First round peer review

Reviewer A

Major Comments

The idea behind this paper is very interesting. They take a food security concept of "food desert" and apply it to surgical outcomes, specifically readmission following esophagectomy. Nutritional status is a central issue to the care of esophageal cancer. In this study, the authors show that the socioeconomic construct of residing in a food desert, an area where there is less nutritious food available, is associated with increased readmission following esophagectomy. It is a contemporary cohort from 2015-2020 in the US.

Comment 1: I congratulate the authors on pursuing this interesting and valuable study. I do have a major concern with the methodological construct of this study. It appears the authors have adjusted for variables they could measure and which were associated with food desert (note: not readmission) on univariable analyses. However, the authors do not appear to have a causal framework that informs their model construction. They adjust for factors that do not meet the definition of a confounder, which can be adding significant noise in their model. For example, "operative time" cannot be associated with food desert status, and therefore cannot be a confounder, but is included in their model. In fact, all of the 3 variables they mention adjusting for would not meet the definition of a confounder.

I suggest the authors start by constructing a causal diagram/framework of the relationship they wish to examine, and this will help identify which factors influence both residing in a food desert and readmission – this will help identify confounders, and the authors can then construct a clinically- and methodologically-informed multivariable model. Some variables that the authors may be considering confounders are in fact mediators. Note – you may not need to adjust for many (or any) factors. Even descriptive and unadjusted data can be valuable and informative. The paper should be revised based on the direction the authors choose in consultation with a methodologist.

I am enthusiastic about this research question and the authors' data, but they do need to consult with the statistician/methodologist on their team, and their analyses (or at least the framing of the paper) will require major revision and reconsideration.

Reply 1: Thank you for your comment. There is a typo in the methods sections, and the it should read "*Multivariable logistic regression was then used to model readmission status (dependent variable) on food desert status (independent variable), adjusted for demographic and clinical measures statistically associated with readmission status at the P<0.10 in univariable analyses*", rather than factors associated with food desert status. This language has been updated in both the abstract and the method.

Changes in the text: We have corrected the methodological language in both the abstract and method section (page 3, line 70 and page 8, line 185).

Minor Comments

Comment 2: Study setting (state, country) should be mentioned in the abstract.

Reply 2: We have added this information to the abstract.

Changes in the text: The methods section of the abstract has been updated to include this information (page 3, line 60)

Comment 3: The term 'univariate' should be replaced with 'univariable'.

Reply 3: Thank you for this comment. We have updated this term.

Changes in the text: The abstract methods and results (page 3, lines, 66, 70 and 72), as well as the methods section (page 8, lines 181 and 185) have been updated.

Comment 4: Introduction is excellent but can be shortened to focus on the study and issue at hand.

Reply 4: Thank you for this comment. After prior JTD review, we feel the current introduction is necessary to fully articulate the background and rationale for this current study.

Changes in the text: No additional changes for this comment

Comment 5: The manuscript overall is well organized and written.

Reply 5: Thank you for this comment.

Changes in the text. No additional changes for this comment

Comment 6: More information should be provided on how postoperative complications were defined and identified (eg standardized definitions and proactive reporting vs opportunistic identification from medical records).

Reply 6: We have updated the methods section to include this information.

Changes in the text: The methods section (page 7, lines 158-160) include this information.

Reviewer B

The authors conducted a retrospective analysis regarding short-term outcomes after esophagectomy by comparing patients from the food desert and not from the food desert.

The study design and statistical analysis have some flaws.

Comment 1: Is there any relevant reason to exclude patients whose BMI was smaller than 18?

Reply 1: As noted in the introduction, BMI's of <18.5 one of the definitions of malnutrition and are known to be associated higher rates of complications after esophagectomy. Since the current study was trying to elucidate food deserts as nutrition-related risk factor, it was felt that those with low BMI's may confound the results, and were thus excluded.

Changes in the text: No additional changes for this comment

Comment 2: Though the readmission within 30 days from esophagectomy was set as a primary outcome, this is not a solid outcome measure.

Reply 2: We respectively disagree that 30-day readmission is not a solid outcome measure. Readmission is a common outcome used in surgical research, and it is also one of the outcomes that the Agency for Healthcare Research and Quality (AHRQ) and the Centers for Medicare and Medicaid Services (CMS) use to assess and compare hospitals. We understand that there are many factors that can contribute to readmission, which is why we conducted an extensive analysis, as noted in the methods section.

Changes in the text: No additional changes for this comment

Comment 3: Did all patients discharge from the hospital within 30 days? There were 2 in-hospital mortality excluded. Such analysis is not fair.

Reply 3: Yes, all patients were discharged from the hospital within 30day of their procedure. Those who died in the hospital were excluded from the primary analysis, as the primary outcome was 30- day readmission, and those who were deceased at the time of their index admission did not have the opportunity to be readmitted.

Changes in the text: No additional changes for this comment.

Comment 4: Multivariate analysis (table 5) using intermediate factors such as operative time, discharge to a Rehab, Grade 3/4 complication is inappropriate.

Reply 4: A typo was noted in the methods sections. These factors were found to be associated with readmission status at the $p < 0.10$ level in univariable analysis, which is why they were also included in the model. The methods section has been updated to correct for this.

Changes in the text: We have corrected the methodological language in both the abstract and method section (page 3, line 70 and page 8, line 185).

Comment 5: It seems their short-term outcomes after robotic esophagectomy were worse than open. The use of the robot was more often in patients from the food desert for some reason.

Reply 5: Thank you for your comment. Short-term outcomes after robotic esophagectomy were not explored in this paper. Additionally, while there were a greater proportion of robotic esophagectomies performed on patients who lived in a food desert, compared to those who did not, there was no significant difference in the surgical approach between the two.

Changes in the text. No additional changes for this comment.

Second round peer review

Comment 1: I am pleased to re-review this manuscript examining the relationship between residing in a food desert with readmission following esophagectomy. My main methodological comment in the last version was the construct of the multivariable model and lack of causal framework informing model construction.

Reply 1: We thank the Reviewer for their time and thoughtful review. We have made revisions to better clarify our conceptual framework regarding food desert (FD) status and readmission. Specifically, we have clarified the distinction between the two sets of analyses presented that assess FD status and 1) perioperative outcomes and 2) readmission status given risk factors at discharge. That distinction provides a framework for our selection of covariates as described below. We revised the project aim in the Introduction, as well as Figure 1 to illustrate these two "stages" of the analysis. Additionally, we clarified in the Methods that the analyses assessing odds of readmission were limited to those alive at discharge. We include footnotes in both Tables 3 and 4 to reinstate that the longitudinal analysis was limited to those alive at discharge.

Changes in the text: We have clarified the aims of the project in the Introduction (page 6, lines 132- 134). Additionally, Figure 1 has been updated.

Comment 2: The authors clarify that their multivariable model was constructed based on variables that were associated with readmission at the p<0.10 level. This is a common approach in the surgical literature, but methodologically very weak. Variables can have spurious associations with an outcome, and have no sensible real-world meaning behind the relationship. Further, one variable's association with an outcome does not satisfy the definition of a confounder, which should on a theoretical basis be associated with both exposure and outcome. I would encourage the authors to revisit the comment in my last review with regards to creating a casual framework for the relationship they are trying to describe, and building a clinically-informed multivariable model. Have they consulted with a methodologist for this study?

See Hernan et al "Causal knowledge as a prerequisite for confounding evaluation" in American Jounal of Epidemiology 2002, Vol 155 No 2, for some guidance.

Reply 2: We agree with adding more clarity regarding our conceptual model and analytic approach. As described above, we have made several revisions to the manuscript to convey the two stages of the analysis that we present, specifically the associations

between FD status and perioperative outcomes and odds of readmission, above and beyond risk factors at discharge.

Regarding our model for readmission, we chose to use an empirical, data-driven approach to identify all potential confounders of the relationship between residing in a food desert and readmission status. As the Reviewer noted, that approach is quite common and appropriate. We indeed selected potential covariates (among the available data) based on their potential associations with residing in a FD and discharge status. Thus, our empirical approach is conservative and considers all sources of potential variation in readmission status given the available data. Importantly, we are transparent regarding the unadjusted and adjusted associations (reported with confidence intervals) between residing in a FD and readmission status, to demonstrate how precision of the reported estimates may change after adjustment. We reviewed all of our methods with the study's biostatistician (Emond, JA).

Changes in the text: We have clarified the selection of the covariates for the multivariable model in the Methods (page 7, lines 168-169).

Comment 3: On a related note, in response to Reviewer B, Comment 1, the authors explain that they excluded patients with BMI<18 as it may "confound" the relationship between food desert status and readmission. In fact, BMI<18 would be considered a mediator, not a confounder, since it is on the causal pathway – residing in a food desert can influence the risk of low BMI, which can influence the risk of readmission. While it is the authors' choice to exclude those patients, I do want to note that this decision may in fact blunt the observed association between food desert residence and readmission.

Reply 3: We agree that excluding the one patient with BMI <18 kg/m^2 was unnecessary, and we intended to repeat the analysis with this one patient included. However, upon review of the participant flow for the creation of Figure 1, we realized that this participant was excluded from the analysis because they lacked pre/post scans for comparison. Thus, this person was excluded from the analysis and our model results remain the same.

We agree that BMI may be on the causal pathway from FD status and readmission status, as well as on the causal pathway from FD status and cancer characteristics / operative outcomes. As better clarified in our revisions described above, our goal when considering readmission was to consider the association between FD status and readmission, given patient status at discharge. As we only have pre-treatment BMI and do not have measures

of post-discharge BMI (or change in BMI post- discharge), we unfortunately cannot truly address the mediating effect of BMI on the relationship between FD status and readmission.

Changes in the text: The methods section has been updated (page 6, lines 145-146), along with Figure 1 to reflect this.

Comment 4: With regards to Reviewer B, Comment 3 about two patients experiencing in-hospital mortality, the reviewer is correct that this biases the results toward less readmission, and makes it less likely for an association to be observed, although the effect will be small. This is a technicality. Methodologically-speaking, those 2 patients should be excluded from the analysis. The analysis can only be conducted on patients who were eligible for the outcome (readmission). Therefore, time zero starts on the day of discharge, and any patients not alive at time zero should not be in the analysis. In addition, 30-day readmission should be calculated from the day of discharge, not from the day of surgery – can the authors confirm the analysis was conducted in this way?

Reply 4: We have clarified that analysis assessing the association between FD status and readmission was completed only among those alive at discharge. Additionally, we include footnotes in Tables 3 and 4 addressing this. Changes in the text: We have clarified this in the Methods section (page 7, line 156, and page 8, lines 186-187), as well as the Results section (page 9, line 211), and have updated Tables 3 and 4.

Comment 5: Reviewer B, Comment 4 is the same as my first comment. The authors have included mediators and non-confounding variables in their model, which is not appropriate. They do need consultation with a methodologist.

Reply 5: We agree that FD status likely affects cancer characteristics / operative outcomes. We report those cross-sectional associations yet are unable to truly address causality because of the study design.

Our analysis of readmission status was to assess the odds of readmission by residing in a FD starting at the point of discharge, above and beyond risk factors for readmission as measured at discharge (including peri-operative outcomes). Thus, we treat cancer characteristics / operative outcomes as "baseline" risk factors. Importantly, we are transparent regarding the unadjusted and adjusted associations (reported with confidence intervals) between residing in a FD and readmission status. Given that the odds ratio for FD status remained similar and statistically significant in both models suggests that those

covariates did not confound or partially mediate the observed association. We have added a line in the Discussion stating that the reported association between FD status and readmission was largely unchanged when adjusting for risk factors at discharge, suggesting that FD status has a unique association with readmission status, independent of initial cancer characteristics or operative outcomes.

We acknowledge that prospective studies with additional data collection post-discharge are needed to address mediating factors (e.g., dietary intake). In summary, our analysis addresses whether FD status relates to readmission status above and beyond risk factors at discharge. Future prospective studies are needed to more fully address how FD status relates to the full spectrum from cancer incidence and severity, operative outcomes and prognosis.

Changes in the text: We have updated the Discussion (page 11, lines 257-259 and page 14, lines 319-320)

Comment 6: I do appreciate this study and the authors' efforts to address the reviewer comments. As explained above there are issues in the methodological construct of this study which are easily remediable and should be pursued. My previous comment that even descriptive and univariable analyses are valuable, and multivariable adjustment in some cases may not be necessary, still stands and can be considered by the study team as well.

Reply 6: Thank you. These clarifications have indeed improved the manuscript. Changes in the text: No additional changes for this comment.