

Peer Review File

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Reviewer A

Reviewer comments to author:

Thank you for the opportunity to review the manuscript entitled “Validating Scores Predicting Atrial Fibrillation (AF) Recurrence Post Catheter Ablation in Patients with Concurrent AF and Pulmonary Diseases”. The study reports on the value of several risk scores for predicting recurrent AF after catheter ablation in patients with both AF and pulmonary diseases. The study covers an actual problem: a high number of patients experience recurrent tachyarrhythmias after AF ablation and prediction who will or will not benefit from AF ablation is hard. The sample size of the study and its power seem sufficient. Most previous studies on risk scores for prediction of AF ablation outcomes have not dealt specifically with AF patients with concomitant pulmonary diseases, and the present study may therefore be of added value. Unfortunately, several major issues prohibit adequate assessment of the value of the present study.

Reply: Thank you.

1. Research aim:

The primary research aim is to compare the performance of risk scores for prediction of AF recurrence after ablation. The authors describe in the abstract that exploring differences between the risk scores could be helpful for making AF treatment decisions. It remains unclear in the remainder of the paper how the authors expect the findings of their study could aid in the decision-making process. The most important finding is that the BASE-AF2 score and MB-LATER were superior to other risk scores for predicting post-ablation AF recurrence; all other risk scores have a C-score <0.60. Yet, both the BASE-AF2 and MB-LATER scores cannot be calculated before ablation, since early AF recurrence (in the first three months after ablation) is part of the score. This is a major issue, as an AF ablation risk score can only be helpful in making treatment choices when it can be used prior to ablation. Please describe how the study results can be translated into clinical practice.

Reply 1: Thank you.

We added “Unfortunately, though the BASE-AF2 and MB-LATER scores were superior to other risk scores for predicting post-ablation AF recurrence, both the scores cannot be calculated before ablation due to involvement of early AF recurrence (in the first three months after ablation) as part of the score. Actually, antiarrhythmic drugs were advised to be used once the patients had early AF recurrence in order to avoid late AF recurrence. There is room for improvement in the progress of these

scores predicting recurrent AF in the subgroup of patients with AF and concomitant PDs.” in the third paragraph of the Discussion part.

Changes in the text: Page 8, line 3-10.

2. Methods:

a. The manuscript lacks any information regarding the ablation procedure. Were all procedures performed using radiofrequency ablation? Was ablation pulmonary vein isolation only, or were additional ablation lines/AF trigger ablation part of the ablation strategy? Was a waiting time/adenosine testing for pulmonary vein isolation to unmask dormant conduction incorporated? Please describe concisely how the ablation procedures were performed.

Reply 2. a: Thank you.

We added “Briefly speaking, the '2C3L' technique is performed with radiofrequency ablation method, which is a fixed ablation approach consisting of bilateral circumferential pulmonary vein antrum isolation (PVAI) and three linear ablation lesion sets across the mitral isthmus, left atrial roof, and cavo-tricuspid isthmus. The procedure was terminated by cardioversion unless a mappable organized atrial tachyarrhythmia was subject to further ablation until non-inducible with burst pacing at 200 ms. ”in the second paragraph of the Methods Part.

Changes in the text: Page 3, line 4-10 from the bottom.

b. It would be useful if the authors elaborated a bit more how patients were followed up. Page 5 – line 8 states “After 13.42 ± 12.82 months of follow-up”. This suggests that some patients completed only a very minimal number of follow-up visits. Alternatively, follow-up duration may not have a normal distribution and should be expressed as Median [interquartile range]. Please describe how often ECG recordings were performed, how often Holter-recordings were performed, and whether patients were only included when they did not complete a minimum number of follow-up visits.

Reply b: Thank you.

“After 13.42 ± 12.82 months of follow-up” has been changed into “After a median of 6 months (interquartile range: 6-18 months) follow-up.”

We added “Follow-up as previously described was performed by the nurses starting from the day on which the patients received RFA until five years after catheter ablation or the end of the follow-up (December, 2015). The follow-up method included inpatients, outpatients, visiting at home or telephone every one to six months. During this period, the patients were scheduled to do ECGs or holtors at each follow-up and were advised to do ECGs in the nearest ECGs if any possible AF symptoms occurred. Any recording of AF lasting >30s by ECG or Holter was considered as AF recurrence, dividing into early AF recurrence if less than 3 months and late AF recurrence if more than 3 months.”

Changes in the text: Page 6, line 8 and Page 5, line 2-7.

c. In the statistical analysis paragraph of the methods section there is no description of normality assessment of variables. Please note that it is important to ascertain whether data show a deviation from normality for the appropriateness of the statistical tests used.

Reply c: Thank you.

We added “Normality assessment of continuous variables was performed using one-sample Kolmogorov-Smirnov test. Continuous variables with normal distribution were indicated as mean \pm standard deviation (SD) and compared using the student's t test. If not, they were reported as medians with interquartiles [median (25th percentile - 75th percentile)] and compared with Wilcoxon rank sum test subsequently.” And the results changed accordingly.

Changes in the text: Page 5, line 11-15 and the results in the Table 1.

d. Page 4 lines 10-11 states: “Variables unavailable were treated as missing data.” It is unclear how the authors handled missing variables. For the correct calculation and use of risk scores it is of utmost importance that all parameters included are complete.

Reply d: Thank you.

Actually, little variables were unavailable for those included scores. What we mean with this statement is to explain the reason why “The ALARMEc score and the ATLAS score” were not included for analysis in the study. That is because of too much missing data on left atrial size and left atrial volume for the current analysis. And this sentence was deleted to reduce misunderstanding. We added “Eighth, several scores were not validated in the current analysis because such data were available only for part of the patients, such as left atrial size in the ALARMEc score and left atrial volume in the ATLAS score.”

Changes in the text: Page 9, line 15-18.

e. In the statistical analysis paragraph of the methods section it is stated that “Clinical usefulness was analyzed by Decision Curve Analysis (DCA), Integrated Discrimination Improvement (IDI) and Net Reclassification Improvement (NRI).” However, it remains unclear how the p values in Figure 2 were calculated. The paper assumes that readers are familiar with DCA/IDI/NRI analyses, which may not be the cases. I suggest to simplify statistical analyses and to remove Figure 1 / Figure 3, as these figures provide more or less the same message as Figure 2.

Reply e: Thank you.

Figure 1 and Figure 3 were removed as suggested and the corresponding statements were also removed in the statistical analysis part and in the results part and in the discussion part.

f. It would be helpful if the items of the different scores would be summarized in a table.

Reply f: Thank you.

The items of the different scores were summarized in Supplementary Table I.

Changes in the text: Supplementary Table I

3. Results:

a. Figure 4 shows Kaplan-Meier curves of patients with and without COPD for AF free rate. The large drops in the curves are somewhat suspicious with a relatively large sample size. It is implausible that >20% of 304 patients experience recurrent AF on the same day.

Reply 3.a: Thank you.

To make it clear, the number at risk was added to the Kaplan-Meier curve in this Figure.

Actually, most of the patients may experience AF recurrence during the similar month, as the follow-up was recorded as month, but not day.

Changes in the text: Figure 2.

4. Discussion:

a. A critical review of the obtained results is lacking. For example: what could be reasons for the risk scores to perform worse than in the original papers?

Reply 4.a: Thank you.

We added “Another possible reason to explain the worse performance in these patients was that AF patients with PDs had somewhat different characteristics. As LA was one important factor involved in most of the scores, but right atrial diameter was neglected which was more often affected by the PDs, which contribute a lot to the recurrent AF after ablation.” In the discussion part.

Changes in the text: Page 7, line 16-20.

b. Although several risk scores were tested in the present study, some scores listed in a recent systematic review were not included. (Dretzke, J., et al. (2020). "Predicting recurrent atrial fibrillation after catheter ablation: a systematic review of prognostic models." EP Europace.) Although it is conceivable that not all scores could be calculated with available data, it could be mentioned in the discussion or limitations section.

Reply b: Thank you.

We added “Eighth, several scores were not validated in the current analysis because such data were available only for part of the patients, such as left atrial size in the ALARMEc score and left atrial volume in the ATLAS score.” as suggested.

Changes in the text: Page 9, line 15-18.

c. In the limitations section the following statement is made: “patients with AF and pulmonary diseases are not usually treated with catheter ablation”. This may suggest that the studied subgroup of patients was a highly selected group of patients who underwent AF ablation, despite concomitant pulmonary disease and AF. This may be an important source of bias and

limit the generalizability of the findings.

Reply c: Thank you.

We added “, which might lead to the source of bias and limit the generalizability of the findings.” in the Limitation part as suggested.

Changes in the text: Page 9, line 8-9.

d. The relatively low c-values of all studied risk scores indicate that there is room for improvement in the prediction of recurrent AF in the studied subgroup of patients with AF and concomitant pulmonary disease. The introduction states that these patients with both AF and pulmonary disease are associated with worse outcomes after AF ablation. It would be helpful if the authors elaborated more on the underlying mechanisms of this association, and if other factors than the studied risk factors should be investigated in future studies. E.g. one could postulate that incorporation of COPD GOLD stage may provide added value.

Reply d: Thank you.

The underlying mechanisms was added as follows.

“Actually, these patients with both AF and PDs were associated with worse outcomes after AF ablation because PDs could be the underlying disease leading to AF. The PDs was not resolved even if the AF ablation was performed, which made AF hardly treated.” in the Discussion part and “though the incorporation of PDs stratification stage may possibly provide added value, which is hardly obtained for the current analysis.” in the Limitation Part.

Changes in the text: Page 7, line 13-16 from the top and Page 8, line 5-7 from the bottom.

5. General:

The manuscript was difficult to read. The authors might want to have someone with full professional proficiency in English proofread the manuscript.

Reply 5: Thank you.

The paper was revised thoroughly as suggested.

Minor issues:

Please provide total number of patients with and without AF recurrence in the results section.

Reply : Thank you.

The total number of patients with and without AF recurrence was provided in Table 1 and “113 AF patients experienced AF recurrence, accounting for 37.2% of the whole population.” was added in the Results part.

Changes in the text: Page 6, line 8-9 and Table 1.

Page 3 – line 6: “Six scores predicting AF recurrence were analyzed.” Seven scores were calculated in the study.

Reply :Thank you.
“Six” was changed into “seven”.
Changes in the text: Page 4, line 10.

Typos:

Page 3 – line 7: Please remove one of two comma’s following “the MB-later score”

Reply :Thank you.
One comma following “the MB-LTER score ”was removed.

Page 4 – line 21: Clinical should be lower case.

Reply :Thank you.
This is changed accordingly.

Page 7 – line 3: “APLLE”

Reply :Thank you.
APLLE was changed into APPLE.

Reviewer B

The authors have shown that the BASE-AF2 score was more useful than CAAP-AF and HATCH scores in AF recurrence after catheter ablation in patients with AF with pulmonary disease. Although their study was very interesting, there are several severe issues limiting the value of the presented study:

Reply : Thank you.

Major

1. First, how many patients actually had AF recurrence in this study? There was no clear statement on this point in the text, tables and figures. This is one of the most important issues in catheter ablation studies.

What about anti-arrhythmic drugs given to patients before and after catheter ablation? Were there any patients with restricted beta blockers due to pulmonary disease?

I am concerned that there was a lot of variability of the follow-up period among patients. For example, it would be better to limit the period, such as 5 years after catheter ablation.

Reply 1: Thank you.
The number of patients of AF recurrence and no recurrence was added in Table 1 as suggested and we added “After a median of 6 months (interquartile range: 6-18

months) follow-up, 113 AF patients experienced AF recurrence, accounting for 37.2% of the whole population.” in the Results part. (See page 6, line 8-9 and Table 1).

We have listed the failed anti-arrhythmic drugs to the patients before catheter ablation and the number of VRCB (beta blockers) was added in Table 1.(See Table 1)

AAD use after ablation was added in Table 1. (See Table 1)

We have limited the follow-up period to 5 years and added “Follow-up as previously described was performed by the nurses starting from the day on which the patients received RFA until five years after catheter ablation or the end of the follow-up (December, 2015). The follow-up method included inpatients, outpatients, visiting at home or telephone every one to six months. During this period, the patients were scheduled to do ECGs or Holter at each follow-up when possible and were advised to do ECGs in the nearest clinics if any suspicious AF symptoms occurred.” (See Page 5, line 2-7 from the top). Actually, there is not much variability in the follow-up information, as only 5 patients who did not experience AF recurrence was followed exceeding 5 years. Most of the patients had follow-up information less than 5 years. Therefore, no change on the results after limit the follow-up to 5 years except Figure 2.

2. Second, the classification of coexisting pulmonary disease was ambiguous. The authors listed COPD, pulmonary tuberculosis, pulmonary embolism, interstitial lung fibrosis, lung cancer, etc. as lung diseases, but it is not preferable to lump them together. Was it possible that the above pulmonary diseases had been combined?

This should be assessed according to the severity of the pulmonary function test and Hugh-Jones classification.

How was each treatment for pulmonary disease? Did any patients have lung resection? These also need to be mentioned.

Reply 2: Thank you.

The pulmonary diseases were also lumped as a whole in this paper “Bai Y, et al. Association of peak atrial longitudinal strain with atrial fibrillation recurrence in patients with chronic lung diseases following radiofrequency ablation. *Internal Medicine Journal*. 2018.48:85-859.”

We added “However, this study proved that the BASE-AF2 score was useful in predicting AF recurrence following ablation in a specific PDs cohort with histories of mild to severe PDs.” in the limitation part (See Page 9, line 2-4) and “the PDs status were hardly accounted for as no uniform indicator was available for each kind of PDs, though the incorporation of PDs stratification stage may possibly provide added value, which is hardly obtained for the current analysis.” in the Limitation Part (See Page 8, line 5-8 from the bottom).

We added “14 lung cancer after lung resection” as suggested.(Page 3,line 7)

3. Third, the authors should discuss why BASE-AF2 score was superior to other scores as a predictor of AF recurrence after catheter ablation in their cohort.

For example, it is better to consider the relationship between the components of the BASE-AF2 score and pulmonary disease.

Reply 3: Thank you.

We added “One possible reason was suspected that smoking involved in the BASE-AF2 score was also risk factor contributing to incidence of PDs.” In the discussion part.

Changes in the text: Page 7, line 1-3 from the bottom.

Minor

1. Please indicate the number of patients of AF recurrence and no recurrence on Table 1, which was also related to Major 1. Also, you probably need to correct the ‘BNP’ line Add the number at risk to the Kaplan-Meier curve in Figure 4.

Reply 1: Thank you.

The number of patients of AF recurrence and no recurrence was added in Table 1 as suggested.

The data was normality assessed and expressed using median (interquartile range) and accordingly the “BNP” line was corrected.

The number at risk was added to the Kaplan-Meier curve in this Figure.

Changes in the text: Table 1 and Figure 2.

2. What was the optimal point for predicting AF recurrence of the BASE-AF2 score in the ROC analysis of Figure 2?

Reply 2: Thank you.

We added “The optimal point for predicting AF recurrence of the BASE-AF2 score in the ROC analysis was 1 point with sensitivity of 69.03% and specificity of 60.21%.” in the Results part.

Changes in the text: Page 6, line 11-13 from the bottom.