November, 19, 2013

Makoto Ohori, M.D.
Editor-in-Chief
*World Journal of Clinical Urology*

Dear Doctor Ohori

Please find attached our manuscript, entitled **"Development of a nomogram for predicting positive repeat prostate biopsy(No.5877)"** which we are re-submitting for consideration of publication in *World Journal of Clinical Urology*as an original article.

We have carefully responded to each questions and comments by the reviewer and explained our thoughts. We colored a yellow in all changes in main text and tables to make what we changed clear. We really appreciate it if you could reconsider our manuscript for publication of *World Journal of Clinical Urology*
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This manuscript has not been published or presented elsewhere in part or in entirety, and is not under consideration by another journal**.** All study participants provided informed consent, and the study design was approved by the appropriate ethics review boards. All the authors have approved the manuscript and agree with submission to your esteemed journal. There are no conflicts of interest to declare.

Thank you for your consideration. I look forward to hearing from you.

Sincerely,

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As the reviewer pointed out, the predictive ability of our nomogram was not superior to the previous reports. However, Dr.Kattan indicated that the meaning of comparison of c-index is questionable unless head to head comparison is employed (Kattan M, European Urol 59:566,2011, Kattan M. Cancer 107(11):2523, 2006). Therefore, we can simply say that our nomogram is reasonably accurate. Main advantage of our nomogram is that we used the readily available factors only to develop a nomogram. We put "readily available factors" into the conclusion in the abstract.

The reviewer questioned about statistically insignificant factors that we included into the nomogram. In present study, we didn't do model selection that would be accomplished on the modeling data alone. Instead, we built the model by including all predictors that were clinically relevant to the disease by literature no matter they were statistically significant or not on the current data. With enough number of events in the modeling data, theory driven models normally have better generalizability than data driven models when applied to other patient populations and would preserve the predictive performance that was evaluated based on the modeling data.

1. Harrell FE , Jr. , Lee KL , Califf RM , Pryor DB , Rosati RA . Regression modelling strategiesfor improved prognostic prediction . Stat Med 1984 ; 3 (2) : 143 - 52 .
2. Clinical Prediction Models: A Practical Approach to Development, Validation, and Updating (chapter 11), Ewout W. Steyerberg, Springer, New York, New York.

We put the same explanation into limitations in the last paragraph of the discussion, and added these references.

Also, the reviewer questioned about the inverse association between several factors in the nomogram and positive rebiopsy. For inclusion of predictors with inverse association with the outcome, the question is related to inclusion of insignificant variables in the full model where variables inclusion is based on clinical literature alone. The inverse association may result from the small effect size and large random error of insignificant predictors where the combination of random noise and small factor effect size accidently presents the inverse association. Another cause may be the collinearity among predictors. With the presence of collinearity, the estimate of regression coefficient for a predictor can be strongly distorted by another predictor that is highly correlated with the first predictor. However, collinearity does not necessarily worsen the overall prediction of the prognostic model. We think this should be fine for our study since we are not doing statistical inference based on individual regression coefficients.

We explained this inverse association as one of limitations in the present study in the discussion, and we believe that we don't need to explain in detail.

The reviewer questioned about selection criteria for variables in the nomogram. We simple included all variables as explained above. We incorrectly named "cumulative number of cores" as "no of negative cores previously biopsy removed". We rename it as cumulative number of cores in the nomogram.

Other minor changes;

1. The AUC of our nomgram was 0.74. We corrected 0.7 in the abstract and Table 4.
2. We incorrectly named "cumulative number of cores" as "no of negative cores previously biopsy removed". We rename it as cumulative number of cores in the nomogram (Figure 1) and on page 3, line 16, and page 9, line 13.
3. We rephrased one sentence in last line in page 11.
4. We deleted min and max values in Table 1.