Peer Review File

Article Information: https://dx.doi.org/10.21037/tau-22-324

Review Comments (Round 1)

First of all, I would congratulate the authors on the work and study that they performed. It was very interesting to read. However, I do have some questions and remarks regarding the study.

Major:

Comment 1. Introduction: describe both posterior and lateral retroperitoneal adrenalectomy and explain why you perform lateral approach.

Reply 1: Thank you for your comments and questions. We have modified our text as advised (see Page Introduction, line 101-111).

Comment 2. What were the criteria for performing partial / total adrenalectomy? Could this influence the results by itself?

Reply 2: Patients underwent laparoscopic surgery either partial or total adrenalectomy, according to tumor size, position, function and physician preference. In the univariate regression analysis, partial/total adrenalectomy was a significant variable that influence surgical difficulty. However, after multivariate regression, it was not significant.

Comment 3. Several studies investigated anthropomorphic factors that influence surgical difficulty (perinephric fat tissue, location of adrenal gland, skin-to-adrenal distance). Were these factors considered for inclusion in the analyses? If not, why?

Reply 3: We have to admit that there are several limitations in this study. Anthropomorphic factors including perinephric fat tissue, location of adrenal gland and skin-to-adrenal distance were not considered for inclusion in analyses due to lack of the radiographic imaging data. In addition, we supplied the limitation of the study in discussion (see Page discussion, line 315-317).

Comment 4. Why did you use the Lasso regression analysis? The explanation in methods section is not clear for me.

Reply 4: Recently, the least absolute shrinkage and selection operator (Lasso) regression has emerged as a powerful tool under the theory of bias-variance tradeoff in the variable selection. In the current study, LASSO regression was applied to reduce data dimension and select predictors. To our knowledge, there are several articles based on LASSO regression for variable selection (PMID: 32779010, PMID: 35069440, PMID: 34402981).

Comment 5. No R-square variable was provided to evaluate model performance.

Reply 5: The R2 of logistic regression model was provided in Figure 5 in training cohorts as well as validation cohorts.

Comment 6. I do not understand figure 6. Maybe explain this better in the text.

Reply 6: Decision curve analysis is a novel method for evaluating diagnostic tests, prediction models and molecular markers. It combines the mathematical simplicity of accuracy measures, such as sensitivity and specificity, with the clinical applicability of decision analytic approaches. In brief, the method is based on the principle that the relative harms of false positives and false negatives can be expressed in terms of a probability threshold (Pt). In the present study, DCA was applied to evaluate the clinical value of the nomogram by assessing net benefits at different threshold probabilities in both the training dataset and validation dataset. As shown in Figure 6, it was revealed that when the threshold probability was 10% to 90%, the use of nomogram to predict surgical difficulty was more beneficial than either the treating all patients or treating none. However, if the threshold probability was less than 10% or more than 90%, the net benefit of nomogram was equivalent to predicting positive results for all patients.

We have add some explanation of DCA in our text as advised (see Page Results, line 237-241)

Comment 7. In the univariate regression analysis many variables are not significant (surgeons experience, diameter of lesion). However, they are subsequently included in the multivariate regression analysis. Is this correct? And after multivariate regression some variables are not significant (type of resection, histology). However, these are included in the definitive nomogram. Maybe it would be better to exclude non-significant predictors to make nomogram more easy to use. Stepwise selection procedure or best subset regression analysis could be used to compare different nomograms which include 1, 2 or more variables and compare the predictive outcomes of these different models. If the predictive power doesn't increase much by adding non-significant variables, these should be excluded.

Reply 7: In this study, the predict variables related to surgical difficulty were selected based on LASSO regression rather than univariate regression analysis. The optimal λ was selected with a 10-fold cross-validation process and one standard error of the minimum criteria, while retaining the non-zero coefficients. On the basis of these results, surgeon's experience, tumor diameter, resection procedure, histological type, patients' gender and BMI were identified as predictors for surgical difficulty. Therefore, the above variables were included in the final models, despite some of predictors have a relatively small influence on model fit.

As your suggestion, considering the relatively small influence on model fit, we excluded the variable of resection procedure from the final analyses.

Comment 8. What will be the consequence of "high risk". Would you then perform TLA? Or is it only used for counselling. Please explain this further in the Discussion.

Reply 8: If the patients seem to be at high risk underwent LRLA, a transabdominal approach for LA might be a potentially approach for the treatment of adrenal disease. We have modified our text as advised (see Page Conclusions, line 329-331).

Minor points:

Comment 1. Change the use of "gender" to "sex". Sex refers to a person's physical characteristics at birth, and gender encompasses a person's identities, expressions, and societal roles. In this context sex is better.

Reply 1: We have modified our text as advised.

Comment 2. Change blood lose to blood loss

Reply 2: We have modified our text as advised.

In general, there are several typing errors and the English sentences are not always correctly phrased. I would suggest that you proof-read and correct the article by a native English speaker before the next submission.

Review Comments (Round 2)

Thank you for making several adaptations to the article and answering my questions. I still have some minor comments:

Comment 1. Introduction, line 98: you state that there is no visual prediction model available for PRA. This is not true, v Uitert et al built a prediction model for posterior retroperitoneoscopic adrenalectomy (your reference 8). No prediction model for lateral retroperitoneoscopic adrenalectomy is available.

Reply 1: We have modified our text as advised (see Page Introduction, line 103-104.)

As previously mentioned, there still are several typing errors and the English sentences are not always correctly phrased. I would suggest that you proof-read and correct the article by a native English speaker before the next submission.