Reviewer’s report

Title: Preoperative Prostate Health Index predicts adverse pathology and Gleason score upgrading after radical prostatectomy for prostate cancer.

Version: 0 Date: 09 May 2020

Reviewer's report:

This is a potentially confirmatory study showing the association of the Prostate Health Index (PHI) with adverse prostate cancer pathology among 472 patients who underwent radical prostatectomy for prostate cancer. I have substantial concerns about the study, including (1) no clear rationale is provided for why the study was performed, (2) it remains unclear how representative the patients included are of all patients who underwent radical prostatectomy at the included institutions (numbers and reasons for exclusion are not provided), and (3) the results reported in the key tables are likely incorrect (e.g., labeled as HR when likely Odds Ratios are reported, direction of the effect for many variables including PSA and PHI is in the wrong direction, AUC seems very low compared to similar studies).

More detailed comments are outlined here:

Abstract:
1. Methods: it should be mentioned how accuracy was determined and compared.
2. Results: Please provide numbers that quantify accuracy for univariable and multivariable analyses results.
3. Results: it is unclear what is meant by "improving accuracy by 5.5% and 5.0%" and the by associated p-values. Please describe more clearly how accuracy was improved. For example, would expect something like "improved AUC from 0.xx to 0.yy (p=x)".
4. Part of the conclusion is not supported by the data. Whether PHI helps with identifying potentially high-risk patients among men with biopsy proven insignificant cancer was not evaluated in the current study, as all these men underwent radical prostatectomy.

Introduction:
1. The introduction could provide a stronger rationale for why the study was performed. Is this to add a new aspect to the literature? If so, what aspect? If not, is it meant to be a study confirming prior studies?

Methods:
1. It would be nice to specify the 4 sites from where the patients were included.
2. How many patients were excluded because of lack of complete information? This should be reported and reasons for exclusion should be shown.
3. Did all patients at the included institutions have a preop PHI done? If not, how many had surgery between 2014-2018 and were excluded because PHI data was not available?
4. A 2016 consensus statement of multiple Journals requests to preferentially use Grade Group instead of Gleason score for reporting prostate cancer studies. I would suggest the authors follow that guidance: for example https://www.goldjournal.net/article/S0090-4295(16)00280-6/fulltext
Results:
1. The authors use the term "significant prostate cancer at final pathology". How was this defined?
2. Table 1: Would be helpful to show a descriptive breakdown of the overall cohort, but then also by pathological GS>=7 vs. GS=6 as this seems to be one of the main comparison that is done in the multivariable analyses later.
3. Tables 2/3/4/5: I assume what is shown here are Odds Ratios and not Hazard Ratios? Please clarify.
4. Tables 2/3/4: something seems to be seriously wrong with the presumed Odds Ratios shown in the tables. For example, they would indicate that older age, higher PSA, and higher PHI are associated with lower risk of pathological Gleason >=7, Gleason sum upgrading, and pT3 disease. This is likely an error, as innumerable other studies have shown the opposite.
5. Tables 2/3/4: would be good to enter a comment why p2PSA and %p2PSA were not incorporated into the multivariable models. I assume this is because they are part of the PHI, but so is fPSA and PSA, so please clarify these decisions.
6. Figure 1: The AUCs of the models, particularly those of the models without PHI are quite low, in fact much lower than what is usually seen in these kind of models. Why is this? Are the authors sure this was calculated correctly?

Conclusion:
1. The statement "higher value of PHI was associated with the risk of GS upgrading, which may help to identify potentially high-risk patients among men with biopsy proven insignificant PC" is not supported by the data. All patients underwent radical prostatectomy in the current study, so presumably there was a clinical suspicion that they don't have clinically insignificant prostate cancer. Whether those that were felt to have insignificant prostate cancer did indeed have significant prostate cancer cannot be gleaned from the current study, because those patients did not undergo radical prostatectomy.

Other: The study appears to have been published as a preprint here https://europepmc.org/article/ppr/ppr122612 - this should be disclosed in the final manuscript.

Please confirm that you have included your review in the ‘Comments to Author’ box?

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- Are the statistical test(s) used in this study appropriate and well described?

- Is the exact sample size (n) reported for each experimental group/condition (as a number, not a range)?

- Are the description of any error bars and probability values appropriate?

- Are all error bars defined in the corresponding figure legends?

- Has a sample size calculation been included, or a description and rationale about how sample sizes were chosen?

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