Peer Review File

Reviewer A

I think it is important to state that the aim of this research has scientific merit and is clinically important. I want to encourage the authors to re-think the way they are measuring outcomes related to swallowing and dysphagia in these populations. The use of a validated patient reported outcome measure would have vastly improved the methodology of this paper and would likely have yielded a different determination by this reviewer. These are easily incorporated into routine clinical visits, even via telehealth. I would also strongly encourage the authors to collaborate with a dysphagia researcher/specialist (speech-language pathologist or laryngologist) in the future.

The aim of this study was to assess the incidence of dysphagia and radiographic outcomes (i.e., lordosis) in adult patients who underwent ACDF with interbody spacer device with integrated anchor fixation. To address this aim the authors conducted a retrospective review of electronic medical record data from a single tertiary medical center. They included patients who underwent first-time ACDF surgery during an ~4 year period with a single surgeon.

This is an important topic to the readership of this journal however I have major concerns regarding the scientific methodology of how dysphagia has been measured.

The introduction is concise and well-written, and the aim of the paper is clearly stated. The methods surrounding study design, inclusion, and exclusionary criteria are clearly outlined, as is the specific data that was harvested from the medical chart. My primary questions regarding the merits of this study relate to (1) a lack of clarity regarding the definition(s) for dysphagia being used and the criteria used to measure dysphagia incidence, (2) the conclusion drawn based on these methods/framing, (3) a lack of acknowledgement by the authors for these flaws in the methods section.

Comment 1a/1b: Beginning at line 85 the authors stated that incidence of postoperative dysphagia was primary outcome collected, however definition provided for dysphagia is unclear and the criteria used for measuring dysphagia is not valid for drawing any sort of associative relationship due to the high likelihood for underreporting and measurement error. Specifically,

The authors define dysphagia as a reported, "difficulty or pain with swallowing that was changed from the patient's preoperative baseline." Unfortunately, no information is provided regarding how dysphagia was measured preoperatively.

Additionally, it appears that the presence of dysphagia was limited to documentation in clinical notes. This is extremely problematic, first and foremost,

because it has been empirically shown that dysphagia after ACDF is underreported.

i.Edwards, C. C. et al. Accurate identification of adverse outcomes after cervical spine surgery. J. Bone Joint Surg. Am. 86, 251–256 (2004).

ii.Shriver, M. F. et al. Dysphagia Rates after Anterior Cervical Diskectomy and Fusion: A Systematic Review and Meta-Analysis. Glob. Spine J. 7, 95 (2017).

iii.Molfenter, S. M., Amin, M. R., Balou, M., Herzberg, E. G. & Frempong-Boadu, A. A scoping review of the methods used to capture dysphagia after anterior cervical discectomy and fusion: the need for a paradigm shift. Eur. Spine J. 1–8 (2023) doi:10.1007/s00586-022-07515-1.

Reply: We agree that our definition of dysphagia was not made completely clear in the initial manuscript and have updated the text to include how dysphagia is evaluated in the clinic of the lead surgeon in this study. To clarify, at pre and postoperative visits, patients are asked about their normal ability to swallow, any new pain or difficulty with swallowing liquids and solids, or any new issues with food or liquid getting stuck in the throat.

Unfortunately, while we completely agree with utilizing an official scale to track and monitor dysphagia, this is something that is not currently part of the workflow for patients who are undergoing ACDF. Given the exploratory, retrospective nature of this study, we did not include a dysphagia scale, but can plan to include this in future, prospective studies. This will also be noted in the limitations section.

Changes in the text: "Dysphagia was defined as any report in the postoperative notes of difficulty or pain with swallowing that was changed from the patient's preoperative baseline. To evaluate this at preoperative and postoperative visits, patients were asked about their normal ability to swallow, any new pain or difficulty with swallowing liquids and solids, or any new issues with food or liquid getting stuck in the throat." – Page 5, Lines 19 – 23.

"A key limitation is that dysphagia, as evaluated in this study, was retrospectively collected through review of medical record reports. However, this has been shown to lead to under-reporting of true dysphagia and is not as granular as certain dysphagia scales such as the SWAL-QOL or EAT-10). These should be addressed in future prospective studies that incorporate these scales in a standardized method by collecting them from patients at each planned timepoint." – Page 14, Lines 17 – 22.

Comment 1c: I take issue with this statement at line 158, "only of the 45 patients (4.4%) required a swallow study at any point."

The type of swallow study is not specified and needs to be (i.e., Clinical evaluation of swallowing by a licensed speech-language pathologist, Videofluoroscopic/Modified Barium Swallow Study, Flexible Endoscopic Evaluation of Swallowing). This matters because Videofluoroscopic/Modified Barium Swallow Studies and Flexible Endoscopic Evaluations of Swallowing are

gold-standard methods for diagnosing dysphagia. They are the only methods by which dysphagia can be definitively captured/measured because swallowing is an internal process that cannot be directly visualized externally.

Reply: We agree with making this change in specificity. Both patients received referrals to get a barium swallow study, which is one of the two gold-standard methods that you outlined.

Changes in the text: "only 2 of the 45 patients (4.4%) reported dysphagia severe enough to necessitate referrals for a videofluoroscopic/barium swallow study" – Page 8, Lines 12 – 14.

Comment 1d: All these exams are frequently used in routine clinical care when dysphagia is suspected so what is meant by the word "required"? This is confusing at best, but also concerning for poor foundational knowledge about the primary outcome of interest. Where any swallowing researchers or specialists included or consulted on the research team?

Reply: The word "required" in this case implied that the patients reported at their postoperative visits that dysphagia was severe enough to warrant a referral for a swallow study. We unfortunately do not have specific speech-language pathologists or dysphagia specialists on our clinical team for these patients, so a referral was deemed necessary for their care. In regard to consulting a swallowing researcher for this team, we did not identify a specific person at our institution to fill this role, and did not deem it feasible to search for such individuals at other institutions given the exploratory nature of this study. With any future studies, we hope to be able to include such an expert for more thorough evaluation of dysphagia.

Changes in the text: "only 2 of the 45 patients (4.4%) reported dysphagia severe enough to necessitate referrals for a videofluoroscopic/barium swallow study" – Page 8, Lines 12 – 14.

Comment 2: Due to significant flaws in the methods described above I do not feel the conclusions made by the authors are well-supported. Dysphagia cannot be the primary outcome in a study where it was not captured using validated methods. At the least, a validated patient reported outcome measure for dysphagia (i.e., EAT-10, SWAL-QOL, HSS-DDI) should have been administered pre-operatively and at each of the stated time points post-operatively.

Reply: We agree with this evaluation of our manuscript. As mentioned above, these dysphagia scales are not currently part of our clinical workflow and cannot be retrospectively collected in such a study. We will address this limitation in the revised manuscript and also change the focus of the manuscript to clinical outcomes as a whole, not just dysphagia.

Modified title: Clinical and Radiographic Outcomes after Index Anterior Cervical Discectomy and Fusion with Interbody Spacer with Integrated Anchor Fixation: A Single-Surgeon Case Series

Changes in the text: "A key limitation is that dysphagia, as evaluated in this study, was retrospectively collected through review of medical record reports. However, this has been shown to lead to under-reporting of true dysphagia and is not as granular as certain dysphagia scales such as the SWAL-QOL or EAT-10). These should be addressed in future prospective studies that incorporate these scales in a standardized method by collecting them from patients at each planned timepoint." – Page 14, Lines 17 – 22.

Comment 3: I do not even see the limitations of these fatal methodologic flaws addressed in the limitations section, which is again concerning that the authorship team had a poor understanding for the outcome they were trying to measure.

The authors may wish to consider the following:

Re-framing the study around a different outcome of interest. Reported dysphagia symptoms (be sure to specify "symptoms") reported by physicians may be included using descriptive statistics, but it is inappropriate to use predictive statistical modeling around this outcome of interest as currently measured. The authors should clearly and explicitly state that no validated measures, nor standardized protocols, where used to measure dysphagia and should acknowledge it is highly likely that dysphagia was underreported.

I think it is important to state that the aim of this research has scientific merit and is clinically important. I want to encourage the authors to re-think the way they are measuring outcomes related to swallowing and dysphagia in these populations. The use of a validated patient reported outcome measure would have vastly improved the methodology of this paper and would likely have yielded a different determination by this reviewer. These are easily incorporated into routine clinical visits, even via telehealth. I would also strongly encourage the authors to collaborate with a dysphagia researcher/specialist (speech-language pathologist or laryngologist) in the future

Reply: We agree completely with the points above and have reframed parts of the manuscript to remove the excessive conclusions from dysphagia with our currently limited methodology. Instead, we have chosen retitle the manuscript to reflect that we are collecting a variety of clinical outcomes. We have removed the predictive logistic model as it is not valid with the small patient sample presented here. We appreciate your ideas for prospective studies and have incorporated these into the limitations section as outlined above.

Modified title: Clinical and Radiographic Outcomes after Index Anterior Cervical Discectomy and Fusion with Interbody Spacer with Integrated Anchor Fixation: A Single-Surgeon Case Series

Additions/Changes in the text: "A key limitation is that dysphagia, as evaluated in this study, was retrospectively collected through review of medical record reports. However, this has been shown to lead to under-reporting of true dysphagia and is not as granular as certain dysphagia scales such as the SWAL-

QOL or EAT-10. These should be addressed in future prospective studies that incorporate these scales in a standardized method by collecting them from patients at each planned timepoint." – Page 14, Lines 17 – 22.

"One of the collected clinical outcomes was the incidence of postoperative dysphagia." – Page 5, Line 18
The entire section on dysphagia in the discussion was modified. These changes served to remove references to the regression model and attenuate some of the conclusions that can be derived from our results. This is the new version:

"This case series presents a set of patients who received ACDF surgeries using a stand-alone anchored spacer system (ISa).   This type of surgery can be considered minimally invasive as it makes use of anchors that require minimum disruption of the neck's anatomy as compared to using screws which would require additional steps for screw preparation and angled instruments for fixation. The ISa spacers described here use anchors that can be inserted in a compact working window due to the use of a streamlined double barrel implant inserter. This inserter allows for reliable and convenient placement of the implant and its anchors (Figure 1). We evaluated the postoperative course of patients, focusing on postoperative dysphagia, complications, readmission, reoperation, and radiographic measures, and found that rates of negative clinical outcomes were comparable or lower than seen in studies analyzing traditional plate-cage systems.

Dysphagia is a common development after ACDF, affecting anywhere from 10-50% of those who undergo the procedure. The proportion of patients with dysphagia in our study decreased over time, suggesting gradual resolution. Dysphagia also only affected those with 2 or 3 level surgeries, which is consistent with literature suggesting that more operative segments increases the risk for dysphagia. Systematic reviews comparing anchored, stand-alone spacers to traditional plated ACDF showed that plated systems have a significantly higher risk of dysphagia compared to anchored, stand-alone systems like the implant we describe here. While most of our patients received preoperative steroids, a systematic review on steroid use in ACDF found that there are no standardized steroid use protocols and that steroids have conflicting outcomes on postoperative dysphagia in different studies. An appropriately powered prospective trial will be needed to evaluate steroid use for the prevention of dysphagia.

Dysphagia rates with plate-cage systems have been reported at 25-70% immediately postoperatively, decreasing to 25-27% at 3 months after surgery and 4-22% 6 months after surgery. Other low-profile or plate-less cages have reported dysphagia rates of 22-57% immediate after surgery, 4-7% 3 months after surgery, and 0-4% 6 months after surgery.   This study showed a much lower immediate dysphagia rate of 17.8% and 6-month dysphagia rate of only 2.2%. A potential driver of lower dysphagia in our stand-along cage patients compared to the literature is the lack of a plate that can irritate the esophagus and the integrated anchoring system. This system allows for the surgery to be carried with less traction on the esophagus as the entire operative length does not need to be exposed to screw in a multi-level plate. Instead, cages can be placed and secured at each vertebral segment with minimal retraction on the surrounding soft tissue."

- Pages 11 – 12.

We also **removed Table 2b** (Dysphagia regression model) and combined **Tables 2 and 3**.

Removed from text: "For the primary outcome, a logistic regression model was used to calculate the odds of dysphagia, accounting for common predictors of postoperative dysphagia, such as C3-C4 or C4-C5 surgery, number of surgical levels, obesity, and the use of intraoperative steroids. "

"The logistic regression analysis for the outcome of dysphagia is shown in Table 2. Across all patients with this outcome, the only factor that significantly increased the odds of dysphagia was an increase of one surgical level, which had an odds ratio of 1.21 per level (OR:1.21, p=0.04)."

General Comments:

General Comment 1: Primary outcome of dysphagia "defined as any report in the postoperative notes of difficulty or pain with swallowing that was changed from the patient's preoperative baseline" - given variation in charting between individuals, a further study could consider using a validated outcome scale for dysphagia

Reply: We acknowledge the limitation of not utilizing the established dysphagia scales such as the SWAL-QOL. This is due to the retrospective nature of the study and has been added to the limitations section.

Changes to the text: However, this has been shown to lead to under-reporting of true dysphagia and is not as granular as certain dysphagia scales such as the SWAL-QOL or EAT-10. These should be addressed in future prospective studies that incorporate these scales in a standardized method by collecting them from patients at each planned timepoint. – Page 14, Lines 17 – 22.

General Comment 2: It is acknowledged that the size of exposure and degree of retraction in a 2- or 3- level case is a confounding factor related to dysphagia. Ideally, the analysis should be matched to a control group of plate-fixation ACDF patients, with results reported by number of levels

Reply: We agree that ideally, this analysis would be matched to a control group of plate-cage ACDF patients. As per your suggestion below, we have expanded the limitations to include a power/sample-size calculation for a future prospective,

controlled trial.

Changes to the text: Based on rough incidence estimates from our study and the literature cited above, a study powered to detect a dysphagia rate of 18% stand-alone vs. 30% plate-cage would require 396 total patients in a 1:1 enrollment with an alpha of 0.05 and power of 0.80. – Page 15, Lines 8 – 10.

General Comment 3: Case example would be more relevant if the patient experienced dysphagia and the requisite changes in post-operative management

Reply: While we understand the intention of using a patient with dysphagia or complications, our goal with this case example was to provide an example of a patient who follows the expected, "normal" progression of a patient undergoing treatment with this novel implant type.

Changes to the text: None

Specific Comments:

Comment 1: P10, line 271 and throughout paragraphs on this page - typographic error in "stand-along" cages and multiple errors in spacing and punctuation.

Reply: This typo has been corrected.

Changes to the Text: "A potential driver of lower dysphagia in our stand-alone cage patients" – Page 12, Line 12

Comment 2: P10, line 271-272 - "A key driver of lower dysphagia in our stand-along [sic] patients is the lack of a plate that can irritate the esophagus" - this statement reflects the hypothesis of the study, which does not have a control group to support this statement.

Reply: We agree that this statement makes a conclusion about dysphagia without a proper control group to compare. We have thus changed the wording of this line to remove the implications of causation or definitive conclusions.

Changes to the Text: "A potential driver of lower dysphagia in our stand-alone cage patients compared to the literature is the lack of a plate that can irritate the esophagus and the integrated anchoring system." – Page 12, Line 14

Comment 3: P10, line 297 - A formal power analysis based on prior literature comparing ACDF/ISa would be useful to quantify the number of patients necessary for this study

Reply: We agree that this would be useful for future studies, and have included a power analysis in the limitations section. Any formal analysis for prospective studies will require further discussion with statisticians.

Changes to the Text: Based on rough incidence estimates from our study and the literature cited above, a study powered to detect a dysphagia rate of 18% stand-alone vs. 30% plate-cage would require 396 total patients in a 1:1 enrollment with an alpha of 0.05 and power of 0.80. – Page 15, Lines 8 – 10.

Reviewer C

Regarding statistical testing, there are questions about the use of logistic regression analysis, which introduces multiple variables as the number of patients with dysphagia was less than 10 at any time point.

Reply: We agree with this point and have removed the logistic regression model as well as all results and conclusions derived from it.

Changes in the text: Removed Table 2b; combined Tables 2 and 3.