Reviewer A

The authors described about the association of body composition with postoperative complications and length of hospital stay after nephrectomy for renal cell carcinoma. In the present study, sample size was relatively larger than previously reported similar studies; therefore, the results were very interested. However, contains some problems. The authors need to address them, and these are detailed below.

Comment 1: The title of the article is "… after nephrectomy in patients with renal cell carcinoma …". In general, "nephrectomy" for renal cell carcinoma means radical nephrectomy, and partial nephrectomy is not included. If the authors want to evaluate both radical nephrectomy and partial nephrectomy, the title should be properly changed (e.g. surgical procedures).

Reply 1: We would like to thank the reviewer for the comment. To clarify the purpose of our article, we adjusted our title to include both partial and radical nephrectomy (see page 1, line 3-5).

Changes in the text:
Line 3-5:
The association of body composition with postoperative complications and length of hospital stay after radical or partial nephrectomy in patients with renal cell cancer: a multicenter population-based cohort study

Comment 2: A partial nephrectomy is completely different surgical procedure from radical nephrectomy; therefore, the cohort of a partial nephrectomy should not be combined with the cohort of a radical nephrectomy. Thus, I think Table 1-3 are unnecessary, and they should not be included in this article. I think supplementary table 1 and 2 are main results in the present study. They are not supplementary information. Similarly, multivariable multilevel logistic regression analyses in partial nephrectomy are also important, and they should be also included in the revised manuscript as main tables.

Reply 2: We agree with the reviewer that the sensitivity analyses show some interesting results. However, the study was not intended to separate all subgroups of surgical procedures as presented in the supplementary files. For that, the study is lacking power as, e.g., only 8 major complications occurred in the partial nephrectomy group. We included the multivariable analyses for partial nephrectomy in the supplementary files as requested (see Supplementary files, page 2-3). However, given the small number of events, estimates have large confidence intervals and are likely to be invalid due to overfitting of the models. Given these issues we

would like to keep the main results as initially intended. However, we extended our discussion with a statement commenting on the results found in our subgroup analyses (See page 16, line 300-306).

Changes in the text:
Line 300-305:
Sensitivity analyses in patients with stage I-III RCC, or with different surgical procedures showed similar associations for SMD and VATI as observed in the complete group of patients. Nevertheless, not all associations were found to be statistically significant. This is probably a power issue due to the small number of patients within each subgroup. Especially for partial nephrectomy, results may also be invalid due to overfitting. Given the low power, no interaction hypothesis could be statistically tested.

Comment 3: As described in "Discussion", postoperative length of hospital stay (LOHS) is extended due to various causes included too many non-medical factors. This is a severe limitation. I think that the association between body composition and postoperative LOHS defined in the present study is not meaning. If authors want to evaluate the association between body composition and postoperative LOHS, the definition should be properly changed (e.g. duration from operation to the date, which physicians allowed the discharge). If the definition of postoperative LOHS is not properly changed, the descriptions regarding the association between body composition and postoperative LOHS should be not included.

Reply 3: The reviewer is correct in pointing out our incomplete description of extended length of hospital stay. Therefore, we adjusted the methodology section accordingly (See page 8 , line 139-140 and page 9, line 145-147).

Changes in the text:
Line 139-140:
Preoperative information (body weight, height, smoking status, American Society of Anesthesiologists (ASA) score) and perioperative information (complications, Clavien Grade classification, <u>date of surgery and date of discharge</u>, surgical blood loss and surgical time) were extracted from medical records by IKNL data managers.

Line 144-146:
The secondary outcome was extended <u>length of hospital stay (LOHS). LOHS was calculated as the date from surgery until discharge date</u>, and extended LOHS was categorized at the 75th percentile into <7 and ≥7 days.

Comment 4: Information regarding surgeons are necessary for analyses of operative results. Because the present study is a multicenter population-based historical cohort study; therefore, collecting information regarding surgeons may be difficult. However, the authors should be included it as much as possible in the revised manuscript.

Reply 4: We recognize the issue raised by the reviewer that the surgeon or surgical team may

affect the results of the surgery and the reporting of outcomes. Unfortunately, we were unable to obtain the characteristics of the surgeons who performed the surgeries. However, we have performed cluster analyses with the hospital being the cluster where the patients have been assigned to as a proxy for the surgeon. With cluster analyses we have taken into account that these patients are more similar because they share the same hospital of surgery, and the associations presented in this article have been adjusted accordingly. We acknowledge that this might not have been sufficiently clear in our article and have added information to the limitation section of our discussion (See page 18, line 338-342)

Changes in the text:
Line 338-342:
Sixth, we could not obtain characteristics regarding the surgeon performing the nephrectomy. As a proxy we performed multilevel analyses taking into account that patients underwent surgery within the same hospital. Nevertheless, differences within hospitals due to differences between surgeons may still exist which we could not adjust for. We included hospital of surgery as a fixed cluster effect in the analysis for major complications because of non-converging random intercept models. However, since the hospitals are a random sample of large community and university hospitals in the Netherlands, results are generalizable to other hospitals.

Comment 5: In conclusion, the authors described "High BMI and lower SMD may be associated with higher risk of major postoperative complications" (Page 15 Line 307-308). What kind of complications were associated with BMI and SMD? The authors should analyze and describe regarding complications in detail (e.g. gastrointestinal, wound infection, bleeding…).

Reply 5: We thank the reviewer for the comment. Regrettably, we do not have this information. Data on complications were collected by data managers from the Netherlands Comprehensive Cancer Organisation (IKNL). They were requested to only register the grade of complications according to the Clavien Dindo scoring system and not the type of complications. Given the small number of major complications that occurred in our study population, analyses by type of complication would not be feasible.

Reviewer B

This is a well-conducted and well-written multicenter, retrospective study aiming to evaluate if BMI and body composition variables could predict postoperative complications and extended length of hospital stay (LOHS) in patients undergoing nephrectomy for malignancy. That is a relevant research topic as we have strived to improve outcomes and minimize complications while operating on older, frail patients with more advanced (and often metastatic) disease.

Comment 6: First, the study outcomes are worth a revision, as 'survival' is mentioned in line 86 but it does not appear in the Outcomes section (line 125). Then, in line 281, it is stated that the study was also set up to evaluate body composition in relation to survival. However, no data on

survival is available throughout the manuscript, suggesting that it would be more appropriate to remove it as an outcome.

Reply 6: We thank the reviewer for the comment. Indeed we mentioned survival as this retrospective cohort study was conducted to assess the association of body composition parameters with both postoperative outcomes and survival. In this article we focus on complications and hospital stay. The results on survival have already been published in another article (1). We have now made this more clear by adding the following text and the reference to the other paper (see page 7, line 97-100 and page 17, line 319-320).

Changes in the text:
Line 97-100:
A population-based historical cohort study on body composition parameters in relation to postoperative outcomes and survival was conducted in 7 Dutch hospitals. Results on survival have already been published elsewhere (1) and this analysis is focused on postoperative outcomes.

Line 319-320:
Second, since this study was part of a larger study to examine body composition in relation to survival outcomes (1), requiring a long follow-up time, the surgical data are relatively old and indications and techniques may have changed over time.

Regarding the primary outcome ("postoperative complications, categorized as any (Clavien grade ≥II) and major (Clavien grade ≥III) postoperative complication"), a significant association was only observed for a BMI > 30. And it did so partially, as it correlated only with major complications, whereas no significant association was found when considering ANY postop complication. Of note, all other body index variables (VATI, SATI, SMI, and SMD), which are less established (and thus worth studying) than BMI, did not correlate with the primary outcome.

As for the secondary outcome (extended LOHS - 7 days or longer), only skeletal muscle density showed a significant association in the study population. BMI, and once more the all the remaining body composition variables, yielded no significant correlation.

Therefore, the study was mostly negative on its aim to identify body composition parameters that could predict the risk of postop complications (the paragraph starting on line 173 illustrates well such perception). This becomes clearer when one considers that neither BMI nor body composition parameters significantly improved the AUC of a model based on established predictors of surgical complications (age, sex, disease staging, and ASA score).

Comment 7: The positive associations reported by the authors arise from subgroup analyses, with the exception of lower skeletal muscle density with extended LOHS. Whereas worth validation by future studies, they are limited by all the biases described in the Limitations in a higher degree. Furthermore, the authors would better support the consistency of such subgroup

analyses by providing hypothesis for their findings. For instance, why a low skeletal muscle density would correlate to higher complication rates only in patients undergoing lap/robot-assisted nephrectomy? Would open nephrectomy be a more "metabolically demanding" procedure and thus be subject to increased sarcopenia-related complications?

Reply 7: We agree with the reviewer that slightly different associations are observed between the subgroup analyses performed. However, all of the associations for skeletal muscle density point in the same direction for each of the subgroups, namely that higher skeletal muscle density seems to be protective for complications and extended length of hospital stay. For visceral adipose tissue also different statistical associations are observed between the subgroups. Nevertheless, also here all associations seem to point in the same direction, i.e. that higher visceral adipose tissue was related to higher risk of extended length of hospital stay. The reviewer is correct that some associations are statistically significant while others are not. We think that this is mainly a power issue because of the smaller number of patients within each subgroup.

It is true that it would be interesting to explicitly test interactions between the surgeries performed. Unfortunately we do not have the power to properly perform statistical tests on these interaction hypotheses. Therefore, we chose to present the associations for each subgroup separately in the supplementary tables. We have added a statement in the discussion to comment on the results found of the subgroup analyses (see page 16 , line 300-306).

Changes in text:
Line 300-305:
Sensitivity analyses in patients with stage I-III RCC, or with different surgical procedures showed similar associations for SMD and VATI as observed in the complete group of patients. Nevertheless, not all associations were found to be statistically significant. This is probably a power issue due to the small number of patients within each subgroup. Especially for partial nephrectomy, results may also be invalid due to overfitting. Given the low power, no interaction hypothesis could be statistically tested.

Comment 8: The fact that the study was overall negative does not invalidate or diminish its relevance. However, it makes it necessary that some of the conclusions be restructured for clarity. For instance, we read in Conclusion that "High BMI and lower SMD may be associated with higher risk of major postoperative complications and higher VATI with higher risk of extended LOHS, depending on surgical procedure". It may be misleading the way it is written, based on the exposed above. It would be more accurate to separate 'high BMI' and 'lower SMD', indicating that the former was significantly associated with major complications, whereas the latter was overall negative except for extended LOHS. The third sentence in Conclusion, and the Abstract's Results and Conclusion sections, would also benefit from restructuring following the same rationale.

Reply 8: We agree with the reviewer that the presentation of the results can be improved. We have now adjusted our statements to be more in line with the results of the study (see page 3-4,

line 50-57 and page 18, line 352-360).

Changes in text:
Line 50-57:
Lower skeletal muscle density was associated with extended length of hospital stay and non-significantly associated with higher risk of major postoperative complications. High BMI was related with higher risk of major postoperative complications. Higher VAT was non-significantly associated with higher risk of extended length of hospital stay. Results by surgical procedure were in the same direction but were statistically significant for some subgroups.

Line 352-360:
Lower SMD was associated with higher risk of extended LOHS and showed non-significant associations with higher risk of major postoperative complications. High BMI was associated with higher risk of major postoperative complications. Higher VAT was non-significantly associated with higher risk of extended LOHS. Results for both SMD and LOHS by surgical procedure were in the same direction but differed in statistical significance between subgroups.

Comment 9: Below you will find some observations not directly related to the core review of the manuscript:

Obs 1: In the Abstract - Results Section: "A 10-unit increase in skeletal muscle density was associated with extended length of hospital stay (OR 0.58; 95%CI 0.44-0.78".
I understand that it should be the contrary, since an inverse relationship between SMD and LOHS was found as per an OR < 1.0.

Obs2: In line 111, 'height' was likely misnamed for 'body surface area' as it was expressed in m² and intended to normalize the skeletal muscle measurements for individual body variation.
Obs 3: there is a typo in line 238 - 'The Thus'

Reply 9: We would like to thank the reviewer for the detailed textual comments. We have adjusted the texts according to the reviewer's suggestions.

Changes in the text:
Line 42-44
A 10-unit increase in skeletal muscle density was inversely associated with extended length of hospital stay (OR 0.58; 95%CI 0.44-0.78).

Line 127-129
Cross-sectional areas were normalized for height squared (m^2) to obtain SMI (cm^2/m^2), subcutaneous adipose tissue index (SATI, cm^2/m^2) and visceral adipose tissue index (VATI, cm^2/m^2)"

Line 265-266
The precise relationship remains to be investigated.