Author's response to reviews

Title: Prevalence and Risk Factors of Depressive Symptoms in a Canadian Palliative Home Care Population: A Cross-Sectional Study

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Author's response to reviews:

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Re: Manuscript ID #1354524161104392 (Revised)

Attention: Dr. Jane Seymour

We would like to thank the reviewers for their thoughtful comments on our original submission of the above manuscript. We believe we have addressed all of the reviewer comments. The attached pages provide a point-by-point response to each reviewer comment, including our understanding of the issue and how we have addressed it.

Revisions to the analysis included restricting the sample to clients without significant cognitive impairment, employing polychoric correlations (and Spearman’s correlations) to address multicollinearity, and using multiple imputation to address missing data. Although these revisions did not result in significant changes to the results (i.e., most of the risk factors were the same in the original and revised manuscript), they nevertheless strengthen the methodology and the results.

We trust that the revised manuscript has adequately addressed all of the reviewer concerns, and look forward to hearing from you soon.

Yours sincerely,

Kathryn Fisher, PhD
REVIEWER 1 (LAURA GOODWIN)

1. Analytical Choices:

a. Spearman’s Rank Correlations vs Polychoric/Tetrachoric Correlations: Issue: The reviewer requested justification for using Spearman’s rank correlations, rather than polychoric/tetrachoric correlations. Both Spearman’s and Polychoric/Tetrachoric correlations are measures of association for ordinal variables (ordered categorical variables). We chose Spearman’s rank correlations because these are used much more frequently in the medical literature, and to our knowledge one measure of association is not superior to the other. We examined both Spearman’s and polychoric correlations, and found that the latter identified additional high correlations, most involving the CHESS score. These high correlations were addressed by removing the individual variables because they are related to items used in calculating the CHESS score. This did not change the results, but is nevertheless important for the conceptual accuracy of the model. Solution: The second paragraph of the “Statistical Analysis” section in “Methods (Section 2.0) has been revised to refer to both measures of association and the results of examining these.

b. Justification for Model Variables: Issue: The reviewer requested clarification of how the variables were selected into the model. Solution: We have expanded the discussion in the “Statistical Analysis” section in “Methods” (Section 2.0) to clarify the rationale for eliminating each of the variables.

c. Mediation Effect (Life Satisfaction & Prognostic Awareness): Issue: The reviewer requested clarification of why the mediation test was performed in relation to the role of prognostic awareness in shaping depression. Solution: The paragraph discussing the examination of prognostic awareness and the mediation testing relating to this in the “Statistical Analysis” section in “Methods” (Section 2.0) has been revised to clarify what was done and why.

d. Goodness of Fit Tests (ROC vs Hosmer & Lemeshow Statistic): Issue: The reviewer requested clarification of why both the ROC curves and the Hosmer & Lemeshow statistics were used to judge the goodness of fit of the model, instead of just the Hosmer & Lemeshow statistic. We examined both statistics, as this
has been recommended in the literature (e.g., (Hosmer & Lemeshow, 2000, pg 163; Cook, 2008). Perhaps the reviewer viewed the Hosmer & Lemeshow statistic as more appropriate because prognostic models (like ours) are concerned with the risk of a future event (depression), and as such estimated probabilities are of primary interest, which the Hosmer & Lemeshow statistic uses directly (and ROC curves do not). (Hosmer and Lemeshow) (ROC curves).

Solution: The paragraph discussing goodness of fit measures in the “Statistical Analysis” of the “Methods” (Section 2.0) has been revised to include justification for choosing both.

2. Results Presentation and Interpretation:

a. Missing Data: Issue: The reviewer is concerned about how missing data have been addressed in the study, and has highlighted the need to explore this further in view of the fact that 2000 clients were eliminated in the complete case analysis. This point was also raised by Reviewer 3 (point 3). We presented the complete case analysis because this is still the most common approach used in medical research (Janssen et al., 2010). However, to address the fact that our missing data may have been “missing at random”, we also used multiple imputation since it has been shown to produce the least biased parameter estimates in this situation (Penny and Atkinson, 2011; Janssen et al., 2010; Donders et al., 2006). Solution: We have revised the manuscript to report/compare the results of both analyses because it is suggested that in reporting the results of multiple imputation, the complete case analysis results should also be provided (Sterne et al., 2009). The “Statistical Analysis” section of the “Methods” (Section 2.0) and the “Risk Factors Associated with Depressive Symptoms” of the “Results” (Section 3.0) have been revised to refer to both forms analyses.

b. Prevalence of Depression (Sample): Issue: The reviewer was unclear regarding which sample was used for calculating the prevalence of depression. The prevalence of depression is 9.4% in the full sample (Table 1) and 9.8% in the complete case and multiple imputation samples. Solution: The “Sample Characteristics” in the “Results” (Section 3.0) has been revised to indicate that the prevalence rate cited here is based on the full sample, and the first sentence of the “Discussion” (Section 4.0) has also been revised.

c. Explanation of Findings (Clarity, Overinterpretation): Issue: The reviewer suggested that the findings could be more clearly explained, and the results may be overinterpreted given the cross-sectional nature of the study. Solution: The “Results” (Section 3.0) and “Discussion (Section 4.0) have been revised to clarify the results and avoid overinterpretation. Related to this, throughout the manuscript we have replaced the words “predictors of depression” with “risk factors associated with depressive symptoms” in order to avoid overinterpretation and the suggestion of causality.

d. Possible Error (Gender Effect): Issue: The reviewer identified a discrepancy between the gender results reported in the Abstract compared to those appearing in the “Results” (Section 3.0) of the manuscript. Solution: In revising
the manuscript for the other issues raised by the Reviewers, we have revised the Abstract, Results, Discussion and Conclusions and all sections are now in agreement.

e. Order of Presentation (Reduced Sample then Full Sample): Issue: The reviewer questioned why the reduced sample results (sub-analysis of prognostic awareness) came ahead of the full sample results, as the reverse presentation would make more sense. Solution: The order of the results presented in the revised manuscript now matches the order recommended by the reviewer.

f. Rephrasing (Sentence in Paragraph 2, pg 13): Issue: The reviewer commented that a sentence did not seem “particularly scientific”. Solution: This sentence and the paragraph that it was in were removed in a rewriting of the results (to improve clarity), so this is no longer an issue.

g. CHESS Cutoff (for Prognostic Awareness Analysis): Issue: The reviewer suggested that making the CHESS cutoff higher could improve the discriminatory power of CHESS in the model. We agree that this makes sense in the sub-analysis since we eliminate patients with prognosis > 6 months, which means focusing on patients closer to death (and thus likely to have a higher CHESS score). Solution: We used a cutoff of 3+ versus <3 for the model that included prognostic awareness. This resulted in CHESS being selected into the model, and improved agreement of the model including prognostic awareness with the one that excluded it.

3. Additional Discussion (Methods):

a. Detail on the DRS: Issue: The reviewer has requested more detail on the DRS, including the evidence supporting its validity and reliability in the palliative population. This issue was also raised by Reviewer 2 (points 3 & 4). Solution: Paragraph 2 of “Measures” in the “Methods” (Section 2.0) has been revised to include more detail on the items making up the DRS and how the DRS is calculated.

b. Disclosing Validation Results: Issue: The reviewer requested inclusion of the evidence supporting the validity of the DRS in a palliative population. This issue was also raised by Reviewer 2 (point 4). We did not disclose the validation results, because this work appears in a manuscript that is currently under review by Quality of Life Research journal. We were concerned about running into a copyright issue. Solution: Paragraph 2 of “Measures” in the “Methods” (Section 2.0) has been revised to include a brief summary of the key results from the work validating the DRS in a palliative population, without including the tables or detailed analytical results that are reported in the validation paper.

c. Life Satisfaction Measure: Issue: The reviewer indicated that there was no information on what this measure is or how it has been developed. Solution: We have added a sentence in the 4th paragraph of the “Measures” section of the “Methods” (Section 2.0) referring the reader to Appendix Table A1 for the definitions of the independent variables.
d. Social Support Measure: Issue: The reviewer indicated that measures of social support were not referred to in the Methods. We have two independent variables that we regard as forms of social support – supportive family and caregiver distress. These are the last two independent variables in Appendix Table A1. Perhaps the term social support is confusing as it may suggest a specific variable, so we have eliminated this term and now refer to the specific variables. Solution: All references to “social support” (other than in the literature review) have been removed. Specifically, we removed “social support systems in palliative care” from the Keywords. We also removed the entire paragraph discussing “low social support” in the “Discussion” (Section 4.0), as this variable was no longer significant in the revised analysis (because of the CPS < 4 constraint introduced to address Reviewer 3’s concern (point 9).

4. Abstract Revisions:

a. Aim: Issue: The reviewer suggested a change to the aim of the study, to focus only on the outcome of depression. We agree. Solution: We have rephrased the study aim to focus only on depression, and it now refers to risk factors associated with depression (rather than the more definitive term “predictors”, given the cross-sectional nature of the study).

b. Results: Issue: The reviewer suggested removing the ambiguity in referring to the mediation role of life satisfaction, located in the Results section of the Abstract. We agree. Solution. The last sentence of the Results section of the Abstract has been revised to remove the speculation. The “Discussion” (Section 4.0) of the manuscript included this same ambiguous phrasing, and it was corrected as well.

5. Sample Details:

a. Sample Recruitment: Issue: The reviewer requested more details about how the sample was recruited. This issue was raised by Reviewer 2 (point 1) and Reviewer 3 (points 1 and 2). Solution: We have revised the “Study Sample” in the “Methods” (Section 2.0) to clarify participation in the pilot (including how patients were classified as palliative, or end-of-life), and the inclusion criteria for this study (including the rationale for each).

b. Missing Data: This restates the importance of addressing missing data, which we discussed in point 2 above.

REVIEWER 2 (WADIH RHONDALI)

1. Categorization of Patients as Palliative Home Care: Issue: The reviewer has requested clarification of how the patients were categorized as palliative. This issue was also raised by Reviewer 1 (point 5) and Reviewer 3 (point 1). Solution: We have revised the “Study Sample” in the “Methods” (Section 2.0) to clarify participation in the pilot (including how patients were classified as palliative, or end-of-life), and the inclusion criteria for this study (including the rationale for each).
2. Value of non-cancer patients in the study: Issue: The reviewer questions the value of the non-cancer patients in the study, in view of the fact that the majority of clients in the sample (86.5%) have a cancer diagnosis. Solution: We removed references in the “Introduction” (last 2 paragraphs) that 1) prior research is limited in its consideration of non-cancer patients, and 2) our sample addresses this limitation. We also removed inclusion of non-cancer patients as a strength of this study in the last paragraph of the “Discussion” (Section 4.0).

3. Choice of the interRAI PC instrument and the Depression Rating Scale (DRS): Issue: The reviewer was not clear on why we chose the interRAI instrument, including the depression tool (DRS). One reason is that the pilot dataset was already available, so we did not have to administer the interRAI PC to conduct this study (this study is a secondary data analysis). The interRAI instruments are currently used as routine assessments in a number of international health care settings. As such, this study is important in adding to the growing literature on interRAI assessments & their scales. Solution: We have revised the “Study Sample” and “Measures” section of the “Methods” (Section 2.0) to provide more information on the interRAI PC and suite of interRAI instruments. We also provide more detail on the DRS, including information on the validation results (the next point), which should help to substantiate the use of the DRS in this palliative care study.

4. Validation of the DRS in a palliative population: Issue: The reviewer questions the value of the validation work on the DRS, given that the results are not published. This issue was also raised by Review 1 (point 3). We did not disclose the results of the validation study because this work appears in a manuscript that has been submitted to Quality of Life Research, and we are currently waiting for a reply from this journal. Solution: We have included a brief summary at the end of the second paragraph in the “Measures” section of the “Methods” (Section 2.0). This summary reports the key results of the validation work, without including the detailed tables or analytical results reported in the validation paper.

5. Use of the word "predictor": Issue: The reviewer questioned the use of the word “predictor” in this cross-sectional study, because of the concern that it might suggest causality when association is what can be reported. Solution: The manuscript has been revised to remove all occurrences of the word “predictor”, replacing it with “risk factors”. Also, we refer to the risk factors as being “associated with depression symptoms”, to reinforce the nature of the relationship (association not causation).

6. Results (Length, Unclear Message): Issue: The reviewer suggested shortening the Results and Discussion, to focus on the main results of the study. He also suggested clarifying the tables. Solution: We have revised the Results and Discussion to re-order the presentation of the results (primary analysis first, then sub-analysis of prognostic awareness), and to discuss in detail only the risk factors amenable to clinical intervention. While the results are a little longer due to introducing multiple imputation (to address the missing data concern), we think
they are clearer and the additional material is required for comprehensive treatment of the issues. We have added a table to include and contrast the multiple imputation results (instead of listing the numbers in the text), and added more information in the title to the tables.

7. Caregiver Distress: Issue: The reviewer suggested avoiding the statement “bolstering the families and caregivers”. Solution: We rephrased the statement to now refer to providing support to caregivers, and trust that this addresses the reviewer’s concern.

REVIEWER 3 (LAUREN RAYNER)

1. Participation Rate: Issue: The reviewer has requested information on participation rates for the pilot. Solution: We have revised the “Study Sample” in the “Methods” (Section 2.0) to clarify participation in the pilot, including how patients were classified as palliative (or end-of-life).

2. Study Inclusion Criteria: Issues: The reviewer requested that the study inclusion criteria be disclosed. Solution: This was addressed under comment 5a for Reviewer 1.

3. Excluding Patients with Missing Data: Issue: The reviewer requested a discussion of why a complete case analysis was undertaken, and what biases may have been introduced by eliminating clients with missing data. This is the same issue raised by Reviewer 1 (point 2a). As mentioned above, we presented the complete case analysis because this is the most common approach used in medical research (Janssen et al., 2010). However, we agree that eliminating many clients (as required in conducting a complete case analysis) can introduce bias. Solution: We present the results for both the complete case and multiple imputation analysis. The results from the two analyses are quite similar. The “Statistical Analysis” section of the “Methods” (Section 2.0) and the “Risk Factors Associated with Depressive Symptoms” of the “Results” (Section 3.0) have been revised to refer to both forms of analysis and the results of each.

4. Discussion of Hayes et al paper: Issue: The reviewer suggested a revision to how the results of the Hayes et al. paper have been discussed. Solution: This is no longer an issue, as the paragraph discussing this article was removed (to shorten the results in response to Reviewer 2’s concerns about length).

5. Figure Labels, Black & White Images; Issue: The reviewer indicated that the figures did not have labels, and that males and females cannot be distinguished in a black & white image. Solution: The figures have been reloaded and the labels now appear on the image. The fill options were changed to slash marks for females and a solid colour for males, so males and females are distinguishable.

6. Additional Reference (Depression is treatable): Issue: The reviewer suggested adding a reference (Rayner et al., 2011) in support of the statement that depression appears to be treatable. Solution: We agree that this is a key
7. Study Sampling Frame, How Case Managers Deemed Patients “Palliative”: Issue: The reviewer requested more information on the sample, including how case managers deemed patients to be “palliative”. Solution: We believe that the revision to the “Study Sample” discussed in point 1 above addresses this issue.

8. Self-Reported versus Assessor-Reported Items: Issue: The reviewer has requested an indication of which interRAI PC items are self-reported versus assessor-reported. Solution: We added column 2 to Table A1 in the Appendix to indicate this.

9. Cognitive Functioning: Issue: The reviewer is concerned about including clients with significant cognitive impairment in the study. This is a common concern for self-report instruments, and interRAI excludes clients with a CPS 4+ in applications of its self-report instruments (e.g., Quality of Life questionnaires). The extent to which this is a concern for the assessor-rated DRS is uncertain. However, we agree with the reviewer that assessors may be unable to accurately assess clients with severe cognitive impairment. Solution: We have revised the analysis to apply the interRAI restriction (CPS <4) as an inclusion criteria for the study. The sample in the revised analysis (n=5144) includes only clients with a CPS <4.

10. Why was the DRS used instead of more widely-used tools (e.g., PHQ, HADS): Issue: The reviewer questioned why we did not choose a more widely-used depression instrument, and one that has been validated in palliative care. Solution: We revised the 4th paragraph of the “Introduction” to state that the study is a cross-sectional analysis of an existing dataset (thus we did not plan and then execute the study and the instrument was not chosen, per se). The revisions made to the “Study Sample” (as discussed in points 1 and 2 above), the provision of more detail on the DRS and the results of validating it in the palliative population (in response to point 3 from Reviewer 1), and more information on the interRAI PC and interRAI instruments generally should also help to address this issue.

11. Low Prevalence of Depression: Issue: The reviewer has suggested that the lower depression rate in the study may be due to the absence of somatic symptoms among the DRS items. The reviewer is right that exclusion of somatic symptoms can be a drawback in a depression scale, although inclusion of them has also been criticized especially in palliative populations. Somatic symptoms have been deemed poor predictors of depression in palliative patients because they overlap with other medical circumstances and can lead to an artificial inflation of depression diagnoses (Knopf and Head, 2012). The most commonly discussed strategy is to consider cognitive and affective rather than somatic symptoms, as done in the DRS (Knopf and Head, 2012). Nevertheless, acknowledging the risk arising from excluding somatic symptoms in the DRS (a lower prevalence rate) can be done in the manuscript. Solution: We have revised the first paragraph (second sentence) of the “Discussion” (Section 4.0) to recognize this risk.
REFERENCES


