

Peer Review File

Article information: <https://dx.doi.org/10.21037/amj-23-196>

Reviewer A:

The article flows well and the authors have made a strong point regarding the influence of surgical decompression on clinical outcomes.

I have three requests for the authors:

Comment 1: I think that it would be important to add that clarifying the impact of timing of surgery on the natural history of DCM is one of the current knowledge gap as nicely explained by Ganau et al. Please include this consideration and related reference in your introduction. (Ganau M, Holly LT, Mizuno J, Fehlings MG. Future Directions and New Technologies for the Management of Degenerative Cervical Myelopathy. *Neurosurg Clin N Am*. 2018 Jan;29(1):185-193. doi: 10.1016/j.nec.2017.09.006.)

Reply 1: We have added in a sentence at the end of the intro highlighting this point. We believe this will help frame the paper and we appreciate the reference provided as well.

Comment 2: Please consider adding a sentence about the difficulty of standardizing clinical assessment despite the very good inter-rater reliability of mJOA as demonstrated by Martin et al. Please include this consideration and related reference in your discussion. (Martin AR, Jentzsch T, Wilson JRF, Moghaddamjou A, Jiang F, Rienmueller A, et al. Inter-rater Reliability of the Modified Japanese Orthopedic Association Score in Degenerative Cervical Myelopathy: A Cross-sectional Study. *Spine (Phila Pa 1976)*. 2021;46(16):1063-1069. doi: 10.1097/BRS.0000000000003956.)

Reply 2: We have added a some additional context to our discussion of the mJOA and included the citation you have graciously provided. This will be helpful to the reader. Thank you.

Comment 3: Please make sure that you have duly obtained the rights to re-print the figure included.

Reply 3: We have direct permission from the editor's office from the source journal giving permission. They're only request was that we credit the authors in our manuscript.

Many thanks for the opportunity to review your article, I look forward to receive your revised manuscript.

Reviewer B:

Here are a few comments that I hope the authors will find useful:

Comment 1: Provide a more detailed explanation of the disease's pathophysiology and how it develops over time. This will help readers differentiate between early-stage

DCM and late-stage DCM. Additionally, explore if there are noticeable differences in symptoms and quality of life between these stages.

Reply 1: We have added an additional section focusing specifically on the pathophysiology of DCM. We had previously included some of this, but we added a more robust explanation of the disease process at the cellular level, which is hopefully helpful to the reader to contextualize the progression of the disease at a both cellular and symptom standpoint. We have also added a more robust discussion of the timing of intervention section tying this back to disease pathophysiology.

Comment 2: Include a broader range of patient-reported outcomes commonly used for diagnosing DCM, such as NDI, PROMIS, NIH-toolbox, etc. Explain what constitutes mild, moderate, and severe DCM, and consider providing specific numerical examples using measures like mJOA.

Reply 2: We have added several paragraphs outlining this topic in greater detail and expanding the scope to including additional diagnostic tools. We agree this will add to a more robust understanding of the clinical evaluation for the reader.

Comment 3: While the authors mention that conventional MRI is the gold standard for DCM diagnosis, it would be valuable to at least briefly (and ideally in detail) discuss advanced MRI techniques like DTI, MRS, and MTR, which can also assess microstructural tissue damage which are otherwise not easily detected or if at all using conventional MRI. This is particularly relevant for early detection of DCM and asymptomatic spinal cord compression. Please refer to the following article for more information and cite if suitable:

Martin, Allan R., Benjamin De Leener, Julien Cohen-Adad, David W. Cadotte, Aria Nouri, Jefferson R. Wilson, Lindsay Tetreault et al. "Can microstructural MRI detect subclinical tissue injury in subjects with asymptomatic cervical spinal cord compression? A prospective cohort study." *BMJ open* 8, no. 4 (2018): e019809.

Reply 3: Thank you for broaching this important topic. We agree it is significant enough to include and we have added a brief discussion on this and included the citation you were helpful enough to provide for us. We also reformatted the "How is DCM Diagnosed?" to accommodate the added information and keep the section readable.

Comment 4: There is emerging evidence in the fMRI literature indicating functional changes in the brain of DCM patients. These upstream effects are associated with compensatory mechanism/neuronal plasticity and their study may help in early detection or disease monitoring. Please refer to the following recent systematic review article for more information and cite if suitable:

Khan, Ali Fahim, Fauziyya Muhammad, Esmaeil Mohammadi, Christen O'Neal, Grace Haynes, Sanaa Hameed, Brynden Walker, Michael L. Rohan, Andriy Yabluchanskiy, and Zachary Adam Smith. "Beyond the aging spine—a systematic review of functional changes in the human brain in cervical spondylotic myelopathy." *GeroScience* (2023): 1-30.

Reply 4: We have added discussion of fMRI in with the above additional

microstructural MRI discussion. Thank you for the helpful reference.

Comment 5: When discussing the overlap of DCM symptoms with those of other neurological conditions, provide specific examples of these neurological diseases for clarity.

Reply 5: We have added additional context her and listed several commonly confused disorders as well as provided citations for these.

Comment 6: Elaborate on the statement "myelopathy symptoms must be present in order to make a diagnosis of DCM" by providing concrete examples.

Reply 6: We have reworded this sentence to be less vague and specify neurologic deficits/symptoms. The preceding paragraph runs through these symptoms in detail and the authors feel that restating specific examples of these symptoms would be redundant.

Comment 7: Consider incorporating actual photographs as figures to illustrate various aspects of this review paper. For instance, providing visual examples comparing the MRI images of the spine in early-stage DCM patients versus late-stage DCM patients would be highly beneficial.

Reply 7: This is an excellent suggestion and can help the reader get a better understanding of the imaging findings associated with DCM. We have included two figures to demonstrate early and late stage DCM.

Reviewer C:

Comment: The authors elaborate on the complexity of spinal degenerative disease in the cervical spine, with a particular focus on myelopathy. In the first part of the manuscript, a description of the causes and clinical manifestations of cervical myelopathy is reported. Furthermore, the authors investigate the role of the timing of surgery in the avoidance of progression or improvement of the neurological status by examining two parameters generally used in clinical settings to define the gravity of the condition: mJOA and time since symptoms onset. Since the second parameter is quite difficult to assess, the former is usually adopted to define the gravity of the condition as well as the probability of a clinical improvement postoperatively. They ultimately conclude that rapid operative management of the condition should be advocated for patients diagnosed with degenerative cervical myelopathy.

Although well-written and informative, this review does not add significant value to the literature since the drawn conclusions are already part of the actual guidelines.

I fail to understand the aim of the present review as well as the methodology used to draw such conclusions. Is there anything new that the authors want to prove?

Reply: Thank you for your feedback. This manuscript was an invited review article for a special issue on degenerative spine diseases. As such, the manuscript is intended to

be a review of current and relevant literature rather than a primary investigation. For this reason, many of the conclusions drawn are from society recommendations and guidelines. We hope that his manuscript provides a concise yet comprehensive review of the timing of intervention for DCM. We have clarified within the title and the manuscript the nature of the article for clarification.