Comments to the Authors

The manuscript "Association between the metabolic score for insulin resistance and the risk of prostate cancer" aims to evaluate whether insulin resistance may be associated with the presence of prostate cancer, addressing a significant public health issue. However, there are major methodological concerns that need to be addressed before publication.

Major changes:

1. The authors should provide more explicit clarification when stating, "However, the association between insulin resistance and prostate cancer is currently uncertain." This statement should be accompanied by a citation supporting their argument and a summary of the existing evidence regarding insulin resistance and prostate cancer, explaining why it is uncertain. Are there inconsistencies in the results of studies? Or is there a lack of evidence regarding this association?
2. One methodological aspect needing clarification is the study design. Based on the flow diagram and description, it appears to be more of a cross-sectional study in the methods section. A case-control study is unlikely due to the method of patient selection. Additionally, since the population under study should consist solely of men, "Being female" cannot be an exclusion criterion, as the event under consideration is prostate cancer. Instead, the authors should clarify the number of men affiliated with the Hospital of Xinjiang Medical University who had prostate cancer and who did not. It would also be crucial to mention the duration of prostate cancer in the study population.

3. Out of the total number of individuals meeting eligibility criteria, how many chose to participate in the study? Were there any differences between participants and non-participants? This information is crucial for assessing potential selection bias that may affect the validity of the study.
4. Figures 2 and 3 do not provide relevant information to the study, primarily because they display the coefficients of each variable in the regression model. The differences in estimators, such as for hypertension, may result from the variable METS-IR being included as continuous in one model and as quartiles in the other. Moreover, interpreting the coefficients of each variable may lead to potentially incorrect conclusions. For instance, there is evidence that calcium levels may affect blood pressure or cause hypertension, and hypertension itself has been independently associated with prostate cancer. Therefore, the coefficient for calcium is being adjusted for a variable (hypertension) that may mediate its association with prostate cancer, leading to overfitting. This possibly explains why the results suggest that higher calcium levels are associated with a lower prevalence of prostate cancer, contrary to existing evidence. Thus, I suggest consolidating the information into a single figure, focusing solely on the coefficients of METS-IR, and discontinuing the presentation of data as in Table 3.
5. The results presented in the supplementary material seem to exceed the scope of this study. Therefore, it would be better to mention in the introduction that there might be a synergistic or antagonistic effect of insulin resistance with other metabolic factors such as hypertension. In other words, the authors should mention that the metabolic syndrome is being evaluated in relation to prostate

cancer because such a combined effect may exist. However, the authors do not provide a biological justification for this analysis.

6. In the discussion section, the authors should consider mentioning that it is unlikely for higher insulin resistance to result in lower prostate cancer risk. It is probably a consequence of reverse causality, and the way exposure was measured. This point is not addressed in the discussion. Additionally, the presence of selection bias cannot be ruled out since there is no information on the participation rate in this study.

Minor changes:

1. I suggest removing the word "risk" from the title, the study design does not permit the evaluation of prostate cancer risk.
2. In line with the above point, the introduction should detail how insulin resistance was evaluated in relation to prostate cancer, thus introducing or justifying the use of METS-IR. The methodological validity aspects should be moved to the discussion section as a potential strength of the study.
3. The flowchart refers to the selection of "Patients with urinary cancer," which should instead be "Patients with prostate cancer."
4. From lines 117-120, the inclusion of covariates in the different regression models is mentioned. However, I consider that this information should be included in the statistical analysis section.
5. The way of measure alkaline phosphatase is not mentioned.

6. Regardless of the statistical analysis section mentioning this, the table footnote of Table 1 should include the statistical tests used to compare the characteristics of interest between individuals with and without cancer.
7. In the methodology, it should be indicated that METS-IR was divided into quartiles and specify whether this was based on the entire population or on subjects without cancer.
8. In line 111, mentioning the suggestion of the statistical test is not relevant. Here, it is essential to be precise about the observed differences between patients with and without cancer.