

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Advanced chronic liver disease in the last year of life: a mixed methods study to understand how care in a specialist liver unit could be improved
<b>AUTHORS</b>	Low, Joe; Davis, Sarah; Vickerstaff, Victoria; Greenslade, Lynda; Hopkins, Katherine; Langford, Andrew; Marshall, Aileen; Thorburn, Doug; Jones, Louise

### VERSION 1 - REVIEW

<b>REVIEWER</b>	Dr Barbara Kimbell Usher Institute of Population Health Sciences & Informatics, University of Edinburgh, UK
<b>REVIEW RETURNED</b>	05-Apr-2017

<b>GENERAL COMMENTS</b>	<p>This paper provides new insights into the care experiences of people with advanced liver disease towards the end of life and the barriers to a timely introduction of palliative care as perceived by liver professionals in a tertiary treatment centre. In particular, the case note analysis provides interesting new background understanding as to how patients' health status in the last months of life contrasts with the care provided in the secondary care setting.</p> <p><b>BACKGROUND</b> p.5, lines 81-83: The wording of this sentence reads a little awkward. Consider tweaking this?</p> <p><b>METHOD</b></p> <ul style="list-style-type: none"><li>• p.8, lines 142-143: Same as above. There appear to be words missing?</li><li>• No details relating to ethics, Caldicott or similar study approvals included.</li></ul> <p><b>RESULTS</b></p> <ul style="list-style-type: none"><li>• p.9, line 178: Given the generalist readership of the journal, it would be helpful to provide a brief description of the MELD and what the scores observed indicate in terms of patients' status.</li><li>• p.11, line 206: It would be interesting to know if the authors observed any differences regarding e.g. documentation of prognosis, ACP discussions, or indeed any other aspect of patient care for those patients in their sample who were on the transplant list compared with those that weren't.</li><li>• p.11, line 218: The authors state that 40% of patients in their sample were still receiving active treatment up until their death. This could be interpreted as a negative. However, liver patients are not typically admitted to hospital for terminal care, but often attend with generally reversible acute complications such as ascites or HE. As such, the active treatment provided at that time must be considered</li></ul>
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	<p>appropriate. Subsequent patient death in hospital is often due to a sudden deterioration in their overall condition. Were the authors able to ascertain from the case notes whether the 'active treatment before death' noted was in response to the acute cause of that admission and as such clinically appropriate, or whether these instances could indeed be considered futile interventions? If so, this would be a useful clarification to add.</p> <ul style="list-style-type: none"> <li>• p.11, line 221: The authors note that only 17% of their sample died outside of hospital, a finding which is in line with previous studies. Are the authors able to discern from the data whether these patients differed in some way from those who died in hospital, e.g. in terms of demographics, disease aetiology, continuity of care, that may have facilitated their out-of-hospital deaths?</li> <li>• p.12, line 246-248: It is suggested here that doctors' limited exposure to a patient contributed to their difficulties and/or reluctance to recognise imminent dying and cease active treatment. This is contrasted with ward nurses' better awareness of a patient's status given their greater involvement. As no supporting quotations are provided in this section, it is unclear whether this observation was made by doctors themselves? If doctors recognised this limitation, were any explanations offered as to why they did not seek closer consultation with ward nurses in this regard?</li> <li>• p.15, line 305-308: This paragraph references doctors' responses only. Did the nurses and other healthcare professionals consulted consider themselves having a role in such conversations? If so, how did they feel about this?</li> </ul> <p><b>DISCUSSION</b> p.18, Strengths &amp; limitations: The authors recognise several limitations of the current study. I would also include the purposive sampling of the case notes, given its potential for selection bias and error.</p> <p><b>SUPPLEMENTARY INFORMATION</b> p.24, Table 2: In this table, the signs and symptoms listed under 'Encephalopathy' and 'Psychological' are largely identical. How were theSE differentiated to arrive at the final numbers cited in the table?</p> <p><b>GENERAL COMMENT</b> While this paper provides a great amount of new and valuable learning, I am a bit confused about the results presented and their link to the study objective as stated in both Abstract and Introduction. A key aspect of this was to identify 'barriers and enablers of shared approaches to care' (see p.3 line 34 and p.6 lines 99-100). The section 'Enablers for palliative care' in Results (p.15) reports liver clinicians' suggestions for closer collaboration with other relevant professionals. However, no findings are provided which detail what the barriers or enablers to this shared approach would be in line with the stated study objective, and no further reference is made to shared care in the Discussion or Conclusion. Also, the topic guide suggests that targeted questions about shared care did not feature. This discrepancy needs clarification.</p>
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<b>REVIEWER</b>	Wei Gao King's College London. UK
<b>REVIEW RETURNED</b>	29-May-2017

<b>GENERAL COMMENTS</b>	This manuscript addresses an under-studied topic in an important
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	<p>research area. It is an overall well-developed study but authors need to explain why caregivers/family members' views are not explored. The authors also need to clarify the ethics of performing case note reviews for this study. I have also the following minor points:</p> <p>Overall: The reporting guideline for mixed method may be a good reference when revise the manuscript</p> <p>Title: should the 'and" be 'in'? Further, the title indicates that the time frame for care provision is "last year". However, the problems and signs from the case note review is limited to the last three months only (Table 1). Please clarify.</p> <p>Abstract: clear and well presented. The sampling method for the focus groups or individual interviews need a bit clarification.</p> <p>Background: it would be good to add some justifications why the mixed method design is applied to answer the research questions</p> <p>Methods: no further comments.</p> <p>Results: no comments.</p> <p>Discussion: the author team should acknowledge the limitations of not exploring the views of carers/family members. It is also important not to use the "palliative care" and "end of life care" interchangeably – as one of the barriers identified is "negative perception of palliative care from patients and family".</p> <p>Table 1:</p> <p>Age: would be more informative to provide minimum &amp; maximum age</p> <p>Ethnicity, Relationship Status &amp; Living arrangement do not add up to 30, please check.</p>
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<b>REVIEWER</b>	Arpan Patel University of California, Los Angeles, United States
<b>REVIEW RETURNED</b>	29-May-2017

<b>GENERAL COMMENTS</b>	<p>In this article, "Advanced chronic liver disease and the last year of life: a mixed methods study to understand how care in a specialist liver unit could be improved", Low. et al. examine two major questions that can help us better understand end-of-life care in patients with chronic liver disease: 1) What are the objective healthcare experiences and recorded goals of care discussions for these patients and 2) What are the perceptions of practitioners responsible for these patients regarding palliative care and end-of-life planning, as well as modifiable behaviors.</p> <p>This is an incredibly important area of research and a mixed-methods analysis is an innovative way of answering both of these questions simultaneously. The introduction features a wonderful review of the literature and states the research question clearly. I have a few criticisms that, if addressed, I believe may make the submitted manuscript stronger:</p> <p>Methods:</p> <p>1. If there was a conceptual model used to guide the development of the topic list and questions for the focus groups and semi-structured interviews, respectively, this information should be included.</p> <p>Results:</p> <p>1. If all patients in the study ultimately died, it would be useful to</p>
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	<p>include information on time from index hospitalization to death.</p> <p>2. For the quantitative results, there appears to be some inconsistent use of medians and means, particularly for the "Health service use in tertiary care" section, which should be corrected (with standard deviations or IQR presented for these continuous variable results). Also, I did not see the results for the "Health service use in tertiary care" section in the attached tables.</p> <p>3. The assertion from Line 197-198: "Most admissions were precipitated by cirrhotic complications, requiring invasive procedures, such as blood transfusions, endoscopic treatment of varices, TIPS, and paracentesis" is does not have any reported numbers associated with this statement. If these frequencies are not explicitly stated in the discussion or in the tables, would consider removing.</p> <p>4. It would be interesting to compare the healthcare utilization of patients between those who are and are not listed for transplant, as that is hypothesized as one reason why care at transplant centers may be more aggressive. Was there a reason for not including this in the analysis?</p> <p>5. I applaud the authors for adhering to the STROBE guidelines for their reporting of the quantitative data. I would similarly consider using the COREQ guidelines for reporting of qualitative data (<a href="https://www.elsevier.com/___data/promis_misc/ISSM_COREQ_Checlist.pdf">https://www.elsevier.com/___data/promis_misc/ISSM_COREQ_Checlist.pdf</a>). While the authors followed most of the guidelines, it would be best to review them in order to state that they were considered when reporting the results of their study.</p> <p>Strengths and Limitations:</p> <p>1. Space providing, I would also comment on the fact that the quantitative chart review dealt only with patients who died during follow-up and not with patients who were still alive and especially those who were still alive with a transplant. This is important since these patients are also often recipients of palliative care and advance care planning.</p>
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### VERSION 1 – AUTHOR RESPONSE

#### AUTHORS' RESPONSES TO REVIEWERS' COMMENTS

##### Editorial Comments/Requests:

A1 - Please carefully check the manuscript for spelling and grammar e.g. abstract >> results: clinicians' does not need an apostrophe; "Contributor ship" (should not be two words) etc.

Authors' responses: We have gone through the manuscript to check for spelling and grammar. In addition, I have asked a colleague independent of the study to proof read the final version of the manuscript.

A2 - Please include the following statement in the methods section of the manuscript: "Ethical approval was sought, but deemed unnecessary by the NRES Committee London - West London & GTAC (ref 14/LO/0799). NHS permission to conduct the clinical case-note review and the qualitative interviews with liver health professionals was obtained from the Royal Free London Clinical

Governance Lead for Hepatology and Palliative Care under the remit of health service improvement.”

Authors' responses: We have added this sentence in the methods section.

A3 - Re reviewer 2's comments about reporting guidelines for mixed methods studies. We are not aware of any reporting guidelines/ checklists that are available for this study design (at least, none that have been endorsed by the EQUATOR Network). We suggest that you complete a COREQ checklist, in addition to STROBE (as per reviewer 3's suggestion).

Authors' responses: We have completed the COREQ form as requested. To ensure our document compiles with the COREQ form, we have had to insert further details to the methods and results section.

Reviewers' Comments to Author:

Reviewer: 1

B1 - p.5, lines 81-83: The wording of this sentence reads a little awkward. Consider tweaking this?

Authors' responses: We have rewritten this sentence to make it clearer.

B2 - p.8, lines 142-143: Same as above. There appear to be words missing?

Authors' responses: We have added the missing words to this sentence.

B3 - No details relating to ethics, Caldicott or similar study approvals included.

Authors' responses: Following editorial comments, we have added a sentence at the end in the methods section re: ethical approval (see A2).

B4 - p.9, line 178: Given the generalist readership of the journal, it would be helpful to provide a brief description of the MELD and what the scores observed indicate in terms of patients' status.

Authors' responses: We have added a sentence, outlining the significance of a median MELD score of 23.6.

B5 - p.11, line 206: It would be interesting to know if the authors observed any differences regarding e.g. documentation of prognosis, ACP discussions, or indeed any other aspect of patient care for those patients in their sample who were on the transplant list compared with those that weren't.

Authors' responses: We have reflected on this comment, which is similar in nature to the one from Reviewer 3 (see D5) and Reviewer 1 (see B7). A preliminary inspection shows that only one person had a discussion on preferred place of care and none had an ACP. However, our research group felt that with only 4 people on the transplant waiting list, we would be unable to draw any generalizable conclusions from such low numbers, so we feel that this analysis is inappropriate. In reviewing this data, we note a mistake in the number of people on the transplant list which should be four and not five. We have rectified the mistake on the revised paper.

B6 - p.11, line 218: The authors state that 40% of patients in their sample were still receiving active treatment up until their death. This could be interpreted as a negative. However, liver patients are not typically admitted to hospital for terminal care, but often attend with generally reversible acute complications such as ascites or HE. As such, the active treatment provided at that time must be considered appropriate. Subsequent patient death in hospital is often due to a sudden deterioration in their overall condition. Were the authors able to ascertain from the case notes whether the 'active treatment before death' noted was in response to the acute cause of that admission and as such clinically appropriate, or whether these instances could indeed be considered futile interventions? If so, this would be a useful clarification to add.

Authors' responses: This is a valid point and similar to the comment raised by Reviewer 3 (see D7) that our quantitative chart review only dealt with patients who died during follow-up and not with patients who were still alive and especially those who were still alive with a transplant. The way that interventions were written in medical notes made it difficult to differentiate whether treatment was considered active or futile.

B7 - p.11, line 221: The authors note that only 17% of their sample died outside of hospital, a finding which is in line with previous studies. Are the authors able to discern from the data whether these patients differed in some way from those who died in hospital, e.g. in terms of demographics, disease aetiology, continuity of care, that may have facilitated their out-of-hospital deaths?

Authors' responses: Although we feel that this analysis of this data is inappropriate with a small sample of 5 (ie the 17% sample), and the inability to draw any generalizable conclusions from such low numbers, initial data exploration does suggest that all 5 who died at home/hospice had a diagnosis of HepC and hepatocellular carcinoma (HCC). If the editors feel this is useful data to include, we can put it in, bearing in mind the limitations.

B8 - p.12, line 246-248: It is suggested here that doctors' limited exposure to a patient contributed to their difficulties and/or reluctance to recognise imminent dying and cease active treatment. This is contrasted with ward nurses' better awareness of a patient's status given their greater involvement. As no supporting quotations are provided in this section, it is unclear whether this observation was made by doctors themselves? If doctors recognised this limitation, were any explanations offered as to why they did not seek closer consultation with ward nurses in this regard?

Authors' responses: We have looked at the data again, and have identified that it was nurses who made this comment. To clarify this situation, I have added in the appropriate place that it was nurses (focus group and interview data) who made this comment and have added a quote to illustrate this point.

B9 - p.15, line 305-308: This paragraph references doctors' responses only. Did the nurses and other healthcare professionals consulted consider themselves having a role in such conversations? If so, how did they feel about this?

Authors' responses: We reviewed the qualitative data focusing on this aspect, which nurses, like doctors, were reluctant to have these conversations. The main difference was that (ward) nurses perceived that were able to identify when patients were approaching death.



B10 - p.18, Strengths & limitations: The authors recognise several limitations of the current study. I would also include the purposive sampling of the case notes, given its potential for selection bias and error.

Authors' responses: We agree with Reviewer 1 valid point and have added a line stating this limitation.

B11 - p.24, Table 2: In this table, the signs and symptoms listed under 'Encephalopathy' and 'Psychological' are largely identical. How were theSE differentiated to arrive at the final numbers cited in the table?

Authors' responses: Reviewer 1 raises an interesting issue in differentiating the signs and symptoms which could be listed under 'Encephalopathy' and 'Psychological'. Following this comment, we have revisited this data, which we discussed with the Clinical Nurse Specialist on the research team (Lynda Greenslade -LG) to confirm the classification. In categorising the symptoms caused by encephalopathy, we ensured that there was a reference in the notes made about these symptoms being caused by encephalopathy. We are happy with these figures. However, in discussing 'confusion' and 'agitation' (which we categorised under Psychological), LG suggested that these could be caused by a variety of different things. As they are important symptoms and often seen in these patients at the end of life and can be difficult to manage, it is important to include. We have therefore transferred these to the 'Other' category, but can put them back to the 'Psychological' category if considered more appropriate. We also removed the drowsiness symptoms from the 'Psychological' category. We have made these changes to Table 2.

B12 - While this paper provides a great amount of new and valuable learning, I am a bit confused about the results presented and their link to the study objective as stated in both Abstract and Introduction. A key aspect of this was to identify 'barriers and enablers of shared approaches to care' (see p.3 line 34 and p.6 lines 99-100). The section 'Enablers for palliative care' in Results (p.15) reports liver clinicians' suggestions for closer collaboration with other relevant professionals. However, no findings are provided which detail what the barriers or enablers to this shared approach would be in line with the stated study objective, and no further reference is made to shared care in the Discussion or Conclusion. Also, the topic guide suggests that targeted questions about shared care did not feature. This discrepancy needs clarification.

Authors' responses: On reflection, we agree with the reviewer 1's comment that the remit of our qualitative arm was wider than specifically looking at 'barriers and enablers of shared approaches to care', as we were interested in the challenges and potential enablers of improving palliative care to patients with liver cirrhosis. We have altered the abstract and introduction to reflect this broader approach, which is now consistent with our findings and discussion.

Reviewer: 2

C1: - This manuscript addresses an under-studied topic in an important research area. It is an overall well-developed study but authors need to explain why caregivers/family members' views are not explored.

Authors' responses Reviewer 2 makes a valid point and we did attempt to recruit close family members, but due to limited resources for this study and the difficulty of recruiting close family, our recruitment was extremely poor. We acknowledge in the discussion that this is a limitation of our study.

C2: - The authors also need to clarify the ethics of performing case note reviews for this study.

Authors' responses: Following editorial comments, we have added a sentence at the end in the methods section outlining our research governance procedures (see Authors' response to A2).

C3: - Overall: The reporting guideline for mixed method may be a good reference when revise the manuscript

Authors' responses: Following the editorial comments, we will use the COREQ guidelines in reviewing the qualitative elements of this study. We will make changes, where possible, to our revised manuscript (see Authors' response to A3).

C4: - Title: should the 'and' be 'in'? Further, the title indicates that the time frame for care provision is "last year".

Authors' responses: We have made the word change to the title as recommended by Reviewer 2.

C5: - However, the problems and signs from the case note review is limited to the last three months only (Table 2). Please clarify.

Authors' response: Although we did collect this data for the whole year, in our finding, we highlight that all our patients were symptomatic. The idea of Table 2 was to illustrate the wide range of symptoms that patients presented 'problems and signs' for the last 3 months before death. The key message of this table is to make clinicians ultimately aware of the complexities of these symptoms and that these patients may benefit from palliative care support.

C6: - Abstract: clear and well presented. The sampling method for the focus groups or individual interviews need a bit clarification.

Authors' responses: We have added a line, stating that participants for the focus groups/interviews were purposively sampled.

C7: - Background: it would be good to add some justifications why the mixed method design is applied to answer the research questions

Authors' responses: We have added a sentence justifying why the mixed method design was applied to the research questions, together with an appropriate reference.

C8: - Discussion: the author team should acknowledge the limitations of not exploring the views of carers/family members. It is also important not to use the "palliative care" and "end of life care" interchangeably – as one of the barriers identified is "negative perception of palliative care from patients and family".

Authors' responses: In the limitation section, we have added a sentence, acknowledging that we did not explore the views of carers/family members. I agree with Reviewer 3 that "palliative care" and "end of life care" should not be used interchangeably so I have re-read the discussion again to identify



where it happens. I have identified the one occasion where this occurs, which refers to be the name of the policy document. In this case, I have not changed the wording, but to make it clear that it is a policy document, I have inserted speech marks around the title of the document.

C9: - Table 1: Age: would be more informative to provide minimum & maximum age Ethnicity, Relationship Status & Living arrangement do not add up to 30, please check.

Authors' responses: As suggested, we have added the minimum and maximum age. In response to Reviewer 2 other comment, we had some missing data. We have now rectified this by adding in brackets, next to the categories listed, the total number of participants that we had data for in those categories.

Reviewer: 3

D1: - 1. If there was a conceptual model used to guide the development of the topic list and questions for the focus groups and semi-structured interviews, respectively, this information should be included.

Authors' responses: Following editorial comments, we have added a sentence at the end in the methods section explaining that the topic guide was pragmatic in its design, specifically exploring limitations in palliative care provision and how it could be improved.

D2: - (1.) If all patients in the study ultimately died, it would be useful to include information on time from index hospitalization to death.

Authors' responses: Whilst we accept that this would be useful information, we would not be able to answer this question as we only collected data one year before death. We assume that the index hospitalisation is defined as the first time the patient presents with problems related to their liver disease.

D3: - (2) For the quantitative results, there appears to be some inconsistent use of medians and means, particularly for the "Health service use in tertiary care" section, which should be corrected (with standard deviations or IQR presented for these continuous variable results). Also, I did not see the results for the "Health service use in tertiary care" section in the attached tables.

Authors' responses: We take on board Reviewer 3's comments and have amended all the mean values to median and IQRs. We have considered putting the values in a Table but felt that this would not be a good use of a Table, as the values could be used in a text to highlight the data descriptively.

D4: - (3) The assertion from Line 197-198: "Most admissions were precipitated by cirrhotic complications, requiring invasive procedures, such as blood transfusions, endoscopic treatment of varices, TIPS, and paracentesis" is does not have any reported numbers associated with this statement. If these frequencies are not explicitly stated in the discussion or in the tables, would consider removing.

Authors' responses: In response to Reviewer 3's comments, we have added the figures which highlighted the interventions that patients received during their admission.

D5: - (4) It would be interesting to compare the healthcare utilization of patients between those who are and are not listed for transplant, as that is hypothesized as one reason why care at transplant centers may be more aggressive. Was there a reason for not including this in the analysis?

Authors' responses: We have reflected on the comments from Reviewer 3, but our research group (which includes a statistician) feels that with only 5 people on the transplant waiting list, we would be unable to draw any generalizable conclusions from such low numbers. Consequently, we felt that this analysis is inappropriate.

D6: - (5). I applaud the authors for adhering to the STROBE guidelines for their reporting of the quantitative data. I would similarly consider using the COREQ guidelines for reporting of qualitative data ([https://www.elsevier.com/\\_\\_\\_data/promis\\_misc/ISSM\\_COREQ\\_Checklist.pdf](https://www.elsevier.com/___data/promis_misc/ISSM_COREQ_Checklist.pdf)). While the authors followed most of the guidelines, it would be best to review them in order to state that they were considered when reporting the results of their study.

Authors' responses: Following Editors' comments, we have completed the COREQ checklist and have added additional information to the various section where possible (see Authors' response to A3).

D7: - (1). Space providing, I would also comment on the fact that the quantitative chart review dealt only with patients who died during follow-up and not with patients who were still alive and especially those who were still alive with a transplant. This is important since these patients are also often recipients of palliative care and advance care planning.

Authors' responses: We agree with Reviewer 3 comments on this and have added a sentence which states this point.

#### VERSION 2 – REVIEW

<b>REVIEWER</b>	Arpan Patel University of California, Los Angeles Division of Digestives Disease United States
<b>REVIEW RETURNED</b>	03-Jul-2017

<b>GENERAL COMMENTS</b>	The authors should be commended for thoroughly addressing the several criticisms made of their work. The methods of both quantitative and qualitative approaches are more explicitly laid out and the "Strengths and Limitations" section is much more developed and reflects the content of the work laid out. I also appreciated the authors addressing the concerns I had regarding the presentation of their quantitative results. I have no further constructive comments to add at this time.
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