

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	End of life care in cancer patients: how much drug therapy and how much palliative care? Record linkage study in Northern Italy
<b>AUTHORS</b>	Formoso, Giulio; Marino, Massimiliano; Guberti, Monica; Grilli, Roberto Giuseppe

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Bennett, Charles South Carolina College of Pharmacy/USC Campus
<b>REVIEW RETURNED</b>	19-Oct-2021

<b>GENERAL COMMENTS</b>	<p>10/19/2021 To the authors:</p> <p>Abstract: Results:</p> <p>Variation is expected and is necessary. How much variation—low of xx% and high of yy%?</p> <p>Likelihood- was associated with LHA—not depended on it.</p> <p>Chemotherapy patients were xx-fold as likely as non-chemotherapy patients to receive as non-chemotherapy patients to receive hospice or palliative care services---</p> <p>Each sentence needs some numbers to indicate the strength or weakness of the associations.</p> <p>The last sentences are speculative—and should be in the paper, not in the abstract.</p> <p>The final sentence is highly speculative.</p> <p>Summary bullets: 2nd bullet- not addressed clearly in the abstract 3rd and 4th—bullets are okay</p> <p>Manuscript.</p> <p>Introduction: Aggressive treatments is colloquial—and should either not be used or should be defined. Almost all treatments have toxicities- it is just that current treatments have less nausea and vomiting and neutropenia but have more -itis like complications. What do you mean by patient “suffering?”—is this meant as pain or other symptoms? Refs 4- 6 are outdated—can more recent references be identified? Refs 8- 10 describe palliative care in settings that are quite old---it is not clear that it is always a team approach.</p>
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	<p>A table may help place the text in the intro into context- and assist with clarity.</p> <p>Does chemotherapy mean iv chemotherapy or does it also include oral chemotherapy? Results: The analyses would be improved if the data included iv versus oral chemotherapy and also immune-oncology drugs versus chemotherapy drugs.</p> <p>Give the recentness of the data, a more nuanced looked at “chemotherapy” is warranted. Is there a transition in use of iv versus oral versus immochemotherapy over time?</p> <p>Discussion</p> <p>I would add some analysis based on the above text?</p> <p>This would make the paper stronger- and also more current?</p>
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<b>REVIEWER</b>	Kane, Eleanor University of York, Health Sciences
<b>REVIEW RETURNED</b>	01-Nov-2021

<b>GENERAL COMMENTS</b>	<p>The paper described chemotherapy and palliative care in the last 30 days of the life of persons who died with cancer in the Emilia-Romagna region of Italy. Using mortality records over 2017-2020, a cohort of over 55000 persons were identified and linked to routine hospital discharge, hospice service, and prescription data. Persons who were admitted to hospital in the last 30 day of life, when compared to those who were not, were more likely to have had chemotherapy and less likely to have received palliative care in the last weeks of life. A similar pattern was seen for persons who had had a haematological malignancy compared to those who had had another cancer. Persons with an aggressive tumour, on the other hand, were less likely to have had chemotherapy and more likely to have received palliative care than those whose cancer was not aggressive. Those who had surgery in the last 30 days of life were less likely to have had chemotherapy but also less likely to have received palliative care than those who had not had surgery. Variation between local health authorities was seen in the proportions of persons who received chemotherapy or palliative care in the last 30 days of life.</p> <p>The use of routine data to answer research questions has utility in provide contemporaneously collected information on [virtually] all relevant persons in large numbers. It is of course not without some drawbacks, but nevertheless, it can provide useful information to stakeholders, healthcare professionals, providers and planners. The present study will do so, but the overall message is impeded by the presentation.</p> <p>The authors should consider that the introduction and discussion are rather long. Both need to be shortened, and the discussion in particular needs to focus on the findings of the study, and similar literature. The abstract and article summary need to be reconsidered in light of the comments below.</p>
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	<p>On the other hand, the methods are too brief. It needs to be clear how the cohort was ascertained from the mortality registry. A list of ICD cancer codes is given but what were the codes applied to: underlying cause of death; all causes of death; other? Also, if the code is from the death certificate, the cohort are not necessarily dying from cancer- consider a different phrase eg persons who had cancer recorded as a [or underlying, if more appropriate] cause of death. How is the linkage of the mortality registry to the other resources conducted, what key information is used, how reliable/complete is the linkage?</p> <p>Also, in the methods, there needs to be explanations of how the routine data were used to obtain the variables of interest. For instance, what information and how were aggressive tumours defined using the available data? What were the sources and how were the chemotherapy and palliative care variables generated? As well as the source/s, what surgery was considered relevant (presumably removal of tumour)? The authors may like to consider providing lists of codes in the Supplementary Materials if needed. Consider that others may like to use same/similar sources to repeat the research so a minimum of information would be helpful.</p> <p>The results should be presented with less reference to the statistical techniques. Sentences should be shorter and focus on one set of associations- the switching to saying that the opposite is seen by another is not always easy to follow. The descriptions of Tables 3a and b are particularly challenging, not just because the sentence is very long; there needs to be reference to the comparison group where chemo or palliative care is increased/decreased. There is little difference in the findings of Tables 3a and 3b, and so probably only one needs to be presented.</p> <p>The authors should also consider the robustness of their analyses. It is difficult here to be prescriptive as the chemo and palliative care variables are not defined, but did the authors consider whether certain sources of data may be more or less reliable at defining these outcomes? For example, a palliative care code may appear in the hospital discharge record; or place of death may have been a hospice? Would either of these contribute to the palliative care variable, and would the results change if they were excluded?</p> <p>There is little on the strengths and weaknesses of the study. In comparison to other studies, it may be that the information available here is wider; thinking here that the routine hospital prescription data and hospice and domiciliary care data are not such common resources. The authors should also comment on the coverage of the routine databases- how reliable are they considered to be, presumably the data are collected as part of the patient's care. Other limitations could relate to the variables of interest or the definition of the cohort. Could any measures be taken to test the robustness of findings depending on these definitions?</p>
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<b>REVIEWER</b>	Zuckerman, Diana National Center for Health Research
<b>REVIEW RETURNED</b>	06-Nov-2021

<b>GENERAL COMMENTS</b>	<p>The issue of end of life care for cancer patients is very important, and although the inverse relationship between chemo and palliative care is not surprising, the large data set from a region of Italy, the differences related to how aggressive the cancer was, and the different results for blood cancers vs. other cancers are all notable. The major weakness of the manuscript is that administrative data can't answer important questions about the implications of the data, such as how the increased or decreased use of chemo or palliative care affected the quality of life of these patients. What was the value or lack thereof of chemotherapy at the end of life, and did it in fact really help patients (as some experts state) by reducing tumor size? What can other studies tell us about those issues that would help us think about the results of this study? And, aren't those the issues that should be the focus of the discussion, instead of generalizations pertaining to empathy, the role of nurses, etc., which are interesting but completely unrelated to the data. Revising the discussion section is the major revision I would recommend.</p> <p>The manuscript also suffers from numerous grammatical errors, especially in the results section, apparently because English is not the usual language of the authors. These need to be fixed prior to resubmission.</p>
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### VERSION 1 – AUTHOR RESPONSE

<p><b>Reviewer: 1</b></p> <p>Abstract, results: variation is expected and is necessary. How much variation—low of xx% and high of yy%? Likelihood- was associated with LHA—not depended on it Chemotherapy patients were xx-fold as likely as non-chemotherapy patients to receive as non-chemotherapy patients to receive hospice or palliative care services--- Each sentence needs some numbers to indicate the strength or weakness of the associations The last sentences are speculative—and should be in the paper, not in the abstract. The final sentence is highly speculative</p>	<p>Thank you, we agree: added percentages and amended the text as suggested</p>
<p>Summary bullets: 2nd bullet- not addressed clearly in the abstract 3rd and 4th—bullets are okay</p>	<p>We removed the second bullet, also considering that we shortened a bit the discussion on multidisciplinary approaches, in keeping with suggestions from other referees</p>
<p>Manuscript Introduction: Aggressive treatments is colloquial—and should either not be used or should be defined. Almost all treatments have toxicities- it is just that current treatments have less nausea and vomiting and neutropenia but have more -itis like complications. What do you mean by patient “suffering?”—is this meant as pain or other symptoms?</p>	<p>We agree. Aggressive treatments are now defined (see appendix). We replaced “suffering” with “condition”</p>

Refs 4- 6 are outdated—can more recent references be identified? Refs 8- 10 describe palliative care in settings that are quite old---it is not clear that it is always a team approach.	Thank you, we agree. We substituted four references with newest ones (the last two highlighting the team approach)
A table may help place the text in the intro into context- and assist with clarity.	We agree and added a box listing main determinants of potential overuse of anticancer drugs
Does chemotherapy mean iv chemotherapy or does it also include oral chemotherapy?	We included both of them. We also realize that we mistakenly tend to use the term “chemotherapy” informally, as an umbrella term, including targeted, hormonal and immuno-therapies. We now use the term “anticancer drugs”
Results: The analyses would be improved if the data included iv versus oral chemotherapy and also immune-oncology drugs versus chemotherapy drugs. Give the recentness of the data, a more nuanced looked at “chemotherapy” is warranted. Is there a transition in use of iv versus oral versus immochemotherapy over time?	We agree, such analyses would enrich the paper. Unfortunately, we lack information on ATC of drugs used for inpatients (we just know that they used anticancer drugs when hospitalized): only drug utilization in outpatients could be more specifically identified through an ATC code, thus identifying route of administration and type of anticancer drug. Therefore, we think that such analysis cannot be adequately performed
Discussion I would add some analysis based on the above text?	See above
<b>Reviewer: 2</b>	
The authors should consider that the introduction and discussion are rather long. Both need to be shortened, and the discussion in particular needs to focus on the findings of the study, and similar literature. The abstract and article summary need to be reconsidered in light of the comments below	Thank you. We shortened both the introduction and the discussion in order to focus more on the study results, although we still try to put these results in context and highlight how local data can foster multidisciplinary analyses and discussion leading to better end of life care. We could include some data in the abstract and stay below the word limit
the methods are too brief. It needs to be clear how the cohort was ascertained from the mortality registry. A list of ICD cancer codes is given but what were the codes applied to: underlying cause of death; all causes of death; other? Also, if the code is from the death certificate, the cohort are not necessarily dying from cancer- consider a different phrase eg persons who had cancer recorded as a [or underlying, if more appropriate] cause of death	Thanks. We now specify that we included subjects who had cancer as the underlying cause of death
How is the linkage of the mortality registry to the other resources conducted, what key information is used, how reliable/complete is the linkage?	We now specify that the unique identification number, assigned to each resident, is present in each of the databases used. Theoretically, this number should allow a complete linkage and no information should get lost. However, although those databases have been and are being continuously used in observational studies performed in our region, they have not been formally validated in this regard. We added this information in the discussion acknowledging this as one of the limits of this study.
what information and how were aggressive tumours defined using the available data?	In keeping with your suggestion, we added this information in appendix 1

<p>What were the sources and how were the chemotherapy and palliative care variables generated?</p>	<p>As for chemotherapies (that now we indicate as anticancer drugs) we included pharmacological prescriptions at discharge or outpatient, considering drugs within ATC (anatomical therapeutic classes) L01 and L02. As for palliative care services, their use is captured in hospice and domiciliary care databases. Such information was already included in the first version but now we tried to make it clearer</p>
<p>As well as the source/s, what surgery was considered relevant (presumably removal of tumour)?</p>	<p>Surgery related information was not specifically limited to removal of tumour (we now say “any surgery” in the methods section). However, since our cohort includes subjects with cancer as the underlying cause of death and since we consider surgery within the last 6 months of life, it is very likely that related data mostly refer to tumour removal</p>
<p>The authors may like to consider providing lists of codes in the Supplementary Materials if needed.</p>	<p>See appendix 1</p>
<p>The results should be presented with less reference to the statistical techniques. Sentences should be shorter and focus on one set of associations- the switching to saying that the opposite is seen by another is not always easy to follow.</p>	<p>Thank you, we amended as suggested</p>
<p>The descriptions of Tables 3a and b are particularly challenging, not just because the sentence is very long; there needs to be reference to the comparison group where chemo or palliative care is increased/decreased. There is little difference in the findings of Tables 3a and 3b, and so probably only one needs to be presented</p>	<p>These two tables show the results of logistic models and specifically the likelihood (expressed as odds ratios) of receiving vs not receiving anticancer drugs (1<sup>st</sup> column), palliative care (2<sup>nd</sup> column) or both (3<sup>rd</sup> column) given the presence of each single covariate in the model. We agree that the descriptions were unclear and shortened them. We also moved table 3b to the appendix</p>
<p>The authors should also consider the robustness of their analyses. It is difficult here to be prescriptive as the chemo and palliative care variables are not defined, but did the authors consider whether certain sources of data may be more or less reliable at defining these outcomes? For example, a palliative care code may appear in the hospital discharge record; or place of death may have been a hospice? Would either of these contribute to the palliative care variable, and would the results change if they were excluded?</p>	<p>We considered palliative care services as those provided in hospices or at home. Therefore, as specified, information about palliative care comes from 2 specific databases: 1) discharge from hospices and 2) implementation of home care services. We do not have (directly) the information about which deaths occurred in hospice</p>
<p>There is little on the strengths and weaknesses of the study. In comparison to other studies, it may be that the information available here is wider; thinking here that the routine hospital prescription data and hospice and domiciliary care data are not such common resources.</p>	<p>Thank you. We integrated the discussion in this regard.</p>
<p>The authors should also comment on the coverage of the routine databases- how reliable are they considered to be, presumably the data are collected as part of the patient's care.</p>	<p>Thank you, we made a comment in the discussion in this regard</p>

Other limitations could relate to the variables of interest or the definition of the cohort. Could any measures be taken to test the robustness of findings depending on these definitions?	Thank you. We did multiple analyses and preferred not to add more. As for the variables of interest, they have been temporally defined and we did not do sensitivity analyses since we were interested in patient care received within the last 30 days of life, often used as a reference period in similar studies. The definition used to select the cohort (cancer as the underlying cause of death) should allow in our opinion to fulfil the objective to describe how subjects with cancer are treated in the last month of life
<b>Reviewer: 3</b>	
The major weakness of the manuscript is that administrative data can't answer important questions about the implications of the data, such as how the increased or decreased use of chemo or palliative care affected the quality of life of these patients. What was the value or lack thereof of chemotherapy at the end of life, and did it in fact really help patients (as some experts state) by reducing tumor size? What can other studies tell us about those issues that would help us think about the results of this study? And, aren't those the issues that should be the focus of the discussion, instead of generalizations pertaining to empathy, the role of nurses, etc, which are interesting but completely unrelated to the data. Revising the discussion section is the major revision I would recommend	Thank you. We revised the discussion section, removing some text pertaining to the wider context of end of life care, although we still try to put these results in context and highlight how local data can foster multidisciplinary analyses and discussion leading to better end of life care. We also briefly discuss the issue of palliative chemotherapy in light of the scant information available in the scientific literature about its added value, and in light of recommendations in guidelines (specifically in the ESMO guideline). In this regard we specifically acknowledge, as you correctly point out, that our administrative data can't say how the increased or decreased use of chemo or palliative care affected the quality of life of these patients, although they can help foster multidisciplinary discussions and the design of ad hoc studies.
The manuscript also suffers from numerous grammatical errors, especially in the results section, apparently because English is not the usual language of the authors. These need to be fixed prior to resubmission	Text revised, thank you for pointing out

#### VERSION 2 – REVIEW

<b>REVIEWER</b>	Bennett, Charles South Carolina College of Pharmacy/USC Campus
<b>REVIEW RETURNED</b>	28-Jan-2022
<b>GENERAL COMMENTS</b>	Please address if IRB approval was obtained to allow the investigators to take an identified database and then de-identify it?
<b>REVIEWER</b>	Kane, Eleanor University of York, Health Sciences
<b>REVIEW RETURNED</b>	01-Feb-2022
<b>GENERAL COMMENTS</b>	Thank you for the revisions to the manuscript which has made many of the issues raised much clearer. However there remain some areas which would benefit from improvement:

	<p>The main issue is that the discussion remains long and includes information that is not part of the presented study; for instance there is a whole page referring to ECOG and other prognostic tools. As this is not examined, it would be better to exclude or substantially reduce this section. Similarly for the paragraphs on the role of nurses and health professional- patient communication.</p> <p>With this in mind, the conclusion also needs to be revised in line with the findings of the study- the study did not examine the use of prognostic tools; specific approaches to end-of-life care; or whether aggressive treatments are beneficial or worsen QoL.</p> <p>There also needs to be clarity when reporting the results. The authors should make reference to the comparison group when discussing whether anticancer drug use or palliative care is more or less likely among those with haematological cancers, etc (e.g. page 9, lines 3-24). The results should also quote the odd ratios and 95% confidence intervals to confirm the reported associations.</p> <p>The same is true in the abstract where the findings need to be written in a clear manner. For instance, the third sentence of the results, “whereas they increased in case of haematologic tumours” would be better as “drug therapy was more likely among those with haematologic tumours...”. In the next sentence, would be better as “palliative care was less likely among those with haematologic compared with other tumours...etc”- please note too that while the other associations are in the same direction, those who had aggressive tumours were more likely to receive palliative care (OR&gt;1). Please add confidence intervals for the odds ratios in the abstract.</p> <p>The authors have added information on potential limitations to the discussion. However the evaluation of those limitations is not clearly expressed. It would be sufficient to say that the administrative data collected during the patient’s care for the purpose of reimbursements to healthcare rather than for research. For the linkage between the different administrative sources, it would similarly be better to say the research used different administrative sources which were linked by a unique patient identification number, which has not been specifically validated.</p> <p>Please check the time period for surgery and hospital admissions- the abstract and methods suggest that these are any surgery or hospital admission within 6 months of death, while Table 3 and the results suggest within 30 days of death.</p> <p>Please consider how to examine age in these data; presently the OR, lower and upper 95% CI values are all the same. As there is probably not much difference between an 70 year old and 71 year old for example, it would be more informative to calculate the risk per 5 year increase in age rather than per year increase in age.</p>
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<b>REVIEWER</b>	Zuckerman, Diana National Center for Health Research
<b>REVIEW RETURNED</b>	10-Feb-2022

<b>GENERAL COMMENTS</b>	This is a solid study on an important issue, but as the authors point out, administrative data has limitations. Given that we don't know why treatment decisions were made, the number of comparisons and amount of data provided is somewhat
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	<p>overwhelming. The authors aren't clear about what's new here or what's most important, and perhaps that is because administrative data can't explain the results in a way that would be more informative, In terms of trying to make sense of the large amount of data, I'd prefer more data in Tables and less data in the narrative.</p> <p>Since geographic differences are to be expected but the differences seem relatively small and the reasons for the differences are unknown (case mix vs. physician attitudes and behaviors), and since the importance of these regional differences are unclear to those of us unfamiliar with this region of Italy, I suggest deleting Table 1 and summarize the information succinctly. In contrast, Tables 2 and 3 are good additions.</p> <p>The discussion and conclusions are somewhat speculative and I would like to see more evidence, perhaps from other studies, to provide clear support for interpreting the findings. Saying more research is needed isn't very useful when administrative data are "grossly descriptive and have obvious limits" as the authors acknowledge.</p>
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#### VERSION 2 – AUTHOR RESPONSE

<b>Reviewer: 1</b>	
Please address if IRB approval was obtained to allow the investigators to take an identified database and then de-identify it?	Thank you. Yes, the ethics committee approved our research. Included subjects were actually never identifiable: when accessing the databases, data are already anonymised (each patient is associated to a unique identification number in each database, allowing record linkage procedures). We added some more explanation in this regard in the methods section
<b>Reviewer: 2</b>	
The main issue is that the discussion remains long and includes information that is not part of the presented study; for instance there is a whole page referring to ECOG and other prognostic tools. As this is not examined, it would be better to exclude or substantially reduce this section. Similarly for the paragraphs on the role of nurses and health professional- patient communication.	Thank you. We further reduced those parts, although left some of those concepts to put results in context and highlight how local data can foster multidisciplinary analyses and discussion leading to better end of life care.
the conclusion also needs to be revised in line with the findings of the study- the study did not examine the use of prognostic tools; specific approaches to end-of-life care; or whether aggressive treatments are beneficial or worsen QoL.	Thank you, revised as suggested
The authors should make reference to the comparison group when discussing whether anticancer drug use or palliative care is more or less likely among those with haematological cancers, etc (e.g. page 9, lines 3-24). The results should also quote the odd ratios and 95% confidence intervals to confirm the reported associations.	Revised as suggested as for the reference group of haematologic cancers. In keeping with the suggestion of another reviewer, we left quantitative data in the tables and refer to them when commenting (qualitatively) results in the text

<p>The same is true in the abstract where the findings need to be written in a clear manner. For instance, the third sentence of the results, "whereas they increased in case of haematologic tumours" would be better as "drug therapy was more likely among those with haematologic tumours...". In the next sentence, would be better as "palliative care was less likely among those with haematologic compared with other tumours...etc"- please note too that while the other associations are in the same direction, those who had aggressive tumours were more likely to receive palliative care (OR&gt;1). Please add confidence intervals for the odds ratios in the abstract.</p>	<p>We revised as suggested. We have to cut some parts in order to comply with the word limit</p>
<p>The authors have added information on potential limitations to the discussion. However the evaluation of those limitations is not clearly expressed. It would be sufficient to say that the administrative data collected during the patient's care for the purpose of reimbursements to healthcare rather than for research. For the linkage between the different administrative sources, it would similarly be better to say the research used different administrative sources which were linked by a unique patient identification number, which has not been specifically validated.</p>	<p>Thank you, amended as suggested</p>
<p>Please check the time period for surgery and hospital admissions- the abstract and methods suggest that these are any surgery or hospital admission within 6 months of death, while Table 3 and the results suggest within 30 days of death.</p>	<p>We corrected the text in table 3, thanks!</p>
<p>Please consider how to examine age in these data; presently the OR, lower and upper 95% CI values are all the same. As there is probably not much difference between an 70 year old and 71 year old for example, it would be more informative to calculate the risk per 5 year increase in age rather than per year increase in age.</p>	<p>We agree, in terms of immediacy 5-year intervals may be preferable, although they should not change the big picture (age inversely related to the likelihood of receiving cancer drugs and palliative care). Unfortunately we would need some time to rerun all the statistical models and prefer not to delay our resubmission further</p>
<p><b>Reviewer: 3</b></p>	
<p>This is a solid study on an important issue, but as the authors point out, administrative data has limitations. Given that we don't know why treatment decisions were made, the number of comparisons and amount of data provided is somewhat overwhelming. The authors aren't clear about what's new here or what's most important, and perhaps that is because administrative data can't explain the results in a way that would be more informative, In terms of trying to make sense of the large amount of data, I'd prefer more data in Tables and less data in the narrative.</p>	<p>Thank you, in principle we agree. Our data are descriptive and add up to the existing literature with findings that are often in line with conclusions of several other studies. We comment on them and refer to the existing literature when available, but cannot escape from their descriptive aims, often preventing a clear interpretation of why treatment decisions were made. Our main point is that clinical and administrative data can help promote multidisciplinary discussion (locally, too) to maximize quality of end-of-life care, also considering that the observed variability suggests that a potential exists to better organize it. We accept your suggestion to leave data only in the tables, although we hope not to displease</p>

	another reviewer (who asked a more detailed presentation of data with confidence intervals also in the text)
Since geographic differences are to be expected but the differences seem relatively small and the reasons for the differences are unknown (case mix vs. physician attitudes and behaviors), and since the importance of these regional differences are unclear to those of us unfamiliar with this region of Italy, I suggest deleting Table 1 and summarize the information succinctly. In contrast, Tables 2 and 3 are good additions.	Table 1 is intended to provide a description of the study population and, as such, we prefer to leave at least the overall data (Region, last column). Detailed data on each LHA would help support the hypothesis that local differences in use of anticancer drugs and palliative care may not depend on differences in case mix. For this reason, we would save these data as extra (online) table
The discussion and conclusions are somewhat speculative and I would like to see more evidence, perhaps from other studies, to provide clear support for interpreting the findings. Saying more research is needed isn't very useful when administrative data are "grossly descriptive and have obvious limits" as the authors acknowledge.	We agree that some (if not many) of our arguments in the discussion are speculative. For this reason, we reduced some of these arguments and revised the conclusion in line with the findings of the study. As said before, we comment on our data and refer to the existing literature when available (see in particular about the association of anticancer drugs with haematologic tumours), but cannot escape from descriptive aims of these data, often preventing a clear interpretation of findings. Our main point is that clinical and administrative data can help promote multidisciplinary discussion (locally, too) to maximize quality of end-of-life care, also considering that the observed variability suggests that a potential exists to better organize it. In any case, our data add up to the existing literature with findings that are often in line with conclusions of several other studies.

### VERSION 3 – REVIEW

<b>REVIEWER</b>	Kane, Eleanor University of York, Health Sciences
<b>REVIEW RETURNED</b>	21-Mar-2022

<b>GENERAL COMMENTS</b>	Thank you for addressing my comments.
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<b>REVIEWER</b>	Zuckerman, Diana National Center for Health Research
<b>REVIEW RETURNED</b>	02-Apr-2022

<b>GENERAL COMMENTS</b>	This manuscript is much improved. There are a few wording issues that should be edited. One more substantive wording issue is: "Aggressive treatments, facilitated by the availability of newer anticancer agents that have fewer side effects, [3] often do not alleviate patients' condition or provide hope for extending significantly life of decent quality. " I suggest revising to say "or significantly extend life of decent quality." In fact, these drugs do provide hope, but it is mostly hope that is based on wishful thinking rather than data.
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