

## Peer Review File

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### **Reply to the comments of reviewer A**

**Comment 1: Methodology: However, a randomized controlled trial would provide stronger evidence by controlling for confounding factors.**

Thank you for your thoughtful and constructive comments. We do agree with the reviewer's comments.

**Reply 1:** The nonrandomized control is a major weakness of our study design and may cause the selection bias. However, by comparing the baseline of the two groups, we found that the risk factors related to the recurrence of non-paroxysmal atrial fibrillation, including age, sex, left atrial size, renal function, and cardiovascular disease were comparable, suggesting that the baseline of the two groups was relatively balanced and selection bias may be not large. At the same time, we declare the flaws in the design of this study in the limitations section of the article, so we should be cautious in interpreting the results of this study.

**Changes in the text:** We have modified our text in the “**Limitations**” part in revised manuscript (see **Page 12, line 315**).

**Comment 2: Also, the criteria for choosing one treatment over the other initially is not explicitly defined. If there was a bias in selecting the initial treatment, it could confound the results.**

Thank you for your thoughtful and constructive comments. We do agree with the reviewer's comments.

**Reply 2:** To further ensure the ethics of the trial, the principle of the different order of ablation of the admitted patients was mainly based on the subjective wishes of the patients after the preoperative interview. In the process of conversation, all the doctors involved in this study did not introduce too much about the advantages and disadvantages of two stepwise ablation strategies, and refused to implement purposeful induction for patients to ensure the randomness of patients' independent choice. In our center, preoperative notification is a very important part of surgery, and

the contents we inform mainly include the risks and benefits of surgery, complications, and the precautions required for postoperative follow-up. The nonrandomized assignment was based on respect for the patient's preferences for surgery.

**Changes in the text:** we have modified our text in the “**Method**” part in revised manuscript (see **Page 6, line 133-140**).

**Comment 3: Methodology: A sample size of 157 is reasonable, but not large. Moreover, a significant imbalance in the number of participants between the two groups (53 in the LASM-first and 104 in the PVI-first) could affect the statistical power of the comparisons. More demographic details such as the average age, sex ratio, or comorbidities, which might impact the treatment outcome, are missing.**

Thank you for your thoughtful and constructive comments. We do agree with the reviewer’s comments.

**Reply 3:** Thank you for fully clarifying the objective value of this study, and we fully agree with you. We have adopted your suggestions in the discussion section. In addition, for the baseline characteristics of the patients you mentioned, we provide table 1 for supplements.

**Changes in the text:** 1. we have modified our text in the “**Limitations**” part in revised manuscript (see **Page 12, line 318**). We added more demographic details (**Table 1; see Page 24**) in revised manuscript.

**Comment 4: Results Interpretation: The study suggests that LASM may provide higher immediate success and a slightly better long-term success rate compared to PVI. However, it's worth noting that the difference in long-term success rates between the two groups was not statistically significant, which suggests that the two treatments might be equally effective. The significant difference in immediate success rates after LASM versus PVI is noteworthy and may have implications for patient comfort and hospital stay duration.**

Thank you for your useful comments. We do agree with the reviewer’s comments.

**Reply 4:** You have fully clarified the objective value of this study, and we fully agree with you. We have included your views in the discussion section.

**Changes in the text:** 1.we added our text in the “**Discussion**” part in revised manuscript(see **Page 16, line406- 413**)

**Comment 5: Follow-up Duration: Although the patients were followed up for a median duration of 16 months, a longer follow-up period would be beneficial to evaluate the durability of the procedure and the long-term safety profile.**

Thank you for your thoughtful and constructive comments. We do agree with the reviewer’s comments.

**Reply 5:** This is a limitation of the study. In the future, more large-sample, multi-center and long-term clinical studies are needed to prove the preliminary findings of this study. At the same time, more studies still need to pay attention to the impact of immediate AF termination on the long-term length of hospital stay, quality of life and medical costs of patients.

**Changes in the text:** We have modified our text in the “**Limitations**” part in revised manuscript (see **Page 13, line 321-324**).

**Comment 6: Adverse Events: The report does not provide details about the nature, frequency, and severity of the adverse events reported, which are crucial for understanding the safety profile of the two strategies.**

Thank you for your thoughtful and constructive comments. We do agree with the reviewer’s comments.

**Reply 6:** We re-examined the manuscript and supplemented the information related to complications with tabular representations.

**Changes in the text:** In the revised manuscript, we added the relevant details in **Table 6 (see Page 31)**.

**Comment 7: References: a more accurate description of the atrial substrate should be added and appropriate reference to previous work describing in**

details the relevance of the atrial substrate on the outcomes (this for example - <https://www.ahajournals.org/doi/full/10.1161/JAHA.122.027795> -

**Characterization of Atrial Substrate to Predict the Success of Pulmonary Vein Isolation: The Prospective, Multicenter MASH-AF II (Multipolar Atrial Substrate High Density Mapping in Atrial Fibrillation) Study)**

**Also other works describing AF ablation based on substrated should be mentioned (e.g. ERASE AF (NEJM), STABLE SR (JACC EP), MiLINE Study (Heart Rhythm))**

Thank you for your thoughtful and constructive comments. We do agree with the reviewer's comments.

**Reply 7:** We have carefully read the research evidence you have provided and cited these four references to the introduction and discussion sections.

**Changes in the text:** Two references you suggested are supplemented in the 8th and 9th references in the introduction section, respectively (**see Page 5, line 108-110**). The other two references are supplemented in the discussion section 17th and 18th references (**see Page 13, line 330-336**).

**Comment 8: Conclusions: The study concludes with an important point, that LASM shouldn't be underestimated in non-paroxysmal AF management. However, as the authors acknowledge, the understanding of the AF mechanism is not complete, and hence, definitive conclusions should be drawn with caution. The paper provides a thought-provoking insight into non-paroxysmal AF management, suggesting a potential shift of focus towards the atria. Future research with a larger randomized sample and long-term follow-up would further validate these findings.**

Thank you for your useful comments. We do agree with the reviewer's comments.

**Reply 8:** We have carefully read and understood your suggestions and revised the conclusion.

**Changes in the text:** we have modified our text in the "Conclusion" part in revised manuscript (**see Page 16, line 421-423**).

**Reply to the comments of reviewer B**

**Comment 9:** There does not appear to be any difference in the long term success rate of starting with left atrial ablation vs PVI (75.5% in the LASM first group and 71.2% in the PVI first group.). Please give Kaplan-Meier/ Cox regression curve for these groups. Please mention this in the discussion.

Thank you for your useful comments and we do agree with the reviewer's comments.

**Reply 9 :** We have carefully read and understood your suggestions and added the Kaplan-Meier survival curves. In addition, we have elaborated in the discussion section.

**Changes in the text:** In the revised manuscript, we added the relevant details in **Figure 2 (see Page 11, line 268-270; Page 34)**. In addition, we also mentioned in the "Discussion" section **(see Page 14, line 370-376)**.

**Comment 10:** Although baseline characteristics were not different among groups, the multivariate analysis with Cox regression analysis should be performed to adjust the impact of the covariate on the outcome of ablation.

Thank you for your useful comments and we do agree with the reviewer's comments.

**Reply 10:** We supplemented the results of Cox regression analysis. We constructed four different models by adjusting different covariates, and the results showed that none of the key covariates in this study were significant in predicting long-term recurrence of non-paroxysmal AF. This suggests that differences in baseline characteristics may have little effect on outcomes in the two groups after sequential ablation.

**Changes in the text:** In the revised manuscript, we added the relevant details in **Table 3 (see Page 26; Page 11, line 271-272)**.

**Comment 11:** One of the main results of this study is the difference in outcomes between those patients with AF termination versus those with not. Baseline characteristics of these two groups should be given to ascertain if there are any predictive factors for AF termination or confounders.

Thank you for your useful comments and we do agree with the reviewer's comments.

**Reply 11:** By comparing the baseline characteristics of the two groups, only the number of ablation points and BNP were statistically different. Among them, BNP was higher in the AF termination group, and the ablation points were higher in the non-termination group, and we explained these results in the discussion section. As was the concern of the reviewers, whether these differences in baseline characteristics were predictive or confounding factors for the termination of atrial fibrillation, we performed cox regression to answer these questions, and no confounding was found.

**Changes in the text:** 1. We describe these results in the “**Results**” part in revised manuscript (see **Page 11, line 277-280**). 2. The baseline data of the two groups were statistically analyzed (**Table 4, see Page 28**). In the revised manuscript, we added the relevant details of the Cox regression analysis in **Table 5 (see Page 29; Page 11, line 280-282)**.

**Comment 12: There are some limitations including being a single centre study and the discontinuous monitoring which underestimates AF recurrence which should be mentioned in the discussion.**

Thank you for your useful comments and we do agree with the reviewer's comments.

**Reply 12:** Single-center studies and discontinuous monitoring underestimated atrial fibrillation recurrence, which we have included in the article limitations.

Changes in the text: 1. we have modified our text in the “**Limitation**” part in revised manuscript (see **Page 12, line 315; Page 13, line 321**).

**Comment 13: There are minor spelling mistakes.**

Thanks for your careful checking. We are very sorry for the spelling mistakes.

**Reply 13:** To avoid such mistakes as much as possible, we have selected medical writing service to check and correct the English words and grammar.

**Changes in the text:** Thanks to the editor for the helpful reminder, we have revised the paper. **Revised papers have been revised through the Medical Writing service, including spelling and grammatic-related checks (Below is the evidence).**

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MANUSCRIPT TITLE

**Acute and long-term outcomes of pulmonary vein isolation and ablation of low-voltage areas for non-paroxysmal atrial fibrillation**

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