systematic Review of Cancer and Cancer Surgical Studies https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6059208/</p> <p>i. Wonder if their Table 4 should be used (in combination with STROBE) as the checklist for this propensity score analysis study?</p>
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REVIEWER	Luciana Rozman Department of Preventive Medicine, University of São Paulo School of Medicine, São Paulo, Brazil
REVIEW RETURNED	28-Aug-2020

GENERAL COMMENTS	<p>Review bmjopen-2020-041432 - End-of-life outcomes with or without early palliative care: A propensity-score matched, population-based cancer cohort study</p> <p>Thank you for the opportunity to review this retrospective cohort study of cancer decedents in Canada that investigated who received palliative care earlier (in home-care or not home-care) at least six months before death compared to those who did not and their outcomes in the last 30 days of life.</p> <p>The paper is well-written, the text is easy to understand and follow and presents large-scale population-based study.</p> <p>The minor comments below are intended to assist the authors in the revision of the manuscript:</p> <p>1 – Introduction I liked the introduction which covers the topic well with relevant references. Please add some information about palliative care in Canada. Providing information on the usage of palliative care among cancer patients in Canada (Ontario) and palliative care services available would be helpful for international readers to understand the real situation.</p> <p>2 – Methods Early Palliative Care definition is described at page 7 line 42. My question is: patients were included at study independent of number of physician consult for palliative care in an outpatient clinic or home visit setting, or a hospitalization in the exposure period? Patients with just one contact with physician between 12 and six months before death were included as well? Palliative care practice in Ontario include a multidisciplinary team: palliative care specialists, nurses, other professionals? All patients enrolled at study received the same care with a palliative care team?</p> <p>3 – Discussion I suggest that the authors present a comparison of results with similar studies and other relevant evidences. In the NO-RAI group and he YES-RAI group, the first initiation of early palliative care was 300 and 330 days before death respectively with the same distribution of palliative care services (Page 10 line 16 to 47) is an interesting development that should</p>
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	<p>be investigated more. Did the authors find any related factors, possible reasons for? Patients in the YES-RAI group were not supposed received palliative care earlier then NO-RAI? Other than presenting results, do the authors have relevant proposal and recommendations? The obvious recommendation for a study of patients at end of life is that palliative care should be started earlier to improve quality of life. I would recommend that they revise the paper to come up with some conclusion and recommendation.</p>
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REVIEWER	Le-Rademacher, Jennifer
REVIEW RETURNED	15-Nov-2020

GENERAL COMMENTS	<p>This paper reports results of a large propensity-score-matched cohort of cancer decedents in Ontario, Canada between 2004 and 2014. The data are robust and support the authors' conclusions. The authors are to be commended for conducting a study with such a large cohort. Below are some issues and questions that need further discussions.</p> <ol style="list-style-type: none"> 1. The results of this study support conclusions from previous studies without additional or new insights. The question of resource utilization which is one of the most important issues related to palliative care is still unanswered. 2. Although propensity score matching was used to minimize selection bias that might confound the difference in aggressive care and at home care, it was limited by the factors that were used in calculating the propensity score. Were there any data on the subject's disease status at the time of starting palliative care and the duration of diagnosis until initiation of palliative care? Did subjects who did not receive early palliative care had more aggressive disease which did not allow for a longer time in palliative care, which also increased the likelihood of receiving more aggressive care, etc.... There are still confounding factors that were not sufficiently addressed in this study. 3. It is curious why some covariates were hard matched between exposure groups in addition to propensity score matching. With such a large sample size and a small number of covariates considered for matching, a hard match on all variables would result in more closely matched cohorts at the individual level which better justifies not needing regression modeling. Propensity score matching only matches subjects based on a summary score of a combination of factors so although Table 1 shows a balance in demographic variables, the balance is only in the marginal distributions. Adjustment for demographics and disease characteristics via regression modeling may be needed.
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Aynharan Sinnarajah
 Institution and Country: University of Calgary, Canada

Comments to the Author

Thank you for the opportunity to review. Please find my comments in the attached Word document.

Thank you for the opportunity to review this study. This is an important topic to explore the end of life (EOL) outcomes with or without early palliative care (PC) for patients living and dying with cancer. What is novel in this study is the addition of patient reported outcomes to the model to adjust for some factors that predict receipt of early palliative care. The comments below are meant to be constructive and help the readers better appreciate the significance of the findings.

1. Introduction: In the first paragraph, the 3rd sentence reads as: "Palliative care is often applied". And the 4th sentence reads as "Palliative care is used". These read awkwardly as one doesn't often think of palliative care as being applied or used (e.g. we wouldn't say 'Cardiology is applied' or 'Cardiology is used'). A palliative care service might be used, or a palliative approach to care might be used. Suggest rephrasing.

REPLY: We have changed both sentences to read as "palliative care services are used..."

2. Study design:
 - a. Why was early palliative care measurement stopped at <12 months? What if they receive palliative care >12 months? There is more evidence that some cancer patients are now receiving very early PC (>12 months before death). Might these be miscounted as 'not-early PC'? Please comment on rationale for this.

REPLY: We used the last year of life as a start point as it aligned with the surprise question (Would you be surprised if the patient died in the next year?) and we thought it a clinically reasonable timeframe to go back from death, given that most of palliative care is delivered in the last months of life. We have added the "surprise question" reference in our methods when we define exposure period.

We also explored our data to determine if there was any misclassification. We found that: Overall, among the RAI-Yes and the RAI-No groups, none of the patients received palliative care services earlier than 1 year before death, who did not also receive palliative care services within the 12 to 6 months before death as well. Specifically, in the RAI-Yes group (n=3,586), 81 patients received palliative care earlier than 12 months before death but also received it in the 12-6 months before death; so, they were counted as receiving it early. Similarly, for the RAI-No group (n=36,238), 325 patients received palliative care earlier than 1 year before death, but they also received care in the 12-6 months before death, and thus were counted as receiving palliative care early.

- b. Why was physician consult narrowly defined to only include outpatient clinic or home visit? What about those physician consults for palliative care occurring in inpatients or long term care sites? Reference #3 employed a more comprehensive measurement of palliative care including all of these settings. It looks like those were excluded from this study. Please comment on rationale or mention in limitations.

REPLY: The physician consults also include in-patient settings (including complex continuing care; and this has been revised and clarified in the methods), however it did not include palliative care codes in long-term care (i.e. nursing homes). We have included the exclusion of LTC in the limitations. To clarify, we used the exact same methods as reference 3 (Tanuseputro, Pall Med, 2016), except we did not include the palliative care billing codes for long-term care homes. Research shows that very little palliative care is delivered to cancer patients in LTC settings (Seow, BMJ Open, 2018) and we felt this group was distinct in needs, and different from the populations in the comparison trials.

- c. How were patients living in Continuing Care sites handled? Were they less likely to receive the Home Care RAI and less likely to receive Supportive Home Care (one of outcomes)? And does living in Continuing Care also predict different hospital based care?

REPLY: I believe the reviewer is referring to Continuing Care as assisted-living facilities. People in assisted living homes would continue to receive home care services and see their family doctors—so they have the same access to palliative care. Whether those who live in assisted-living facilities have different hospital-based care has not been studied, as there isn't a database that tracks care in assisted living homes.

If the reviewer is referring to Continuing Care as complex continuing care, which would include palliative care units (which often occur near death), we did indeed capture this as the physician billing code for palliative care in this setting was included/used. We've added a note that "complex continuing care" was included as well in our exposure.

Note The Continuing Care Reporting System (CCRS) databases is the name of the database that captures long-term care data (i.e. nursing homes), which we did not link to as stated above. Whether those who live in LTC care use hospital differently was not the focus of this study.

- d. Since this is one of the few studies that also adjusted for patient specific variables around function, cognition, pain, depression and caregiver, it would be good to see the distribution of all of the values of each field in each group (prior to propensity score matching). **i.e. expand on the bottom of Appendix S1.** This will allow for interested readers to see what possible gaps in access to Early PC might be.

REPLY: We have reviewed all the variables that we matched on (both hard match and in the PS score). The ones missing in Appendix S1 were: age, health region, prior hospital utilization, and duration of cancer disease (this replaces index year of death [See response to 1g]). They have all been added to Appendix S1 as suggested. We have also added these to Table 1 (except health region).

- e. Similarly, please list all variables included in propensity score matching in Appendix S1.
e.g. I don't see 'prior hospital utilisation 24-12 months before death', nor 'year of death' etc.. Similar to above, the distribution of the population used in this model is of interest to readers to see how this might apply to their jurisdictions.

REPLY: As stated above, we have added all the variables that we matched on (both hard match and in the PS score) to Appendix S1 as suggested.

- f. Please comment on why radiation or cancer surgery was included in the model. It's not a variable that one often sees in these EOL prediction models related to PC. Ref #22 also doesn't mention these 2 variables.

REPLY: We included cancer surgery or radiation because we believed that those with similar treatments might be more similar in-patient profile (unmeasured confounders) and in unmeasured symptoms than those who never received any treatment. For instance, a prostate cancer patient who received treatment vs. one who received surgery vs. one who did neither, might have different trajectories in their last year of life. So, it was an attempt to try to match similar cancer types and stages, with similar treatment profiles.

- g. Disease duration is sometimes employed in these models as it can independently predict EOL outcomes as well as PC access. e.g. those diagnosed < 6 months before death, by definition, will never be eligible for Early PC. I don't see where this variable is included during propensity score matching. Please explain how this was accounted for, or if not, provide rationale or mention in limitations.

REPLY: Thank you for this comment. The prior variable "year of death" was an error. It was meant to be "duration from diagnosis date to year of death", shortened to

'disease duration'. We did in fact include this in the PS match and is included in Appendix S1 and Table 1.

Moreover, your point about those being diagnosed <6 months from death is very important. We did in fact exclude these patients (n=84,673 unique patients had a diagnosis within 6 months from death) from our analysis because, as you point out, they are not eligible to receive the exposure. We have added this exclusion criterion into our methods. And stated this more clearly in our first sentence of our results. (i.e. we had 228,978 unique patients with a cancer dx before death; and we removed those with dx within 6 months of death (n=84,673), leaving 144,306 in our cohort).

- h. Sensitivity analysis: I'm unclear on why this is being conducted. Rationale for this perhaps is best mentioned here rather than later in Results.

REPLY: We have moved the rationale and hypothesis for the sensitivity analysis to the methods, as suggested. We have also expanded the explanation in the rationale. It reads: *“As a sensitivity analysis, we divided the not-early group—i.e. unexposed group—into late palliative care (i.e., only received palliative care in the last six months of life) and never received palliative care. We conducted a sensitivity analysis to examine early vs. late and early vs. never subgroups separately in an attempt to control for unmeasured patient preferences. The hypotheses were that some patients may refuse palliative care altogether (which would appear in our data as never receiving any palliative care services even near death); and other patients might have been willing to receive palliative care but were offered it late (which would appear in our data as receiving it in the final six months of life). Analyzing the late users compared to the early users specifically, was an attempt to separate out those patients who might have refused palliative care as per their preference.”*

3. Results:

- a. Patients section, 3rd para: The first sentence refers to 'homecare but without end-of-life intent'. What group does this reference specifically? In Methods, there is mention of 'long stay home care'. Is this the same group that is being referenced? Please clarify.

REPLY: We have added a sentence in the methods to explain this more clearly. It reads: *“Of note, long-stay home care patients were classified as either receiving homecare with (exposed) or without (unexposed) palliative care intent.”* Moreover, we have clarified this sentence in the 3rd paragraph of Patients section: *“In the Yes-RAI group, we matched 59.9% of patients who received regular homecare in the exposure period to those who received palliative homecare services in the exposure period for a total of 3,586 matched pairs.”*

- b. Sensitivity analysis: I have not seen evidence nor see a reference for this hypothesis. i.e. Late sub-group were willing to receive palliative care early but offered late. And never sub-group were more likely to refuse palliative care. Please provide evidence for this hypothesis. I can think of alternative, equally plausible hypotheses: a) Individual provider preferences leads to patients with those providers receiving later Palliative care; b) Certain tumor groups (e.g. Hematology) traditionally receive late PC because of higher chances of 'curative intent' treatments (e.g. bone marrow transplant); c) Late cancer diagnoses groups more likely to receive late PC (e.g. lung, pancreatic)
- i. Therefore, if no evidence for this hypothesis, and I'm not sure this is clinically valid, suggest there's no need for this sensitivity analysis.

REPLY: In our description of the rationale and hypothesis for the sensitivity analysis, we more clearly explain why we did this (See response to 1h). It has been a comment from prior reviewers that the largest “unmeasured confounder” is patient preferences (i.e. that

some patients may refuse palliative care and want aggressive treatment until death); while imperfect, this sub-analysis helps to split the two groups up to see if those never-users versus the late-users are different than the intervention group. As to your alternative suggestions: a) It is true we are not able to control for provider preferences (which is noted as a limitation); though our sample size is very large, hopefully mitigating individual provider preferences somewhat. b) We do include tumor type in our PS hard match. c) We excluded those with late-stage diagnosis (less than 6 months from death).

4. Limitations:

- a. There are more limitations than outlined here including Disease duration, provider preferences etc. Please expand.

REPLY: Looking at this list and the above comment: our matching does account for disease duration (See response to 1g), we do not have late diagnoses (i.e. dx within last six months of life), and we do match on cancer type (including hematology and lung directly). We have added the lack of measuring provider, patient and family preferences to our limitations.

5. Tripod Checklist: Why was the Prediction Model Development checklist used for this study? This is not a prediction model study. I'm not sure whether there's an accepted checklist for propensity score instead that can be used. It also seems that a STROBE list is more suitable (if no other list is available)?
 - a. A quick literature scan showed: Yao et al. JNCI. **Reporting and Guidelines in Propensity Score Analysis: A Systematic Review of Cancer and Cancer Surgical Studies** <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6059208/>
 - i. Wonder if their Table 4 should be used (in combination with STROBE) as the checklist for this propensity score analysis study?

REPLY: Thank you. The prediction model development checklist was attached in error. We did in fact complete the STROBE checklist for this study, and have attached the correct version now. We have referenced it as well. Moreover, we have also reviewed Table 4 of the Yao et al. JNCI publication as suggested, and ensured that we have complied with those criteria.

Reviewer: 2

Reviewer Name: Luciana Rozman

Institution and Country: Department of Preventive Medicine, University of São Paulo School of Medicine, São Paulo, Brazil

Comments to the Author

Review bmjopen-2020-041432 -

End-of-life outcomes with or without early **palliative** care: A propensity-score matched, population-based cancer cohort study

Thank you for the opportunity to review this retrospective cohort study of cancer decedents in Canada that investigated who received palliative care earlier (in home-care or not home-care) at least six months before death compared to those who did not and their outcomes in the last 30 days of life. The paper is well-written, the text is easy to understand and follow and presents large-scale population-based study.

The minor comments below are intended to assist the authors in the revision of the manuscript:

1 – Introduction

I liked the introduction which covers the topic well with relevant references. Please add some information about palliative care in Canada. Providing information on the usage of palliative care

among cancer patients in Canada (Ontario) and palliative care services available would be helpful for international readers to understand the real situation.

REPLY: Thank you for this comment. We have added a paragraph in the introduction, providing a detailed description of the variety of palliative care services that are available, though these are often accessed late. It reads: *“Usual care in Ontario means that cancer patients have access to publicly-subsidized palliative care in the form of: a palliative care outpatient clinic (e.g. multidisciplinary pain and symptom management clinic); palliative home care services by a nurse or personal care worker; or a family doctor providing palliative care via clinic or rarely via home-visit. Generally, these 3 services are independent of one another and uncoordinated.¹⁴ This contrasts the community-based, multidisciplinary team approach of palliative care delivery found in the United States via home hospice care⁶ or in the United Kingdom via Macmillan cancer support program.¹⁵ Although a small minority of patients might have access to a multidisciplinary, specialist palliative care team that makes home visits or a residential hospice, especially if they lived in a major city, this is haphazard and accessed typically in the last weeks of life.¹⁶ If the patients were hospitalized, they could also receive a consult from a palliative care doctor individually or a multidisciplinary team (e.g. admitted to a palliative care unit) in the hospital. Unfortunately, data shows palliative care services are often used very late in the disease trajectory or not at all. For example, in Ontario, Canada, palliative care services are used in 50% of all deaths for a median of 30 days before death.¹⁷ In the United States, statistics are very similar, where palliative care via the Medicare”*

2 – Methods

Early Palliative Care definition is described at page 7 line 42. My question is: patients were included at study independent of number of physician consult for palliative care in an outpatient clinic or home visit setting, or a hospitalization in the exposure period? Patients with just one contact with physician between 12 and six months before death were included as well?

Palliative care practice in Ontario include a multidisciplinary team: palliative care specialists, nurses, other professionals? All patients enrolled at study received the same care with a palliative care team?

REPLY: The review is correct. Patients were included as “early/exposed” independent of how many palliative care services they received during the exposure window. We have however, for context, added additional sentences for the Yes-RAI (n=3,586) and No-RAI (n=36,238) groups to describe the average amount of services used by the groups during the exposure period.

- *“In the No-RAI group, during the exposure period the group received 53,787 palliative care services, of which approximately 40% of services were homecare and 40% were outpatient physician billings.”*
- *“In the Yes-RAI group, during the exposure period the group received 5,468 palliative care services, of which nearly half were homecare services.”*

With respect to access to a palliative care, multidisciplinary, specialist team: we have clarified this in our introduction about delivery and access to palliative care in Canada. This is not common. In the description, we explain where they might receive a multidisciplinary team. (e.g. outpatient cancer clinic, admission to hospital palliative care unit, or a specialized community-based team (though the latter is haphazard and rare).

3 – Discussion

I suggest that the authors present a comparison of results with similar studies and other relevant evidences.

In the NO-RAI group and the YES-RAI group, the first initiation of early palliative care was 300 and 330 days before death respectively with the same distribution of palliative care services (Page 10 line 16 to 47) is an interesting development that should be investigated more. Did the authors found any related factors, possible reasons for? Patients in the YES-RAI group were not supposed received palliative care earlier then NO-RAI?

REPLY: We have added a paragraph in the discussion explaining the significance of our results, the policy/practice implications, in the context of results of other studies. It reads: *“The results of this study support policies to enable earlier access to end-of-life homecare services and outpatient physician services for palliative care. In particular, policies that prohibit the access of palliative care services unless one forgoes curative treatments or is certified as expected to die within 6 months or less are disincentives to earlier and concurrent access to palliative care. For instance in the United States, the Medicare Hospice Benefit provides access to community-based hospice care but requires a physician to certify a life expectancy of less than six months and a patient commitment to forgo curative treatment.³⁷*

Besides policies, education is critical because research shows that patient preferences sometimes change over time,³⁸ and that clinicians play an important role in introducing and initiating palliative care (e.g. Serious Illness Conversations) and helping patients make informed treatment decisions about goals of care for end of life.³⁹

With respect to the data showing that those in the Yes-RAI group (i.e. were receiving home care) received palliative care earlier than those in the No-RAI group (i.e. not receiving home care)—upon reflection, this is an unsurprising finding. This is because the delivery of palliative care home care is itself one of the ways to be counted in the exposure group. Therefore, those receiving home care (required to receive a RAI assessment), could also have been receiving palliative home care (and make them more likely to be counted as receiving palliative care). This is also why we a priori split up our analysis by RAI-Yes and RAI-No, because we suspected that those needing home care earlier (RAI-Yes) were sicker or more symptomatic than the RAI-No group. Moreover, this is also likely why the RAI-Yes group are far more likely to receive supportive care (because home care is counted as a supported care service) than the RAI-No group (Table 3)

4 – Conclusion

Other than presenting results, do the authors have relevant proposal and recommendations? The obvious recommendation for a study of patients at end of life is that palliative care should be started earlier to improve quality of life. I would recommend that they revise the paper to come up with some conclusion and recommendation.

REPLY: As suggested, we have added a recommendation to our conclusion. It reads: “Our findings suggest that policies and education strategies to support the delivery of early palliative care might reduce the risk of dying in hospital and receiving aggressive care at end-of-life in real-world settings.”

Reviewer: 3

Le-Rademacher, Jennifer

Comments to the Author

This paper reports results of a large propensity-score-matched cohort of cancer decedents in Ontario, Canada between 2004 and 2014. The data are robust and support the authors' conclusions. The authors are to be commended for conducting a study with such a large cohort. Below are some issues and questions that need further discussions.

1. The results of this study support conclusions from previous studies without additional or new insights. The question of resource utilization which is one of the most important issues related to palliative care is still unanswered.

REPLY: We believe that our study adds some new insights, which we highlight in our “strengths and limitations of our study” preamble. Namely:

- **We used population-based data, with consistent exposure and outcome definitions over a long period of time, which provides high external validity in real-world settings.**
- **Our study included and controlled for previously unmeasured confounders (in a large observational study) known to be associated with receipt of early palliative care (i.e. worse pain, ADL dependency, depression, cognitive decline, and health instability).**

We agree with the reviewer that resource utilization and costs at end of life is of interest. And we have a manuscript under development focusing specifically on that. We have added this as future research needed in the conclusion.

2. Although propensity score matching was used to minimize selection bias that might confound the difference in aggressive care and at home care, it was limited by the factors that were used in calculating the propensity score. Were there any data on the subject's disease status at the time of starting palliative care and the duration of diagnosis until initiation of palliative care? Did subjects who did not receive early palliative care had more aggressive disease which did not allow for a longer time in palliative care, which also increased the likelihood of receiving more aggressive care, etc.... There are still confounding factors that were not sufficiently addressed in this study.

REPLY: We agree that propensity score matching minimizes selection bias, and that our covariate list does not include every possible variable associated with receipt of palliative care

(exposure) and aggressive care (outcome). However, we feel like we have included a large number of very important clinical variables that are known confounders, namely:

- a) with respect to disease status: we matched on cancer type, cancer stage, and duration of diagnosis (This is now clarified in the methods, see response to Reviewer 1, comment 1g), as well as treatment of chemotherapy and/or cancer surgery which would influence the disease status.
- b) with respect to aggressiveness of diseases: this is exactly where we felt that the RAI-HC data would allow us to look at unique previously unmeasured confounders including: CHES score (a measure of performance status—i.e. physical function, which is directly related to disease progression)—hard matched; and also Activities of Daily Living dependency, cognitive impairment, depression, pain (which is also a sign of disease progression). While not comprehensive, they are important factors that can indicate a progression of the disease—which were matched on in the propensity score (at a group level).

We feel the biggest confounders are provider preferences or comfort with initiating palliative care; and patient and family preferences to accept or refuse palliative care services, which we have listed as limitations. As well, we implemented a sensitivity analysis to look at the late vs. early receipt of palliative care users (i.e. they did not refuse palliative care) to also try to tease this apart somewhat.

3. It is curious why some covariates were hard matched between exposure groups in addition to propensity score matching. With such a large sample size and a small number of covariates considered for matching, a hard match on all variables would result in more closely matched cohorts at the individual level which better justifies not needing regression modeling. Propensity score matching only matches subjects based on a summary score of a combination of factors so although Table 1 shows a balance in demographic variables, the balance is only in the marginal distributions. Adjustment for demographics and disease characteristics via regression modeling may be needed.

REPLY: We hard matched on the key clinical factors—the likely most prognostic for death and thus referral to palliative care (which are cancer type, stage, age, sex, and performance status/CHES score). And we listed the others in the propensity score, in part because there are other unmeasured confounders associated with each factor, and also to ensure we had a high match percentage. Had we hard matched on every variable, our match percentage would diminish, and thus our generalizability. Currently, we had high match percentages (83% and 60%), and good balance between the two groups. Had we hard matched on many more variables, it is not clear we would end up with a similarly good balance—and we would certainly have a much lower match percentage.

VERSION 2 – REVIEW

REVIEWER	Luciana Rozman Department of Preventive Medicine, University of São Paulo School of Medicine, São Paulo, Brazil
REVIEW RETURNED	19-Jan-2021
GENERAL COMMENTS	The authors have addressed each of concerns and make clear points that left doubts in first submission.