PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

This paper was submitted to a another journal from BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

(This paper received three reviews from its previous journal but only two reviewers agreed to published their review.)

ARTICLE DETAILS

TITLE (PROVISIONAL)	A retrospective cohort analysis of real-life decisions about end-of-life care preferences in a Southeast Asian country
AUTHORS	Tan, Woan Shin; Bajpai, Ram; Ho, Andy H Y; Low, Chan Kee; Car, Josip

VERSION 1 – REVIEW

REVIEWER	Simon Noah Etkind King's College London, UK
REVIEW RETURNED	18-Jun-2018

GENERAL COMMENTS	Thanks for the opportunity to review this interesting manuscript, in which the authors analyse routinely collected data to describe the content of advance directives in the population of Singapore. They additionally investigate the associations of age and gender with different end of life care preferences in this large sample. I agree that it is important to understand end of life preferences, and it is good to do so in such a large sample. I feel therefore that this study makes a useful contribution, however it could be presented more clearly, and I think the following points need to be addressed prior to publication. Major points 1. The study design is reported as a "cross sectional" study, which doesn't provide enough detail to reflect the methods used. My understanding is that this is a retrospective analysis of routinely collected data. The study design should be more clearly described. 2. The analysis section of the methods requires further detail beyond that 'descriptive statistics were used'. Could the authors describe in more detail the steps they took? 3. In the results section, comparisons are made between sub-groups on a number of occasions: (eg P11 line 19 "there was demographic variation across the three types of ACP, with younger age profiles for those who completed the general and disease-specific forms." and P14 line 5 "The share of individuals who had appointed a substitute decision-maker varied across the three types of ACP.") However no statistics demonstrating these differences are presented. For the first example, I'd expect the

authors to present mean or median age for each sub-group, with a measure of variance, and a statistical test demonstrating the difference between the groups. The authors should ensure they present this data where they are comparing groups in their analysis, as well as recording this in the analysis section of the methods.

4. Could the authors explain more clearly how each disease stage was defined? It's not clear how participants were allocated into a disease category. Was this based on clinical decision, or something else?

Minor points

Abstract

5. The abstract needs to include details of the data sources. I think (as in point 1 above) you also need to more clearly state the study design.

6. Could the authors add more detail to the results section of the abstract? They say "age and sex significantly predict preferences" – could they add odds ratios and confidence intervals to demonstrate this more clearly

Background

7. I think this section is quite long and the authors spend too much time discussing advance care planning in general, which doesn't specifically relate to their research question: "to describe preferences of those who have completed ACP, and examine the influence of age and gender". I suggest the authors revise this section focused more on the study question. For example:

o Patient preferences are key to delivery of high quality end of life care. This is important in older populations which are growing worldwide.
o Individual preferences may not accurately reflect 'real world' preferences when family/health professionals are involved, but real world preferences are reflected in advance care plans.
o Therefore we undertook to describe preferences of those who have completed ACP, and examine the influence of age and gender

The authors could then describe details of the advance care planning context in the beginning of the methods.

8. P5 line 47 "with earlier referrals to community-based palliative care." I don't quite see how this fits in. Could the authors rephrase +/- add a reference

Methods

9. To make it clearer to the reader, could the authors explain why the questions asked of participants differed at different disease stages?

10. Why did the authors only look at the potential influence of age/gender on preferences? There is evidence that many factors may influence preferences towards the end of life. Were they limited by the available data? Could the authors explain this choice in more detail? If they were limited by the data, this should be included as a limitation. For examples of factors associated with preferences at the end of life, see this paper:(1)

11. It is a bit confusing at first-read that each disease stage is linked to a different advance care planning form. Could this be more clearly described? Perhaps a box or figure describing the ‘living matters’ intervention would be helpful?

Results
12. The methods describe disease stages, but the results are presented based on the type of ACP form that was completed. I can see these correspond to each other, but could the authors use one or the other for clarity.

13. Tables 1 and 3. I assume the format is n (%)? Please could this be added for clarity

14. Table 4. Are the numbers percentages? I agree there is a clear relationship between PPOC and PPOD, but it would be better if the authors could show statistically the relationship between preferred place of care and PPOD rather than extrapolating from the percentage agreement.

15. Could the authors comment on how the small number in the ‘chronic disease’ group might affect their analysis?

Discussion
16. This is generally well referenced and clearly linked to the existing evidence.

17. Second sentence of discussion “ACP is, therefore, an important channel that supports the expression of one’s preferences, and to minimize care that is not wished for” I don’t understand how this follows from the first sentence. Please rephrase.

18. In their introduction, the authors talk about potential differences between patient expressed preferences in the existing research, and ‘real world’ preferences expressed in advanced care plans. Could the authors comment a bit more in the discussion as to whether their findings match these existing studies or whether their findings are different.

19. The authors could consider linking their results to theories such as prospect theory which propose to explain changes in preferences across the disease course.(2)

20. The limited number of factors that were investigated for associations with preferences is a further limitation.

References:
1. Etkind Simon N, Bone Anna E, Lovell N, Higginson Irene J, Murtagh Fliss EM. Influences on Care Preferences of Older People with Advanced Illness: A Systematic Review and Thematic Synthesis. Journal of the American Geriatrics Society. 2018;66(5):1031-9. doi: 10.1111/jgs.15272.
2. Kahneman D, Tversky A. Prospect theory: An analysis of decision under risk. Econometrica: Journal of the econometric society. 1979:263-91.

REVIEWER	Dr. Benjamin Hon-Wai CHENG Medical Palliative Medical Unit, Department of M&G, Tuen Mun Hospital, Hong Kong.

REVIEW RETURNED	20-Sep-2018

GENERAL COMMENTS	Thanks for the invitation to review this manuscript. While the authors addressed an important research topic, i.e. Advanced Care Planning and end-of-life care preferences in individuals who have completed ACP in Singapore, the content need to be major revised due to the following stated limitations & recommendations. 1.) The study adopted a cross-sectional design and included 3380 patients who have completed an ACP in Singapore. However, only gender and age were included into statistical analysis regarding their treatment preferences and place of care / place of death. This would much carry much limit as other important information, including Ethnicity, underlie disease status (e.g. advanced malignancies, end-stage organ failure or neuro-degenerative diseases like ALS/MND), and religious beliefs could all carry significance in their EOL preferences. More importantly, these would be important baseline demographics that could be easily drawn from database. For instance, patients suffering from MND would mostly require non-invasive ventilation and artificial nutrition compared with advanced cancer patients. I would suggest authors to seriously consider regain these important data and include them into statistical analysis. If not, authors should state with very good reasons in the "Limitations" section why were these data not available. 2. Taking into account the readership of BMJ open Journal, readers might not be working in palliative care field and I am not sure the discussion on ACP preferences in a single Southeast Asian country (Singapore) would be of interest. To make the discussion part more fruitful, I would suggest authors to have deep discussion on contents that are specific to Singapore. What's so special of Singapore? From my understanding it might the mixed ethnicity and highly accessible healthcare system. Therefore, again, the cultural values on EOL (e.g. in Chinese patients, Indian ethnicity and Malay ethnicity) might carries different impact and I am sure the discussion on this would enrich the discussion part.

VERSION 1 – AUTHOR RESPONSE

Response to reviewer 1

	Comments	**Response**	**Revisions**
1.	The study design is reported as a “cross sectional” study, which doesn’t provide enough detail to reflect the methods used. My understanding is that this is a retrospective analysis of routinely collected data. The	Thank you for your comment. To better reflect the retrospective nature of the study, we have amended the title as well as the methods section.	A retrospective cohort analysis of real-life decisions about end-of-life care preferences in a Southeast Asian country (page 1)

	Comments	Response	Revisions
	study design should be more clearly described.		A retrospective cohort study was conducted to profile the end-of-life care preferences. (page 3) This is a retrospective cohort study that included all individuals aged 21 years and above, who have completed their ACP between January 2011 and December 2015 across all participating acute care hospitals, specialist care centres, and social care providers in Singapore. (page 9)
2.	The analysis section of the methods requires further detail beyond that 'descriptive statistics were used'. Could the authors describe in more detail the steps they took?	We have amended this section to provide a more detailed description of the statistical methods.	Descriptive statistics were used to characterise the sample and to summarise the basic characteristics of the data. Frequency distribution tables were created to profile the characteristics of the study samples and to describe the documented end-of-life care preferences. A chi-square test was used to determine whether a statistically significant relationship exists between two or more categorical variables. We examined the independent effects of age and gender on four different end-of-life care statement of preference. We dichotomised the preferences for: (i) cardiopulmonary resuscitation (CPR) ("attempt" or "do not attempt"), (ii) medical

	Comments	**Response**	**Revisions**
			intervention ("treatment" or "comfort measures"), (iii) preferred place of medical treatment ("home" or "others") and (iv) preferred place of death ("home" or "others"). Multivariable logistic regression was performed to investigate the relationship between age and sex with these preferences. All statistical tests were conducted using Stata version 12 (34), and a two-sided p-value of 0.05 was set as the level of statistical significance. (page 11-12)
3.	In the results section, comparisons are made between sub-groups on a number of occasions: (eg P11 line 19 "there was demographic variation across the three types of ACP, with younger age profiles for those who completed the general and disease-specific forms." and P14 line 5 "The share of individuals who had appointed a substitute decision-maker varied across the three types of ACP.") However, no statistics demonstrating these differences are presented. For the first example, I'd expect the authors to present mean or median age for each sub-group, with a measure of variance, and a statistical test demonstrating the difference between the groups. The authors should ensure they present this data where they are comparing groups in their analysis, as well as recording this in the analysis section of the methods.	Thank you for the comment. We have revised Tables 1 and 3 to include results of statistical tests to support these statements. From the revised Table 1, the statistical significance of the differences in age and gender across the three types of forms were illustrated. In the revised Table 3, the statistical significance of the differences in the relationship with the substitute decision maker between individuals who filled out the three forms was illustrated.	Please refer to Tables 1 and 3. (page 13, 15)

	Comments	**Response**	**Revisions**
4.	Could the authors explain more clearly how each disease stage was defined? It's not clear how participants were allocated into a disease category. Was this based on clinical decision, or something else?	The decision was based on clinical judgement of the attending clinician. We have revised the manuscript to reflect this.	Currently, referral to ACP and the staging of one's health status is largely based on clinical judgement. (page 8)
	Abstract		
5.	The abstract needs to include details of the data sources. I think (as in point 1 above) you also need to more clearly state the study design.	Thank you for your comment. We have revised the abstract to include information on the data sources.	Data were extracted from the national and Tan Tock Seng Hospital ACP database. (page 3)
6.	Could the authors add more detail to the results section of the abstract? They say "age and sex significantly predict preferences" – could they add odds ratios and confidence intervals to demonstrate this more clearly	We have included the odds ratios and their corresponding 95% confidence intervals in the abstract. However, to accommodate this within the 300 word limit for the structured abstract, we have revised the abstract.	Older age (>=75 years) showed higher odds for home as preferred place of medical treatment (odds ratio (OR): 1.52; 95% CI: 1.23-1.89) and place of death (OR: 1.29; 95% CI: 1.03-1.61) and lower odds for CPR (OR: 0.31; 95% CI: 0.18-0.54) and full treatment (OR: 0.32; 95% CI: 0.17-0.62) respectively. However, the female gender exhibited lower odds for home as preferred place of medical treatment (OR): 0.69; 95% CI: 0.57-0.84) and place of death (OR: 0.70; 95%CI: 0.57-0.85) and higher odds for full treatment (OR: 2.35; 95% CI: 1.18-4.68). (page 3)
	Background		
7.	I think this section is quite long and the authors spend too much time discussing advance	Thank you for your suggestion. We have removed the second and third paragraphs to	Surveys have been conducted locally to profile the end-of-life care

	Comments	**Response**	**Revisions**
	care planning in general, which doesn't specifically relate to their research question: "to describe preferences of those who have completed ACP, and examine the influence of age and gender". I suggest the authors revise this section focused more on the study question. For example: o Patient preferences are key to delivery of high quality end of life care. This is important in older populations which are growing worldwide. o Individual preferences may not accurately reflect 'real world' preferences when family/health professionals are involved, but real world preferences are reflected in advance care plans. o Therefore we undertook to describe preferences of those who have completed ACP, and examine the influence of age and gender. The authors could then describe details of the advance care planning context in the beginning of the methods.	refocus the introduction on the points raised by the reviewer. We have also included additional discussion about the importance of "real world" preferences captured in this study.	preferences across different patients and community-based samples (14-17). However, surveys often require individuals to respond to a single question about their preferred place of death, based on a hypothetical end-of-life scenario (18) without having to trade-off against other priorities or account for other than one's personal concerns. Therefore, choices elicited through a survey could reflect what is preferred under more "ideal" circumstances. Since an illness impacts the individual biologically as well as socially (19), the survey process may not mirror real-life decision-making processes well (20). (page 7)
8.	P5 line 47 "with earlier referrals to community-based palliative care." I don't quite see how this fits in. Could the authors rephrase +/- add a reference	We have removed this sentence.	
	Methods		
9.	To make it clearer to the reader, could the authors explain why the questions asked of participants differed at different disease stages?	We have revised the manuscript to explain this.	Individuals identify a substitute decision-maker and also establish the goals of care relevant to their disease stage. They are intended to update

	Comments	**Response**	**Revisions**
			their decisions as they transit health states. For instance, questions regarding disease-related complications are not applicable to a healthy individual whereas, for an individual with a poor prognosis, questions related to disease-related complications may no longer be applicable. Rather, they may be concerned about care during the terminal phase. (Pages 8)
10.	Why did the authors only look at the potential influence of age/gender on preferences? There is evidence that many factors may influence preferences towards the end of life. Were they limited by the available data? Could the authors explain this choice in more detail? If they were limited by the data, this should be included as a limitation. For examples of factors associated with preferences at the end of life, see this paper:(1)	Thank you for this question. We would have liked to examine the relationship of preferences with other variables but we were limited by the availability of data. We have included this under limitations of the study.	Other studies have also highlighted the importance of the family and care context on care preferences. A recent systematic review highlighted the lack of research evidence on ethnicity and religion, which is also absent from this study. Future research should explore the influence of these pertinent elements including a closer examination of the influence of different illnesses (advanced malignancy, end-stage organ failure or neuro-degenerative diseases) on end-of-life care preferences. (page 21)
11.	It is a bit confusing at first-read that each disease stage is linked to a different advance care planning form. Could this be more clearly described? Perhaps a box or figure describing the ‘living matters’ intervention would be helpful?	We have included Figure 1 to describe this.	Please refer to Figure 1.

	Comments	**Response**	**Revisions**
	Results		
12.	The methods describe disease stages, but the results are presented based on the type of ACP form that was completed. I can see these correspond to each other, but could the authors use one or the other for clarity.	Thank you. We have amended all descriptions in the tables to report the data by disease stages instead of type of forms.	Please refer to Tables 1-3. (page 13, 15)
13.	Tables 1 and 3. I assume the format is n (%)? Please could this be added for clarity.	Yes. We have amended the tables to reflect that it refers to absolute numbers and proportions.	Please refer to Tables 1 and 3. (page 13, 15)
14.	Table 4. Are the numbers percentages? I agree there is a clear relationship between PPOC and PPOD, but it would be better if the authors could show statistically the relationship between preferred place of care and PPOD rather than extrapolating from the percentage agreement	Thank you for your comment. We have computed the statistical significance for the diagonal proportions.	Please refer to Table 4. (page 16)
15.	Could the authors comment on how the small number in the 'chronic disease' group might affect their analysis?	We have profiled the end-of-life care profile and preferences of the "chronic disease group" but due to the limitations of the small sample size as the reviewer has rightly pointed out, we did not conduct further statistical analysis beyond univariate analysis.	No changes made.
	Discussion		
16.	Second sentence of discussion "ACP is, therefore, an important channel that supports the expression of one's preferences, and to minimize care that is not wished for" I don't understand how this follows from the first sentence. Please rephrase.	We have removed this sentence and will focus on discussing the implications of real-world preferences. Please also refer to our amendments to comment (17) below.	The findings offer insights into decisions made under real-life situations, where there is a level of expectation that after having stated a preference, attempts by the individual, his/her family or healthcare

	Comments	**Response**	**Revisions**
			professionals will be made to adhere to them. (pages 17)
17.	In their introduction, the authors talk about potential differences between patient expressed preferences in the existing research, and 'real world' preferences expressed in advanced care plans. Could the authors comment a bit more in the discussion as to whether their findings match these existing studies or whether their findings are different. The authors could consider linking their results to theories such as prospect theory which propose to explain changes in preferences across the disease course. (2)	We have revised the discussion section to discuss this a little further and to utilize Kahneman's previous work on difference between decision utility and experience utility.	Other research, such as those examining health state valuation, have pointed out the differences between these two groups (30); reflecting different priorities and changing experiences. The complexity of choices also grows as death draws near (31). When healthy participants are asked to make decisions regarding hypothetical scenarios about death and dying, the 'shock' or fear that he or she experiences (32) about potentially dying in an unfamiliar environment, could sway decisions towards the familiar – meaning the home. Juxtaposed against other priorities, such as pain and symptom management, and alleviating caregiver burden, the "cost" of maintaining one's decision to die at home may also increase (33). At the same time, the fear of the unfamiliar could decrease over time, as patients increasingly adapt to new living and care arrangements in other settings, such as nursing homes or hospices (34). One in five individuals have been found to change their preferences over time (18). (page 18-19)
19.	The limited number of factors that were investigated for	We have address this under our response to comment (10).	Please see amendments for comment (10).

	Comments	Response	Revisions
	associations with preferences is a further limitation.		

Response to reviewer 2

	Comments	Reply	Revision
1.	The study adopted a cross-sectional design and included 3380 patients who have completed an ACP in Singapore. However, only gender and age were included into statistical analysis regarding their treatment preferences and place of care / place of death. This would much carry much limit as other important information, including Ethnicity, underlie disease status (e.g. advanced malignancies, end-stage organ failure or neuro-degenerative diseases like ALS/MND), and religious beliefs could all carry significance in their EOL preferences. More importantly, these would be important baseline demographics that could be easily drawn from database. For instance, patients suffering from MND would mostly require non-invasive ventilation and artificial nutrition compared with advanced cancer patients. I would suggest authors to seriously consider regain these important data and include them into statistical analysis. If not, authors should state with very good reasons in the "Limitations" section why were these data not available.	Thank you for your comments. This is indeed a very important point that you have raised. We have expanded the section in limitations to highlight the unavailability of this data.	Other studies have also highlighted the importance of the family and care context on care preferences. A recent systematic review highlighted the lack of research evidence on ethnicity and religion, which is also absent from this study. Future research should explore the influence of these pertinent elements including a closer examination of the influence of different illnesses (advanced malignancy, end-stage organ failure or neuro-degenerative diseases) on end-of-life care preferences. (page 21)

2.	Taking into account the readership of BMJ open Journal, readers might not be working in palliative care field and I am not sure the discussion on ACP preferences in a single Southeast Asian country (Singapore) would be of interest. To make the discussion part more fruitful, I would suggest authors to have deep discussion on contents that are specific to Singapore. What's so special of Singapore? From my understanding it might the mixed ethnicity and highly accessible healthcare system. Therefore, again, the cultural values on EOL (e.g. in Chinese patients, Indian ethnicity and Malay ethnicity) might carries different impact and I am sure the discussion on this would enrich the discussion part.	Thank you for this excellent point. We have expanded the first paragraph of the discussion to discuss the relevancy of our findings to readers of BMJ Open.	Singapore stands apart being an Asian country that is strongly influenced by Western culture where the people have a strong desire for independence together with a collectivist mentality (27). The results of this study could therefore be of relevance to other Asian countries that are also experiencing rapid socioeconomic and demographic transitions. (page 17-18)

VERSION 2 – REVIEW

REVIEWER	Dr Simon Noah Etkind King's College London, London, UK
REVIEW RETURNED	07-Dec-2018

GENERAL COMMENTS	Thanks for the opportunity to read this revised manuscript. I think the revised manuscript addresses most of the issues raised. There are a few minor points that should still be addressed as follows: 1. Background last paragraph. I'm not sure of the meaning of "preferences are profiled by their health status". Could this be revised to "preferences are profiled according to the health status of those expressing them" or similar? 2. Results 1st paragraph – suggest you change "PPC" to "advanced disease" to keep consistent with changes made in the rest of the manuscript 3. Results. I think there might be an error in this sentence: "One highlight is that although only 4.1% did not state any preference or were unsure about the place of care, 23% of respondents did indicate their preferences with regards to the preferred place of death" correct. Shouldn't this actually read "23% of respondents did NOT indicate their preferences"?

	4. Thanks for clarifying that factors beyond age and sex were not investigated due to limited availability of data. I think this should be stated more directly in the limitations section i.e. by saying "we were only able to examine the relationship between preferences and patient age and sex due to limited availability of data". It might also be worth referring to this in the methods section. i.e. in the measures and data extraction section of methods, the authors could state that "available personal characteristics of patients (age/gender) were also extracted" 5. The "other studies" and "recent systematic review" mentioned in the limitations section of the discussion are not referenced. If included in the manuscript, these should be included in the reference list.

REVIEWER	Dr. Hon Wai Benjamin CHENG Medical Palliative Medicine Unit, Department of Medicine & Geriatrics, Tuen Mun Hospital, Hong Kong.
REVIEW RETURNED	13-Dec-2018

GENERAL COMMENTS	All of my raised concerns in first review had been properly addressed.

VERSION 2 – AUTHOR RESPONSE

Response to reviewer 1

	Comments	Response	Revisions
1.	Background last paragraph. I'm not sure of the meaning of "preferences are profiled by their health status". Could this be revised to "preferences are profiled according to the health status of those expressing them" or similar?	We have revised the sentence as you have suggested.	Preferences are profiled according to the health status of those expressing them (Page 7)
2.	Results 1st paragraph – suggest you change "PPC" to "advanced disease" to keep consistent with changes made in the rest of the manuscript	Thank you for pointing this out. We have amended the sentence.	Individuals with advanced illnesses (Page 12)
3.	Results. I think there might be an error in this sentence: "One highlight is that although only 4.1% did not state any preference or were unsure about the place of care, 23% of	Thank you for highlighting this. It is an error and should read as you have pointed out. We have made the necessary changes.	23% of respondents did not indicate their preferences with regards to the preferred place of death. (Page 14)

	Comments	Response	Revisions
	respondents did indicate their preferences with regards to the preferred place of death” correct. Shouldn’t this actually read “23% of respondents did **NOT** indicate their preferences”?		
4.	Thanks for clarifying that factors beyond age and sex were not investigated due to limited availability of data. I think this should be stated more directly in the limitations section i.e. by saying “we were only able to examine the relationship between preferences and patient age and sex due to limited availability of data”. It might also be worth referring to this in the methods section. i.e. in the measures and data extraction section of methods, the authors could state that “available personal characteristics of patients (age/gender) were also extracted”	Thank you for your suggestion. We have more clearly stated this limitation both in the methods section and under the limitations section.	We extracted data on available personal characteristics of patients (age/gender) (Page 11) We were only able to examine the relationship between preferences and patient age and sex due to limited availability of data. (Page 21)
5.	The “other studies” and “recent systematic review” mentioned in the limitations section of the discussion are not referenced. If included in the manuscript, these should be included in the reference list.	We have included the references.	Other studies (49) have also highlighted the importance of the family and care context on care preferences. A recent systematic review (50) highlighted the lack of research evidence on ethnicity and religion, which is also absent from this study. (Page 21)

Response to reviewer 2

	Comments	**Reply**	**Revision**
2.	All of my raised concerns in first review had been properly addressed.	Thank you so much for your comments on the first submitted manuscript.	None.