Peer Review File

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Review comments

Reviewer A

Thank you for the opportunity the review your manuscript. There is a key need for examination of this topic in the literature. Please see my specific comment below:

Reply: The authors would like to thank you very much for your detailed and thoughtful review—in making the changes suggested we agree that it has a better flow and information balance. We very much appreciate the commentary on what information to include in this piece and this was a question we highlighted to the editors as we submitted. Given the course and management of HCC patients (especially how liver transplant may factor into decision-making) may not be as familiar to palliative clinicians, we have kept some of the background information on the disease itself in order to inform the audience on salient points to better understand this patient population. We have added a note on this subject in the Objective section of our Introduction (see pages 5-6, lines 114-117: "Given the common co-occurrence of HCC with cirrhosis as well as the complexities of treatment (including transplant), a summary overview of diagnosis, prognosis and therapeutics salient to symptom management and goals of care is included to give context to discussed palliative care approaches.")

We hope that deleting portions of the HCC sections and adding additional content as you described in your review helps us strike a balance that will allow readers who pull this article in a search to understand the nuances of this population without detracting from describing the palliative considerations that agreed are the intent of this article. Thanks again for highlighting this!

• I would encourage you to broaden your view of the multidisciplinary team that has input in the management of HCC. Your list only includes physician partners which is a very limited view of these management teams. Also, interestingly, your paper discusses the role of palliative care, yet they are not included in this team approach.

Reply 1: We have updated our phrasing (see Page 5, Lines 95-106): "Importantly, the management of HCC requires a multidisciplinary approach, with input from hepatology, radiology, oncology, and transplant surgery teams, and where available, palliative care, psychology, social work, and other disciplines. A multi-team approach is required as treatment options range from those offered by interventional radiology to orthotopic liver transplantation, discussed further below (7). Although advances have been made in treatments for HCC, quality of life has been less thoroughly studied, with notable gaps in addressing the burdens experienced by patients (8). The relatively small number of studies on the intersection of HCC and PC limits what evidence-based recommendations can be made at this time and necessitates further

study. In general, there are a limited number of publications on symptom management, palliative care, or hospice in HCC specifically."

• You have a clear background on HCC, however the role of palliative care in relationship to HCC is unclear in the background and objective.

Reply 2: We have added a comment on the aim of our narrative review, identifying opportunities for further integration of PC in HCC care, in the abstract's background and objectives section (see Page 2, Lines 42-43: "This narrative review aims to identify opportunities for further integration of palliative care (PC) in HCC care.") We have also added a reference to the high symptom burden of HCC patients and the benefits of palliative care in the main body/Introduction/Background section (see page 4, lines 86-90): "Palliative care (PC) is interdisciplinary by nature and aims to relieve symptom burden and improve quality of life for patients and caregivers through holistic, patient-centered care. PC may be offered concurrently with disease-focused care at any stage and throughout the course of illness (4). Given the high symptom burden faced by patients with HCC, early PC consultation can be beneficial for patients."

• Background and object also lack clear explanation of the symptom burden and impact on quality of life of HCC that really underlines the case for palliative care consultations.

Reply 3: In addition to what is noted in Reply 2, in the Background section we have added commentary on the room for improvement in the study of quality of life in the HCC patient population (See Page 5, Lines 99-101): "Although advances have been made in treatments for HCC, quality of life has been less thoroughly studied with notable gaps in addressing the burdens experienced by patients (8)."

• You present a very clear and complete discussion on HCC, how it is unclear how this discussion related to the objective of this article of the benefit of PC consultation in HCC. I would recommend significant consolidation of these pages discussing the clinical presentation, diagnosis, staging, and treatment modalities as they do not seem relevant to the objective of this paper.

Reply 4: We have condensed these sections accordingly. See strikethroughs on pages 6-14.

• There is actually significant literature regarding the symptom burden of HCC. Discussion on symptom burden is significantly lacking.

Reply 5: We have added discussion of symptom burden (see Page 15, Lines 316-327):

"As noted above, palliative teams caring for HCC patients will often manage symptoms of both HCC and ESLD. One systematic review and meta-analysis on ESLD patients notes that the most frequent symptoms reported are pain, dyspnea, muscle cramping, insomnia, and mental health issues (36). Pain can be seen in HCC patients and when present requires a thoughtful approach as some of these patients

will have co-existing substance use disorders (34). Fatigue is often related to a number of underlying physical and psychological factors, and multimodal treatments may lead to the best outcomes. Anorexia and cachexia, as in many cancers, is often a late stage finding and benefits from a thorough assessment of underlying contributors (37). The additive nature of multiple symptoms was found to be common and was noted to negatively impact quality of life and ability to function (38). Given the co-occurrence of symptoms and barriers to management, focus of future study and guidelines on the confluence of effects for HCC and ESLD have been recommended (39)."

• I encourage you to evaluate the flow of your article. PC is one of the key concepts of your paper, yet it is not defined or described until page 15, halfway through your article. I would encourage you to evaluate what is relevant to your topic and object and cut what is not relevant to palliative care in HCC.
Reply 6: We have added introductory information regarding palliative care to the background section of our paper, see (see page 4, lines 86-90) "Palliative care (PC) is interdisciplinary by nature and aims to relieve symptom burden and improve quality of life for patients and caregivers through holistic, patient-centered care. PC may be offered concurrently with disease-focused care at any stage and throughout the course of illness. Given the high symptom burden faced by patients with HCC, early PC consultation can be beneficial for patients.").

• Citation list is not complete. Last reference given is 39, yet citation go to 61.
Reply 7: We have inserted the missing references (see pages 25-34).

• I am confused by your paragraph that starts on line 326 – it sounds like you are advocating not for PC referrals, but for increased training for hepatologist in PC practices. I am very confused by this and am unable to look up the reference you have cited because it is not in the reference page.
Reply 8: Thank you for this question—you're correct, in addition to advocating for PC consultation we also wanted to highlight the additional benefit of primary palliative care skills in hepatology teams. The start of the paragraph has been reworded (see page 17, lines 362-363): "In addition to PC consultation, HCC patients would benefit from the addition of primary palliative care approaches to their overall care." Additionally, the reference in question here has been added to the full reference list along with the other previously missing references: *DeNofrio JC, Verma M, Kosinski AS, Navarro V, Taddei TH, Volk ML, et al. Palliative Care Always: Hepatology-Virtual Primary Palliative Care Training for Hepatologists. Hepatol Commun. 2022 Apr;6(4):920–30.*

Reviewer B

The paper investigates an interesting and important topic about supportive and end of life care in advanced HCC.

Reply: Thank you very much for your detailed feedback! We addressed most of the items and agree that this has helped with providing a better understanding of the literature review conducted for this article. We also appreciate your questions about the searches performed and have clarified what we could with the hope it is acceptable that for several of the points that would have been necessary for systematic reviews we utilized the lower standards for narrative reviews instead.

Comments

1. It may be good to include "narrative review" in the title, as there is now no method description exist in the title.
Reply 1: We have edited the title accordingly; the full manuscript title is now "A Narrative Review of Supportive and End of Life Care Considerations in Advanced HCC" with a running title (max. 60 char.) "Supportive & End of Life Care Considerations in Advanced HCC" (see page 1, lines 3-4)

2. Consider clarifying the aim/purpose/objective in both abstract and introduction part.
Reply 2: Agree! We have added a statement on the aim of this narrative review to the abstract (see page 2, lines 42-43): "This narrative review aims to identify opportunities for further integration of palliative care (PC) in HCC care."

3. Abstract: Maybe only write the search database Pubmed in abstract. And also include the timeframe of included studies, and also number of studies that the review is based on.
Reply 3: We have edited accordingly. See page 2 line 46: "A search of PubMed was…". Additionally, we added to the search strategy summary table the number of articles referenced in the review and the publication date range of those articles (See page 35, Line 727 (Table 1)):

Table 1. The search strategy summary

Items	Specification
Date of Search	March 1, 2023
Databases and other sources searched	MEDLINE via PubMed
Search terms used	**Free text terms:** palliative medicine, palliative care, hospice, symptom management, liver transplantation, liver transplant, end stage liver, hepatocellular carcinoma **Mesh terms:** "Palliative medicine", "Palliative Care", "Hospice Care", "Liver Transplantation", "End Stage Liver Disease", "Carcinoma, Hepatocellular"
Timeframe	Search not restricted by publication date. Publication dates included articles from 1996 through 2023.
Inclusion criteria	We selected articles about adult hepatocellular carcinoma and excluded publications based on pediatric populations. We excluded articles which were not in English.
Selection process	Authors screened abstracts and full texts to remove those not applicable
Additional considerations	Additional articles were identified through search engines and hand searching of reference lists. Relevant articles and other references included: 65.

4. It is not consistent with HCC as abbreviation and hepatocellular carcinoma, please revise. (for example, line 47, page 2)

Reply 4: In the abstract, we have standardized the use of the abbreviation "HCC" for all instances after the first use of the term "hepatocellular carcinoma" (see page 2, lines 40-41); we have used "hepatocellular carcinoma" again once in the introduction and have changed all subsequent uses to "HCC" throughout the paper.

5. Page 5, line 95: Is this sentence about limited evidence more relevant in the "Rationale and knowledge gap"?

Reply 5: We have moved this sentence to the rationale and knowledge gap section, see Page 5, lines 105-106 "In general, there are a limited number of publications on symptom management, palliative care, or hospice in HCC specifically."

6. Method: You state the date of the search, but in which years were the studies included from?

Reply 6: The search was not restricted by publication date and as such included all publications from inception of the database through March 1, 2023. The first sentence of this paragraph was updated to read: "A search of Medline via PubMed was conducted from inception of the database to March 1, 2023 and included articles ranging in publication date from 1996-2023." (page 6, lines 122.)

7. Do you have any specific search strategy/structure? PICO, Spice?

Reply 7: We have altered the Methods section to include reference to the PICO framework and vocabulary search (see page 6, lines 122-125): "The search for this narrative review was created using the PICO framework and a combination composed of keywords and controlled vocabulary terms for concepts related to palliative medicine and symptom management in the setting of HCC."

8. Please write how many articles your results are based on. Also missing information in a table about the included items.

Reply 8: Our results are based on the 65 articles and references noted in the reference list; this information was added to Table 1 (See page 35, Line 727 (Table 1)):

Table 1. The search strategy summary

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Since this was not a systematic review, we did not perform a single comprehensive search to answer one specific focused question. In this narrative review, we employed an iterative search process to address the multiple questions required to fully cover the broad nature of the review. As such, there was no single results set or final set of included studies other than those cited in the reference list. We hope this addresses your concern.

9. I miss the analysis procedure. Clarify and add in the method section.
Reply 9: The focus of our paper is a narrative review and therefore does not offer a complete review of the literature on this topic as a systematic review would have revealed. As such we did not follow the standards and guidelines described for conducting a systematic review.

10. Was there a quality assessment performed of included studies?
Reply 10: Because this was a narrative review, we did not include a risk of bias/quality assessment. We agree that bias is a risk and have included this in our limitations section.

11. Should the heading "results" be added?
Reply 11: Since this narrative review does not use the same formal evidence synthesis methodology as would a systematic review, we did not include results as a heading but certainly could if based on the rest of the answers it is felt to be fitting.

12. It is possible to clarify the order of presenting results. It is based on the analysis?
Reply 12: Because this was a narrative review, we did not include a formal ordered presentation of results as would be common for a systematic review.

13. Revise the abbreviation PC, so it is printed before it is presented in the heading (line 377), and then printed as abbreviation. Now this varies in the text.
Reply 13: We have updated the manuscript to include an abbreviation "PC" in lieu of the words "palliative care" throughout the text with the exception of the first use of

the term in both the abstract (see page 2, line 43) and main body text (see page 4, line 86).

14. Is the headline "Putting it all together" a synthesis? And if so, in what way, or is it a discussion part?
Reply 14: Great question! We have retitled this section "Reflections on integrating palliative care in management of HCC" (See page 21, line 466)

15. Although it is a narrative review, it would be valuable to include reflections on method choices, searches, selection of only one database and validity and more in "Limitations". Maybe discuss generalizability of your results in relation to an international audience.
Reply 15: We have added the following comment on the generalizability of results to the limitations section (See Page 23, Lines 502-503): "We did not include other databases such as Embase, CINAHL, or other international databases, which may limit the generalizability of our results." In the preceding section "Reflections on integrating palliative care in management of HCC", we have noted that authors are based in the United States (See Page 21, Lines 467-468): "The authors of this paper are a mix of PC and transplant hepatology with specialty in HCC care based in the United States."

16. Table 1. Consider including more specific information about the time frame.
Reply 16: The search was not restricted by publication date and as such included all publications from inception of the MEDLINE database through March 1, 2023. The final article count and publication date ranges were added to the table (See page 35, Line 727 (Table 1)):

Table 1. The search strategy summary

Items	Specification
Date of Search	March 1, 2023
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Additional considerations	Additional articles were identified through search engines and hand searching of reference lists. Relevant articles and other references included: 65.

17. Consider to include number of included- and excluded articles and the articles included in the search terms, but excluded due to selection criteria ("remove those not applicable").

Reply 17: We have added the number of included reference articles in Table 1 (please see preceding response/image). As a narrative review, this paper does not follow the standards and guidelines described for conducting a systematic review and therefore did not include a specific methodology for exclusion criteria.

Reviewer C

This in an important topic and you have done a good job in not only giving a brief overview of the management of HCC, but also the opportunities to integrate PC at the various stages of care.
It may have been stronger with an actual systematic review, but it does cover a lot as written.
Reply: We thank you for your review and support of our article.

Reviewer D

This is an important topic that defines a large patient population with potentially high symptom burden and variable acuity currently underserved. Given the lack of available data this narrative review advances the knowledge by consolidating current literature and proposing future directions for more robust future studies and collaborations. Agree with reviews and recommend acceptance with minor revisions.

Reply: Thank you for the great feedback!

127-131 Recommend defining BCLC as staging system may not be familiar for some readers or alternatively discuss prognosis following staging section (142-149) where concept is defined.
Reply 1: We have moved the discussion of prognosis to after the description of BCLC staging as recommended (see page 8, lines 168-172)

156 Add ESLD as used later in publication
Reply 2: We have added the abbreviation ESLD (see page 8, line 179): "The natural history of cirrhosis can be characterized by a "compensated" phase and "decompensated" phase, also known as end stage liver disease **(ESLD)**."

198 correct typo ELSD to ESLD
Reply 3: We have corrected this error (see page 10, line 223): "Unlike most other populations referred commonly to PC, **ESLD** patients represent…"

362 "One area that circumstance that could be readily agreed upon would be" consider replacing with "One set of circumstances…"

Reply 4: We have edited per reviewer recommendation. “One set of circumstances…” (See page 18, line 399)

510-616: Please confirm references (1-39) align to numbering in text (1-60)
Reply 5: We have inserted the missing references (see pages 25-34)