Peer Review File

Reviewer A

I am afraid that there might be significant overlap of the patients with their previously published study (Int J Environ Res Public Health. 2022 Jan 21;19(3):1185. doi: 10.3390/ijerph19031185). Although the authors focused on the impact of race and ethnicity on RCC treatment outcomes, they have already performed this kind of research with much larger population (238,141 cases) (Int J Environ Res Public Health. 2022 Feb 12;19(4):2050. doi: 10.3390/ijerph19042050). Why did not they use this population to perform current study?

Response: Thank you for your comments. There are several important differences between two studies. Our previous study published in Int J Environ Res Public Health used data from Arizona Cancer Registry to explore general patterns of RCC treatment disparities in State of Arizona, while current study used hospital data focusing on data not available in state cancer registry, such as BMI, ischemia time, estimated blood loss, length of hospital stays, and comorbidity. Using these data, we asked if obesity impacts ischemia time, estimated blood loss, and length of hospital stays accounting for race and ethnicity and neighborhood characteristics. In the introduction (the third paragraph in the introduction), we added sentences to explain the findings from hospital-based database and population-based registry and needs for more detailed analysis for surgical outcomes to understand the treatment disparities.

Furthermore, this study is somewhat superficial. They did not show any perspective how their results contribute to improve the outcomes of patients with RCC.

Response: We added following sentences to the Discussion section (the end of fifth paragraph in Discussion section. "Given the complex relationship among race and ethnicity, socioeconomic challenges, comorbidities, and obesity, it is necessary to further investigate how this relationship affects surgical and oncologic outcomes. It is also important to consider a larger societal context

to assess individual risk of negative surgical treatment outcomes, relationships between obesity and surgical outcomes, and financial burden among patients with socioeconomic challenges."

In this single center retrospective study the authors investigated whether obesity was associated with worse perioperative outcomes and if there were heterogeneous effects based on race, ethnicity, and socioeconomic factor. This is a very well performed study with interesting results.

Response: Thank you for reviewing our manuscript and providing comments.

I have some comments:
-Renal cell carcinoma (RCC) is essentially a metabolic disease characterized by a reprogramming of energetic metabolism (PMID: 36960789; PMID: 30983433, PMID: 36430837,PMID: 36310399). In particular the metabolic flux through glycolysis is partitioned (PMID: 29371925, PMID: 28933387, PMID: 25945836), and mitochondrial bioenergetics and OxPhox are impaired , as well as lipid metabolism (PMID: 30538212; PMID: 32861643, PMID: 29371925, PMID: 36430448). In this scenario RCC associated with metabolic disorders show a more aggressiveness and poor clinical outcomes. These findings should be referenced and discussed.

Response: Thank you for your suggestions. We discussed RCC and metabolic reprograming in the introduction (the beginning of the second paragraph) incorporating some of these papers.

I have read carefully the authors manuscript. Bellow my comments:
1. Abstract: Report in methods if patients were treated with radical or partial nephrectomy. The term surgical treatment is too general. In results please report the p value for BMI and report if the

association was found in the univariate analysis. Again report OR, CI and p values for the association with EBL and for all the variables of multivariate analysis. Don't report just stronger association; be precise.

Response: We included patients who underwent both radical and partial nephrectomy. We added this information to abstract. In our analysis, we either adjusted for nephrectomy type or performed stratified analysis. We added p-value for BMI difference among racial and ethnic groups as well as OR, CI, and p-values for other analysis.

2. Introduction: Try to report separately the literature for partial and radical nephrectomy. I suggest not using the term surgical treatment; be precise.

Response: We separated the literature for partial and radical nephrectomy in introduction (the Second paragraph). We replaced "surgical treatment" with "nephrectomy" throughout the manuscript to be specific, when we are talking about nephrectomy.

3. Methods: Provide ethical approval number. Again I suggest separating the results for partial and radical nephrectomy. Report also the statistical package you used.

Response: The University of Arizona Institutional Review Board protocol number was added to method section (the last sentence in the first paragraph of method section). We expanded stratified analysis based on nephrectomy type and sub-analysis for partial nephrectomy, and results were incorporated in revised manuscripts. We added information on statistical software used.

4. I suggest deleting the mean values and report only median and IQRs. Also report p values with CIs and ORs. Also report AUCs.

Response: We replaced mean (SD) with median (IQR) for BMI. We added ORs, CIs, and p-values in appropriate places on the results. We decided not to report AUCs, because of small sample size and lack of information on RENAL nephrometry scores and other potentially important information to predict outcomes.

The study addresses a relevant topic as 1) Obesity rates are growing; 2) RCC incidence is up, especially small renal masses; 3) Evidence on benefits of nephron sparing has pushed partial nephrectomy (PN) for larger and more complex tumors.

All combined drive the importance to improve risk stratification to choose the best surgical approach for each patient.

Finally, after 20 years of minimally invasive nephrecotmy, studies remain conflicting whether obesity has a negative, neutral, or even positive (so called obesity paradox) impact on perioperative outcomes.

The authors propose a single-center, retrospective analysis on the impact of obesity on nephrectomy (partial and radical) periop outcomes in a ethnically and socially diverse population. They a found obesity associated with higher EBL and BMI ≥ 35 with an IT > 18min, while LOS was not associated with BMI. Lower socieconomic status and being non-hispanic white (but not hispanic) correlated with high EBL in obese; the other socio-ethinic analyses being non-significant.

Response We describe in the introduction that RCC incidence rates increased with obesity rate (the first paragraph in the Introduction). We also described benefits of partial nephrectomy over radical nephrectomy in the first paragraph in the Introduction. We added a sentence in the introduction on better survival in obese compared to normal weight patient after surgical treatment (the second paragraph in the Introduction). We performed stratified and/or sub-analysis based on nephrectomy type and we report the results in the revised manuscript.

1. Ischemia time:

- Authors argue that BMI≥35 kg/m2 was more common in patients with longer IT (IT) and refer the reader to Table 2, but it is not mentioned that this was not statistically significant.

Response: We indicated that the difference was not statistically significant in the revised version (paragraph 2 in the results).

2. Significant missing data for outcomes of interest in study population - IT (22%), EBL (24%). Authors didn't address how missing data was distributed among BMI (obese vs non-obese) and ethnic groups. This might be a source of major selection bias.

Response: We did not observe statistically significant difference between patients with missing data on ischemia time and EBL and patients with data. Among patients who underwent partial nephrectomy (n=244), data for ischemia time was not available for 42 of them (17.2%). Median BMI (and IQR) was 31.8 (28.5-36.7) for patients with missing ischemia time and 31.0 (25.8-35.4) for patients with ischemia time (P=0.15). EBL data was not available for 86 patients (19.9%). Mean BMI (and IQR) was 28.9 (25.8-33.7) for patients without EBL data and 30.6 (26.5-35.6) for patients with EBL data (P=0.09). There may be selection bias, but effect of bias may be minimal. We added this about missing data and selection bias as one of limitations in the discussion section (Discussion Section the last paragraph).

3. It is not disclosed how many patients were obese in the study population nor in each ethnic group (NHW, H, AI).
- In contrast to all other variables, author used mean + SD for BMI. It is not stated or demonstrated if it us normally distributed.

Response: We added number (and %) of patients with BMI ≥30, <35 and BMI ≥35 for all patients and each racial and ethnic groups on Table 1. Nearly half of AI patients (46.7%) had Class II/III obesity. This information was added to result section (the 1st paragraph of results).   In revised

manuscript, we report median BMI and Interquartile range based on the comments by Reviewer C and D.

3. Ethnicity and neighborhood-level analysis are limited by:

- Significant differences in mean BMI among each group.

- Major variation in socioeconomic hardship (SDI >70) - 100% for AI, 30% for NHW) prevents individualization of which variable is behind periop outcomes.

Response: Race and ethnicity, neighborhood-level social deprivation, and obesity are interconnected factors potentially influencing comorbid conditions, access to care, and potentially perioperative outcomes. Race and ethnicity and SDI were not associated with ischemia time, EBL, and length of hospital stay in our study (information was added to results – fifth paragraph). Then, we decided to assess relationship between obesity and perioperative outcomes accounting for this relationship by stratifying based on race and ethnicity and neighborhood social deprivation. Small sample size limited our ability to assess this in full extent, but we believe it is important to start considering larger societal contexts to assess individual risk of negative surgical treatment outcomes and relationships between obesity and surgical outcomes.

4. In Results, morbid obesity is defined as a BMI$\geq$35 kg/m2. However, according to CDC / Endocrine Society guidelines, class 3 / severe obesity (formerly known as morbid obesity) is defined by a BMI$\geq$40 kg/m2. What reference did the authors use to define morbid obesity?

Response: In the revised manuscript, we categorized obesity into Class 1 (BMI 30.0-34.9) and Class II/III (BMI $\geq$35.0) following World Health Organization.

5. Table 1: There's a statement about pT1a / pT1b in Results, but we don't find the pT stage distribution in study population. Authors acknowledge that lack of data on tumor complexity

(RENAL or PADUA) limits analysis and could change the panorama. Both are major determinants of periop outcomes (EBL, IT, LOS) which were not accounted for in the analysis.

Response: We added pathological tumor stage information to the Table 1. Unfortunately, we no longer have access to clinical data of some patients to collect necessary information to calculate RENAL and PADUA score. We updated the discussion section where we talked about lack of RENAL data.

6. Table 2 legend mentions rates of obesity and comorbidities, but does not show any data on the later.

Response: Thank you for catching our error, we removed "comorbidities" from the Table 2 legend.

7. Table 3: wide CIs, many non-significant. In 3 / 4 significant variables the CI approaches 1.00, limiting the strength of associations.

Response: We agree with the reviewers. Because we have small samples size for some BMI categories, we have very wide confidence intervals for both statistically significant and non-significant BMI categories. We added this to one of limitations of study (Discussion section, the last paragraph). We decided to have four BMI categories to show trend trends of increasing odds ratio as BMI increase. We also realized that BMI does not have linear relationships with perioperative outcomes. This information was added to the method/statistical analysis section.

8. Table 4 explores the relationship between comorbidities, SDI (socioeconomic status), and EBL on hospital stay. It does not relate to the study objective (i.e. impact of obesity on PN periop outcomes and how this might be modulated by socio ethnic variables). Besides, one would expect longer LOS in patients with more comorbidities and bleeding in any procedure or condition.

Response: We removed Table 4 in the revised manuscript. We reanalyzed the data, and now we report the results in text only (the last sentence of the last paragraph in the Results section). In the

All in all, the study's argument for an association between obesity (+ - socioeconomic and ethnic variables) and nephrectomy periop outcomes, if any, is blurred and weakened in the midst of major heterogeneity, significant missing data, and not accounting for relevant factor like pT stage and RENAL score. These associations could clarify if more data (tumor size, stage distribution, proportion of obese) were available, providing a more appropriate assessment of selection bias.

1. https://www.cdc.gov/obesity/basics/adult-defining.html
2. https://www.endocrine.org/-/media/endocrine/files/obesity/obesity-playbook-final_use.pdf

Response: Thank you for your comments. We agree with the reviewer that relationships between obesity and perioperative outcomes are not clear because of those reasons. We try our best to address the concern raised by the reviewer. However, we would like to note that our main goal was to show importance of considering socioeconomic backgrounds (race and ethnicity and neighborhood-level socioeconomic factors) because renal cell carcinoma and obesity disparities have previously been reported.

Reviewer E

Authors tested the effect of BMI/Obesity and perioperative outcomes after kidney surgery, according to races.

Response: Thank your reviewing our paper and providing comments.

Some comments:
-Some important contributions are missing in the references: PMID: 32151650; PMID: 33401103

Response: We included sentences on metabolic syndrome including these two papers and two additional papers on metabolic syndrome and RCC survival in the fifth paragraph in the Discussion section.

-Authors presented results considering a binary outcome. I suggest to repeat the analyses by considering the outcome ad continuously coded (linear regression? Poisson regression?)

Response: We considered using linear regression approach and did some exploration with linear regression in earlier phase of project. In the end we decided to use logistic regression for easier interpretations.

-It's quite difficult to derive meaningful conclusions since this analysis represent a mix of procedures (partial vs radical nephrectomy), approaches (robotic vs lap vs open) and tumor characteristics. I suggest performing subgroup analyses.

Response: As suggested by the Reviewer C, D, and E, we added results of stratified and sub-analysis results, mainly based on nephrectomy in this revised. Wherever necessary, we adjusted for nephrectomy type, surgical approach, and tumor characteristics (stage and grade).

-Any information about surgeons' experience?

Response: We did not collect information on surgeons' experience. We added this as one of limitations of study (Discussion section, last paragraph).

-I believe that a possible explanation for the different effect of BMI according to races is probably related to differences in visceral obesity (maybe some races have different distribution of fat). DO authors believe this is a valid explanation?

Response: I agree with reviewers that variation in visceral adiposity or body composition across racial and ethnic groups may explain the relationships between obesity and perioperative outcomes. The information is currently available only a small subset of patients, and we are working on measuring visceral and subcutaneous adiposity for our future study. We added this information to the discussion section (the third paragraph in the discussion section).