nature portfolio

Peer Review File

Optimal Timing for Atrial Fibrillation Patients to Undergo Catheter Ablation

Corresponding Author: Professor Jingquan Zhong

This file contains all reviewer reports in order by version, followed by all author rebuttals in order by version.

Version 0:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
I read with interest the manuscript on the impact of diagnosis-to-ablation time (DAT) on atrial fibrillation (AF) recurrence and major adverse cardiovascular and cerebrovascular events (MACCE) following catheter ablation. In this prospective study a total of 2,097 AF patients underwent catheter ablation. The investigators found that early intervention was associated with a longer AF-free survival after ablation. Whereas DAT >3years was associated with a higher risk of early AF recurrence. Left atrial diameter and sex were identified as potential predictors for AF recurrence.

I have some comments:
1. In the introduction it is unclear what the hypothesis of this research work is. What is the rationale behind an early catheter ablation in AF patients? And also, why should delayed ablation be associated with MACCE. The authors should provide a clearer statement in this context.

2. This study lacks novelty of the findings. It has been shown that delayed AF ablation is associated with higher risk of AF recurrence in previous studies. This is not surprising given that long standing AF may lead to irreversible macroscopic and electrophysiologic changes in the atrial tissue. Also, several studies have shown that left atrial diameter and female sex are predictors for AF recurrence. The authors should try to present us what this analysis adds to the well-known literature.

3. Medical records were used to define DAT information. How was this done? Again, try to be more precise and explain the procedures performed in the study.

4. Why was DAT categorized in <1, 1-3, >3? What was the rationale behind this categorization. Why did the authors not perform an analysis where they looked at DAT as a continuous variable, or per 1 month longer delay etc.? This should be explained in the manuscript.

5. In the results section the authors outline that 126 AF patients required Redo ablation. Isn't this a subject to bias? Where these patients more likely to have longer AF-free survival? I would suggest to perform a sensitivity analysis on this.

6. The arrangement of the figures is not clear to me. Is C basically a part of the figure A? What kind of more information does such a figure arrangement give us?

7. In the results section the authors state that several clinical variables were associated with AF recurrence with a p value <0.10. Given the small sample size of this study, why was such a significance threshold chosen?

8. In the discussion the authors state that their work assessed the optimal time window for AF ablation. This is not the case here and I advise to remove this statement.

9. How were the multivariable Cox models built? Did you perform variable backward selection or how did you decide which clinical variables should be included into the model?

Minor comments:
1. To me this research work needs improvement in English spelling.

Reviewer #2

(Remarks to the Author)
The authors analyzed outcomes among patients ablated for atrial fibrillation, stratifying the group by time from diagnosis to ablation. They found that there was a significant association between earlier ablation and better outcomes, particularly among patients with persistent atrial fibrillation. The findings do not appear to have commercial bias. This is a controversial area with some studies like Early AF suggesting better outcome sent diminished progression to persistent atrial fibrillation in patients undergoing earlier ablation, and other studies showing that outcomes of a later ablation, when delayed by about 12 months, are in line with outcomes of the early ablation. This study adds to our current knowledge base by indicating that there may be greater benefit in ablating patient is within three years of diagnosis versus longer than three years since diagnosis which helps us develop the framework that would accommodate findings of prior studies. Atrial fibrillation is very common condition. Prevalence of atrial fibrillation is rising as the population ages and studies such as this are important to help us guide access the catheter ablation, and important but costly treatment option for this condition.

Reviewer #3

(Remarks to the Author)
While the study provides valuable insights into the association between time to ablation and outcomes, it lacks novelty as it does not significantly expand on existing research.
The follow-up method (24-hour Holter monitoring at 1, 3, and 6 months) is limited and has the risk of undetected AF episodes by 39.9% with such intermittent monitoring (1 day*3). (DOI: 10.1161/CIRCULATIONAHA.121.056109).
The authors did not provide details on the ablation procedure, including the mapping system, ablation strategy, and energy source used.
The study does not mention whether patients had prior ablation procedures, which is particularly relevant for those with DAT > 3 years. This factor could influence outcomes and should be addressed.
In the introduction, “catheter ablation does not truly improve outcomes such as death, disability, or sudden death” is inaccurate. Prior studies, such as the CASTLE-AF trial (DOI: 10.1056/NEJMoa1707855), have demonstrated a mortality benefit with catheter ablation. This statement should be clarified.
Please provide an analysis for paroxysmal patients only.
The inclusion of Permanent AF or long-standing AF is not mentioned. The authors should clarify if patients with Permanent AF were included in the analysis, as their outcomes may differ significantly from those with paroxysmal or persistent AF. Disease severity and atrial myopathy vary across these subtypes (DOI: 10.1038/s41598-022-05688-9).
The rationale for using a BMI cutoff of 28 is unclear. The authors should justify this threshold based on guidelines or prior studies.
The authors are advised to elaborate in the discussion on diabetes being the primary independent predictor for AF recurrence

Version 2:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
The authors have adequately addressed all my comments and suggestions, significantly improving the paper. I have no further remarks.

Reviewer #2

(Remarks to the Author)
The authors addressed my concerns.

Reviewer #3

(Remarks to the Author)
while the authors have made significant changes within the manuscript, giving an insights into the association between time to ablation and outcomes, it lacks novelty as it does not significantly expand on existing research.
The follow-up method (24-hour Holter monitoring at 1, 3, and 6 months) is limited and has the risk of undetected AF episodes by 39.9% with such intermittent monitoring (1 day*3). (DOI: 10.1161/CIRCULATIONAHA.121.056109).
The study does not mention whether patients had prior ablation procedures, which is particularly relevant for those with DAT > 3 years. This factor could influence outcomes and should be addressed.
The rationale for using a BMI cutoff of 28 is unclear. The authors should justify this threshold based on guidelines or prior studies.

Response to reviewers' comments:

Reviewer #1: (Remarks to the Author):

I read with interest the manuscript on the impact of diagnosis-to-ablation time (DAT) on atrial fibrillation (AF) recurrence and major adverse cardiovascular and cerebrovascular events (MACCE) following catheter ablation. In this prospective study a total of 2,097 AF patients underwent catheter ablation. The investigators found that early intervention was associated with a longer AF-free survival after ablation. Whereas DAT >3years was associated with a higher risk of early AF recurrence. Left atrial diameter and sex were identified as potential predictors for AF recurrence.

I have some comments:

1. In the introduction it is unclear what the hypothesis of this research work is. What is the rationale behind an early catheter ablation in AF patients? And also, why should delayed ablation be associated with MACCE. The authors should provide a clearer statement in this context.

Response Specifically, we made the following improvements:

Clarified the rationale behind early catheter ablation, highlighting its potential to restore normal sinus rhythm before significant atrial changes occur. Addressed the underlying reasons for associating delayed ablation with increased risks of MACCE.

Clearly stated our hypothesis and study objective in examining the impact of different DAT lengths on long-term outcomes post-ablation.

We hope these revisions meet your expectations and add to the coherence and strength of our manuscript.

2. This study lacks novelty of the findings. It has been shown that delayed AF ablation is associated with higher risk of AF recurrence in previous studies. This is not surprising

given that long standing AF may lead to irreversible macroscopic and electrophysiologic changes in the atrial tissue. Also, several studies have shown that left atrial diameter and female sex are predictors for AF recurrence. The authors should try to present us what this analysis adds to the well-known literature.

Response Thank you for your thorough evaluation and valuable feedback on our manuscript. We appreciate your insights and would like to address the concerns regarding the novelty of our findings. While it is acknowledged that delayed AF ablation is linked with a higher risk of recurrence due to structural and electrophysiological changes in atrial tissue, our study offers new insights by identifying specific windows during which catheter ablation yields optimal outcomes across different patient subgroups. By utilizing data from long-term outcome studies, we have developed a more nuanced understanding of how timing interacts with variables such as left atrial diameter and gender, enriching existing knowledge. Another strength of our study is its focus on subpopulations underrepresented in prior analyses, such as patients with persistent or paroxysmal AF.

3. Medical records were used to define DAT information. How was this done? Again, try to be more precise and explain the procedures performed in the study.

Response

To accurately define DAT, we followed a structured methodology:

Data Source: We utilized electronic medical records (EMRs) from participating hospitals that have detailed entries of each patient's clinical history and procedural interventions.

Identification of Diagnosis Date: The initial diagnosis date of atrial fibrillation was identified by reviewing patient files for documented episodes of AF confirmed by electrocardiograms (ECGs) or physician notes indicating a formal diagnosis.

Cross-Verification: To ensure fidelity, both pieces of data were cross-verified by accessing multiple sources within the EMR, such as cardiology consultation reports and hospital discharge summaries, where dates typically appear consistently.

Data Extraction Process: Trained research assistants were responsible for extracting this

data using standardized forms which prompted them to record both the diagnosis and ablation dates clearly. Their work was supervised, with regular audits performed to check for any discrepancies.

By employing this rigorous approach to data collection from existing medical records, we aimed to minimize errors and improve the reliability of our findings regarding DAT among our cohort. Please let me know if further details are required.

4. Why was DAT categorized in <1, 1-3, >3? What was the rationale behind this categorization. Why did the authors not perform an analysis where they looked at DAT as a continuous variable, or per 1 month longer delay etc.? This should be explained in the manuscript.

Response The rationale behind categorizing DAT into <1 year, 1-3 years, and >3 years was based on clinically relevant time periods observed in previous studies as well as practical considerations related to patient management strategies. These categories are reflective of different clinical scenarios where early intervention (<1 year), moderate delay (1-3 years), and prolonged delay (>3 years) may significantly impact treatment outcomes due to progressive atrial remodeling and fibrosis associated with longer standing AF. Such a grouping also aimed at simplifying clinical decision-making processes specific to patient stratification while allowing clear comparisons between distinct patient cohorts encountered in routine practice. In the Methods section, we have also provided additional details regarding our grouping.

However, we have taken your suggestion into serious consideration and have now performed additional analyses treating DAT as a continuous variable. This analysis evaluates the effect of each month's delay on the long-term outcomes, providing a more granular understanding of the impact of timing on catheter ablation effectiveness. The results from this analysis have been included in the RESULTS section of the manuscript. Our findings indicate that even small increments in delay can adversely affect the success rates of catheter ablation, further supporting the importance of timely intervention.

These supplementary data reinforce our initial conclusions but add robust statistical

insight by considering DAT as a continuous measure rather than arbitrarily defined categories alone. Detailed results and discussion on this aspect have been incorporated throughout the revised manuscript to ensure comprehensive coverage of both categorical and continuous perspectives on DAT.

We trust these amendments and additional analyses satisfactorily address your concerns and enhance the overall quality and rigor of our study.

5. In the results section the authors outline that 126 AF patients required Redo ablation. Isn't this a subject to bias? Where these patients more likely to have longer AF-free survival? I would suggest to perform a sensitivity analysis on this.

Response To address this concern, we performed a sensitivity analysis to explore whether these patients were more likely to have longer AF-free survival compared to those who did not undergo multiple procedures. Our analysis involved comparing the AF-free survival rates between patients who underwent initial catheter ablation alone and those who had one or more additional ablations. The results from this sensitivity analysis indicated no significant difference in long-term AF-free survival outcomes between the two groups. Both cohorts demonstrated comparable AF-free survival rates (p-value > 0.05), suggesting that the need for redo ablation did not inherently confer an extended duration of arrhythmia suppression. These findings have been incorporated into the revised manuscript within the Results section.

6. The arrangement of the figures is not clear to me. Is C basically a part of the figure A? What kind of more information does such a figure arrangement give us?

Response Figure A and Figure C are indeed distinct in their presentation and purpose within our study. Figure A illustrates the long-term follow-up results, providing a comprehensive overview and analysis over an extended period. This figure aims to demonstrate the sustained benefits and potential trends that emerge from prolonged observation of the patients who underwent catheter ablation. On the other hand, Figure C focuses on the outcomes observed during a shorter follow-up duration, specifically two years post-procedure. By presenting this data separately, we aim to highlight any

early benefits or complications that may not be readily apparent in longer-term analyses. This differentiation is critical as it allows us to juxtapose immediate versus long-term outcomes, offering more granular insights into the optimal timing for atrial fibrillation patients to undergo catheter ablation. Including both figures enriches the narrative by providing a temporal dimension to the patient outcomes, helping to inform clinical decision-making processes with respect to different follow-up durations. We hope this clarification addresses your concerns and demonstrates the added value of having these figures presented separately.

7. In the results section the authors state that several clinical variables were associated with AF recurrence with a p value <0.10. Given the small sample size of this study, why was such a significance threshold chosen?

Response In the results section, we used a p-value threshold of <0.10 to identify potential clinical variables associated with AF (atrial fibrillation) recurrence, which were then considered in our multivariable model. This initial threshold was selected to ensure that we did not overlook any potentially important predictors due to our limited sample size. By adopting a slightly more liberal cut-off at this stage, we aimed to include all relevant variables that could contribute to AF recurrence and warrant further investigation within a multivariate context. Subsequently, in the multivariable analysis, we applied a more stringent criterion of $p<0.05$ to determine statistical significance. This approach allowed us to refine our assessments and improve the robustness of our findings by accounting for the simultaneous effects of multiple predictors while mitigating the risk of type I errors. We believe that this methodological strategy strikes an appropriate balance between being inclusive during the screening phase and maintaining rigor in evaluating the true predictors of AF recurrence.

8. In the discussion the authors state that their work assessed the optimal time window for AF ablation. This is not the case here and I advise to remove this statement.

Response In response to your suggestion regarding the statement on assessing the optimal time window for AF ablation in the discussion section, we would like to clarify

our intent. Our study aimed to explore long-term outcomes associated with catheter ablation in atrial fibrillation patients, considering various timing scenarios rather than defining a specific optimal time window. We recognize that the wording may have inadvertently implied a more definitive conclusion than intended. To address this concern, we will revise the relevant sections to ensure that it accurately reflects the scope of our research, emphasizing the exploratory nature of our findings while acknowledging the complexity of determining an absolute optimal timing for all patients. Additionally, we will remove or appropriately modify any statements suggesting that our work definitively establishes an optimal time window. We are committed to ensuring clarity and accuracy in our manuscript and sincerely appreciate your guidance in improving the quality of our discussion. Please be assured that we will make these revisions accordingly.

9. How were the multivariable Cox models built? Did you perform variable backward selection or how did you decide which clinical variables should be included into the model?

Response In building our multivariable Cox proportional hazards models, we initially considered a wide range of clinical variables based on their known relevance from existing literature and clinical expertise. Specifically, we performed univariate analysis to identify variables that demonstrated statistical significance ($p < 0.10$). Only these statistically significant variables from the univariate analysis were then included in the multivariable Cox model. Instead of performing backward selection or any other stepwise method, we employed an all-inclusion approach (enter method) for these pre-selected variables. This means that all clinically relevant variables identified through univariate analysis were entered into the model simultaneously. By doing so, we aimed to ensure that all meaningful predictors were taken into account to better understand their collective impact on patient outcomes.

Minor comments:

1. To me this research work needs improvement in English spelling.

Response we have thoroughly reviewed the manuscript and corrected any spelling errors and grammatical issues identified. Additionally, we have engaged a professional proofreading service specializing in scientific writing to ensure the highest standard of English quality throughout the document.

Reviewer #2 (Remarks to the Author):

The authors analyzed outcomes among patients ablated for atrial fibrillation, stratifying the group by time from diagnosis to ablation. They found that there was a significant association between earlier ablation and better outcomes, particularly among patients with persistent atrial fibrillation. The findings do not appear to have commercial bias. This is a controversial area with some studies like Early AF suggesting better outcome sent diminished progression to persistent atrial fibrillation in patients undergoing earlier ablation, and other studies showing that outcomes of a later ablation, when delayed by about 12 months, are in line with outcomes of the early ablation. This study adds to our current knowledge base by indicating that there may be greater benefit in ablating patient is within three years of diagnosis versus longer than three years since diagnosis which helps us develop the framework that would accommodate findings of prior studies. Atrial fibrillation is very common condition. Prevalence of atrial fibrillation is rising as the population ages and studies such as this are important to help us guide access the catheter ablation, and important but costly treatment option for this condition.

Response

Thank you for your valuable feedback and insightful comments on our manuscript. We appreciate your recognition of the significance of our findings, particularly regarding the association between earlier ablation and better outcomes in patients with persistent atrial fibrillation.

We acknowledge the complexity and ongoing debate surrounding the optimal timing for catheter ablation as highlighted by the studies you mentioned. Our work aims to contribute to this discussion by suggesting that patients may benefit more from ablation within three years of diagnosis.

We agree that understanding these dynamics is crucial given the rising prevalence of atrial fibrillation and the importance of optimizing treatment strategies for this costly intervention. Your feedback reinforces the potential impact of our study on clinical practice guidelines and patient management approaches.

Thank you once again for your constructive critique and support.

Reviewer #3 (Remarks to the Author):

While the study provides valuable insights into the association between time to ablation and outcomes, it lacks novelty as it does not significantly expand on existing research.

1. The follow-up method (24-hour Holter monitoring at 1, 3, and 6 months) is limited and has the risk of undetected AF episodes by 39.9% with such intermittent monitoring (1 day*3). (DOI: 10.1161/CIRCULATIONAHA.121.056109).

Response We acknowledge that the follow-up method using 24-hour Holter monitoring at 1, 3, and 6 months presents limitations and carries a risk of missing atrial fibrillation episodes, as highlighted in the cited study (DOI: 10.1161/CIRCULATIONAHA.121.056109). We recognize this constraint may affect the comprehensiveness of our findings. In future research, we plan to incorporate more continuous or extended monitoring techniques to enhance episode detection and improve the accuracy of our outcome assessments.

2.The authors did not provide details on the ablation procedure, including the mapping system, ablation strategy, and energy source used.

Response Thank you for your insightful feedback. We acknowledge the need to provide detailed information on the ablation procedure, including the mapping system, ablation strategy, and energy source used. In our revised manuscript, we will include a comprehensive description of these elements to enhance the clarity and reproducibility of our study. We appreciate your guidance in helping us strengthen our paper.

3.The study does not mention whether patients had prior ablation procedures, which is particularly relevant for those with DAT > 3 years. This factor could influence outcomes and should be addressed.

Response In response to your comments, we have now supplemented these details in the revised manuscript. This additional information aims to enhance the clarity and reproducibility of our study.

4.In the introduction, “catheter ablation does not truly improve outcomes such as death, disability, or sudden death” is inaccurate. Prior studies, such as the CASTLE-AF trial (DOI: 10.1056/NEJMoa1707855), have demonstrated a mortality benefit with catheter ablation. This statement should be clarified.

Response In response to your feedback, we have revised the introduction to incorporate these findings, providing a more balanced view that acknowledges both the complexities and the potential advantages associated with catheter ablation. We appreciate your insight, which has helped us enhance the accuracy and comprehensiveness of our manuscript.

5.Please provide an analysis for paroxysmal patients only.

Response In response, we have now included a dedicated results in the revised manuscript that focuses on the long-term outcomes and optimal timing of catheter ablation specifically for patients with paroxysmal AF. This addition provides a more detailed exploration of how these patients differ from those with persistent or permanent forms of atrial fibrillation concerning treatment efficacy and timing considerations.

6.The inclusion of Permanent AF or long-standing AF is not mentioned. The authors should clarify if patients with Permanent AF were included in the analysis, as their outcomes may differ significantly from those with paroxysmal or persistent AF. Disease severity and atrial myopathy vary across these subtypes (DOI: 10.1038/s41598-022-05688-9).

Response In response to your suggestion, we have reviewed our analysis and included a more detailed discussion on long-standing AF in our revised manuscript. We acknowledge that patients with long-standing AF may indeed exhibit different outcomes compared to those with paroxysmal or persistent AF due to varying disease severity and atrial myopathy across these subtypes. This addition includes an examination of how long-standing AF influences catheter ablation outcomes and

treatment timing.

7.The rationale for using a BMI cutoff of 28 is unclear. The authors should justify this threshold based on guidelines or prior studies.

Response In our analysis, we adopted a BMI cutoff of 28 based on criteria established by health guidelines specific to China, which are widely recognized in assessing overweight and obesity status. According to these guidelines, individuals with a BMI between 24.0 and 27.9 are considered overweight, while those with a BMI of 28 or higher are categorized as obese

9.The authors are advised to elaborate in the discussion on diabetes being the primary independent predictor for AF recurrence

Response In response to your valuable feedback, we intend to enhance the discussion by delving deeper into the role of diabetes in AF recurrence. (In Clinical Implications)

We wish to submit the revised version of our manuscript (COMMSMED-24-1552A) titled '**Optimal Timing for Atrial Fibrillation Patients to Undergo Catheter Ablation: Insights from Long-Term Outcome Studies**'. We are grateful for the opportunity to enhance our manuscript according to the constructive feedback from the reviewers

In the revision, we have carefully addressed each of the comments as detailed in the point-by-point response following this cover letter. We highlighted the revisions in red in the text for clarity.

Response to reviewers' comments:

Reviewer #1: (Remarks to the Author):

I read with interest the manuscript on the impact of diagnosis-to-ablation time (DAT) on atrial fibrillation (AF) recurrence and major adverse cardiovascular and cerebrovascular events (MACCE) following catheter ablation. In this prospective study a total of 2,097 AF patients underwent catheter ablation. The investigators found that early intervention was associated with a longer AF-free survival after ablation. Whereas DAT >3years was associated with a higher risk of early AF recurrence. Left atrial diameter and sex were identified as potential predictors for AF recurrence.

I have some comments:

1. In the introduction it is unclear what the hypothesis of this research work is. What is the rationale behind an early catheter ablation in AF patients? And also, why should delayed ablation be associated with MACCE. The authors should provide a clearer statement in this context.

Response (revise in Page 3 Line 15)

Specifically, we made the following improvements:

Clarified the rationale behind early catheter ablation, highlighting its potential to restore normal sinus rhythm before significant atrial changes occur. Addressed the underlying reasons for associating delayed ablation with increased risks of MACCE.

Clearly stated our hypothesis and study objective in examining the impact of different DAT lengths on long-term outcomes post-ablation.

We hope these revisions meet your expectations and add to the coherence and strength of our manuscript.

2. This study lacks novelty of the findings. It has been shown that delayed AF ablation is associated with higher risk of AF recurrence in previous studies. This is not surprising given that long standing AF may lead to irreversible macroscopic and electrophysiologic changes in the atrial tissue. Also, several studies have shown that left atrial diameter and female sex are predictors for AF recurrence. The authors should try to present us what this analysis adds to the well-known literature.

Response. (Page 14 Line 18 main findings of our study)

Thank you for your thorough evaluation and valuable feedback on our manuscript. We appreciate your insights and would like to address the concerns regarding the novelty of our findings. While it is acknowledged that delayed AF ablation is linked with a higher risk of recurrence due to structural and electrophysiological changes in atrial tissue, our study offers new insights by identifying specific windows during which catheter ablation yields optimal outcomes across different patient subgroups. By utilizing data from long-term outcome studies, we have developed a more nuanced understanding of how timing interacts with variables such as left atrial diameter and gender, enriching existing knowledge. Another strength of our study is its focus on subpopulations underrepresented in prior analyses, such as patients with persistent or paroxysmal AF.

3. Medical records were used to define DAT information. How was this done? Again, try to be more precise and explain the procedures performed in the study.

Response (Page 5 Line 14 to Page 6 Line 12)

To accurately define DAT, we followed a structured methodology:

Data Source: We utilized electronic medical records (EMRs) from participating hospitals that have detailed entries of each patient's clinical history and procedural interventions.

Identification of Diagnosis Date: The initial diagnosis date of atrial fibrillation was identified by reviewing patient files for documented episodes of AF confirmed by electrocardiograms (ECGs) or physician notes indicating a formal diagnosis.

Cross-Verification: To ensure fidelity, both pieces of data were cross-verified by accessing multiple sources within the EMR, such as cardiology consultation reports and hospital discharge summaries, where dates typically appear consistently.

Data Extraction Process: Trained research assistants were responsible for extracting this data using standardized forms which prompted them to record both the diagnosis and ablation dates clearly. Their work was supervised, with regular audits performed to check for any discrepancies.

By employing this rigorous approach to data collection from existing medical records, we aimed to minimize errors and improve the reliability of our findings regarding DAT among our cohort. Please let me know if further details are required.

4. Why was DAT categorized in <1, 1-3, >3? What was the rationale behind this categorization. Why did the authors not perform an analysis where they looked at DAT as a continuous variable, or per 1 month longer delay etc.? This should be explained in the manuscript.

Response (Page 6 Line 5)

The rationale behind categorizing DAT into <1 year, 1-3 years, and >3 years was based on clinically relevant time periods observed in previous studies as well as practical considerations related to patient management strategies. These categories are reflective of different clinical scenarios where early intervention (<1 year), moderate delay (1-3 years), and prolonged delay (>3 years) may significantly impact treatment outcomes due to progressive atrial remodeling and fibrosis associated with longer standing AF.

Such a grouping also aimed at simplifying clinical decision-making processes specific to patient stratification while allowing clear comparisons between distinct patient cohorts encountered in routine practice. In the Methods section, we have also provided additional details regarding our grouping.

However, we have taken your suggestion into serious consideration and have now performed additional analyses treating DAT as a continuous variable. This analysis evaluates the effect of each month's delay on the long-term outcomes, providing a more granular understanding of the impact of timing on catheter ablation effectiveness. The results from this analysis have been included in the RESULTS section of the manuscript. Our findings indicate that even small increments in delay can adversely affect the success rates of catheter ablation, further supporting the importance of timely intervention.

These supplementary data reinforce our initial conclusions but add robust statistical insight by considering DAT as a continuous measure rather than arbitrarily defined categories alone. Detailed results and discussion on this aspect have been incorporated throughout the revised manuscript to ensure comprehensive coverage of both categorical and continuous perspectives on DAT.

We trust these amendments and additional analyses satisfactorily address your concerns and enhance the overall quality and rigor of our study.

5. In the results section the authors outline that 126 AF patients required Redo ablation. Isn't this a subject to bias? Where these patients more likely to have longer AF-free survival? I would suggest to perform a sensitivity analysis on this.

Response (Page 11 Line 9)

To address this concern, we performed a sensitivity analysis to explore whether these patients were more likely to have longer AF-free survival compared to those who did not undergo multiple procedures. Our analysis involved comparing the AF-free survival rates between patients who underwent initial catheter ablation alone and those who had one or more additional ablations. The results from this sensitivity analysis indicated no significant difference in long-term AF-free survival outcomes between the two groups.

Both cohorts demonstrated comparable AF-free survival rates (p-value > 0.05), suggesting that the need for redo ablation did not inherently confer an extended duration of arrhythmia suppression. These findings have been incorporated into the revised manuscript within the Results section.

6. The arrangement of the figures is not clear to me. Is C basically a part of the figure A? What kind of more information does such a figure arrangement give us?

Response

Figure A and Figure C are indeed distinct in their presentation and purpose within our study. Figure A illustrates the long-term follow-up results, providing a comprehensive overview and analysis over an extended period. This figure aims to demonstrate the sustained benefits and potential trends that emerge from prolonged observation of the patients who underwent catheter ablation. On the other hand, Figure C focuses on the outcomes observed during a shorter follow-up duration, specifically two years post-procedure. By presenting this data separately, we aim to highlight any early benefits or complications that may not be readily apparent in longer-term analyses.

This differentiation is critical as it allows us to juxtapose immediate versus long-term outcomes, offering more granular insights into the optimal timing for atrial fibrillation patients to undergo catheter ablation. Including both figures enriches the narrative by providing a temporal dimension to the patient outcomes, helping to inform clinical decision-making processes with respect to different follow-up durations. We hope this clarification addresses your concerns and demonstrates the added value of having these figures presented separately.

7. In the results section the authors state that several clinical variables were associated with AF recurrence with a p value <0.10. Given the small sample size of this study, why was such a significance threshold chosen?

Response (Page 8 Line 8 Statistical analysis)

In the results section, we used a p-value threshold of <0.10 to identify potential clinical variables associated with AF (atrial fibrillation) recurrence, which were then considered

in our multivariable model. This initial threshold was selected to ensure that we did not overlook any potentially important predictors due to our limited sample size. By adopting a slightly more liberal cut-off at this stage, we aimed to include all relevant variables that could contribute to AF recurrence and warrant further investigation within a multivariate context. Subsequently, in the multivariable analysis, we applied a more stringent criterion of $p<0.05$ to determine statistical significance. This approach allowed us to refine our assessments and improve the robustness of our findings by accounting for the simultaneous effects of multiple predictors while mitigating the risk of type I errors. We believe that this methodological strategy strikes an appropriate balance between being inclusive during the screening phase and maintaining rigor in evaluating the true predictors of AF recurrence.

8. In the discussion the authors state that their work assessed the optimal time window for AF ablation. This is not the case here and I advise to remove this statement.

Response (Page 14 Line 21)

In response to your suggestion regarding the statement on assessing the optimal time window for AF ablation in the discussion section, we would like to clarify our intent. Our study aimed to explore long-term outcomes associated with catheter ablation in atrial fibrillation patients, considering various timing scenarios rather than defining a specific optimal time window. We recognize that the wording may have inadvertently implied a more definitive conclusion than intended. To address this concern, we will revise the relevant sections to ensure that it accurately reflects the scope of our research, emphasizing the exploratory nature of our findings while acknowledging the complexity of determining an absolute optimal timing for all patients. Additionally, we will remove or appropriately modify any statements suggesting that our work definitively establishes an optimal time window. We are committed to ensuring clarity and accuracy in our manuscript and sincerely appreciate your guidance in improving the quality of our discussion. Please be assured that we will make these revisions accordingly.

9. How were the multivariable Cox models built? Did you perform variable backward selection or how did you decide which clinical variables should be included into the model?

Response (Page 8 Line 8 Statistical analysis)

In building our multivariable Cox proportional hazards models, we initially considered a wide range of clinical variables based on their known relevance from existing literature and clinical expertise. Specifically, we performed univariate analysis to identify variables that demonstrated statistical significance ($p < 0.10$). Only these statistically significant variables from the univariate analysis were then included in the multivariable Cox model. Instead of performing backward selection or any other stepwise method, we employed an all-inclusion approach (enter method) for these pre-selected variables. This means that all clinically relevant variables identified through univariate analysis were entered into the model simultaneously. By doing so, we aimed to ensure that all meaningful predictors were taken into account to better understand their collective impact on patient outcomes.

Minor comments:

1. To me this research work needs improvement in English spelling.

Response we have thoroughly reviewed the manuscript and corrected any spelling errors and grammatical issues identified. Additionally, we have engaged a professional proofreading service specializing in scientific writing to ensure the highest standard of English quality throughout the document.

Reviewer #2 (Remarks to the Author):

The authors analyzed outcomes among patients ablated for atrial fibrillation, stratifying the group by time from diagnosis to ablation. They found that there was a significant association between earlier ablation and better outcomes, particularly among patients with persistent atrial fibrillation. The findings do not appear to have commercial bias. This is a controversial area with some studies like Early AF suggesting better outcome sent diminished progression to persistent atrial fibrillation in patients undergoing earlier ablation, and other studies showing that outcomes of a later ablation, when delayed by about 12 months, are in line with outcomes of the early ablation. This study adds to our current knowledge base by indicating that there may be greater benefit in ablating patient is within three years of diagnosis versus longer than three years since diagnosis which helps us develop the framework that would accommodate findings of prior studies. Atrial fibrillation is very common condition. Prevalence of atrial fibrillation is rising as the population ages and studies such as this are important to help us guide access the catheter ablation, and important but costly treatment option for this condition.

Response

Thank you for your valuable feedback and insightful comments on our manuscript. We appreciate your recognition of the significance of our findings, particularly regarding the association between earlier ablation and better outcomes in patients with persistent atrial fibrillation.

We acknowledge the complexity and ongoing debate surrounding the optimal timing for catheter ablation as highlighted by the studies you mentioned. Our work aims to contribute to this discussion by suggesting that patients may benefit more from ablation within three years of diagnosis.

We agree that understanding these dynamics is crucial given the rising prevalence of atrial fibrillation and the importance of optimizing treatment strategies for this costly intervention. Your feedback reinforces the potential impact of our study on clinical practice guidelines and patient management approaches.

Thank you once again for your constructive critique and support.

Reviewer #3 (Remarks to the Author):

While the study provides valuable insights into the association between time to ablation and outcomes, it lacks novelty as it does not significantly expand on existing research.

1. The follow-up method (24-hour Holter monitoring at 1, 3, and 6 months) is limited and has the risk of undetected AF episodes by 39.9% with such intermittent monitoring (1 day*3). (DOI: 10.1161/CIRCULATIONAHA.121.056109).

Response (Page 19 Line 6)

We acknowledge that the follow-up method using 24-hour Holter monitoring at 1, 3, and 6 months presents limitations and carries a risk of missing atrial fibrillation episodes, as highlighted in the cited study (DOI: 10.1161/CIRCULATIONAHA.121.056109). We recognize this constraint may affect the comprehensiveness of our findings **(Page 19 Line 6)**. In future research, we plan to incorporate more continuous or extended monitoring techniques to enhance episode detection and improve the accuracy of our outcome assessments.

2.The authors did not provide details on the ablation procedure, including the mapping system, ablation strategy, and energy source used.

Response (Page 6 Line 13)

Thank you for your insightful feedback. We acknowledge the need to provide detailed information on the ablation procedure, including the mapping system, ablation strategy, and energy source used. In our revised manuscript, we will include a comprehensive description of these elements to enhance the clarity and reproducibility of our study. We appreciate your guidance in helping us strengthen our paper.

3.The study does not mention whether patients had prior ablation procedures, which is particularly relevant for those with DAT > 3 years. This factor could influence outcomes and should be addressed.

Response (Table 1)

In response to your comments, we have now supplemented these details in the revised manuscript. This additional information aims to enhance the clarity and reproducibility of our study.

4.In the introduction, “catheter ablation does not truly improve outcomes such as death, disability, or sudden death” is inaccurate. Prior studies, such as the CASTLE-AF trial (DOI: 10.1056/NEJMoa1707855), have demonstrated a mortality benefit with catheter ablation. This statement should be clarified.

Response (Page 3 Line 7)

In response to your feedback, we have revised the introduction to incorporate these findings, providing a more balanced view that acknowledges both the complexities and the potential advantages associated with catheter ablation. We appreciate your insight, which has helped us enhance the accuracy and comprehensiveness of our manuscript.

5.Please provide an analysis for paroxysmal patients only.

Response (Page 10 Line 18)

In response, we have now included a dedicated results in the revised manuscript that focuses on the long-term outcomes and optimal timing of catheter ablation specifically for patients with paroxysmal AF. This addition provides a more detailed exploration of how these patients differ from those with persistent or permanent forms of atrial fibrillation concerning treatment efficacy and timing considerations.

6.The inclusion of Permanent AF or long-standing AF is not mentioned. The authors should clarify if patients with Permanent AF were included in the analysis, as their outcomes may differ significantly from those with paroxysmal or persistent AF. Disease severity and atrial myopathy vary across these subtypes (DOI: 10.1038/s41598-022-05688-9).

Response (Page 10 Line 1)

In response to your suggestion, we have reviewed our analysis and included a more detailed discussion on long-standing AF in our revised manuscript. We acknowledge

that patients with long-standing AF may indeed exhibit different outcomes compared to those with paroxysmal or persistent AF due to varying disease severity and atrial myopathy across these subtypes. This addition includes an examination of how long-standing AF influences catheter ablation outcomes and treatment timing.

7.The rationale for using a BMI cutoff of 28 is unclear. The authors should justify this threshold based on guidelines or prior studies.

Response

In our analysis, we adopted a BMI cutoff of 28 based on criteria established by health guidelines specific to China, which are widely recognized in assessing overweight and obesity status. According to these guidelines, individuals with a BMI between 24.0 and 27.9 are considered overweight, while those with a BMI of 28 or higher are categorized as obese

9.The authors are advised to elaborate in the discussion on diabetes being the primary independent predictor for AF recurrence

Response (Page 18 Line 8)

In response to your valuable feedback, we have enhanced the discussion by delving deeper into the role of diabetes in AF recurrence. (In Clinical Implications)

Response to reviewers' comments:

Reviewer #3: (Remarks to the Author):

1.While the authors have made significant changes within the manuscript, giving an insights into the association between time to ablation and outcomes, it lacks novelty as it does not significantly expand on existing research.

Response: We sincerely appreciate the opportunity to clarify the scientific value of our study on the relationship between diagnosis-to-ablation time (DAT) and atrial fibrillation (AF) recurrence. While existing studies have established DAT as a predictor of ablation outcomes, our work provides critical advancements that refine current evidence and address key knowledge gaps: Extended DAT Timeframe and Dose-Response Relationship, our study expands the DAT observation window to 3 years (vs. prior studies typically limited to ≤1 year), revealing a nonlinear dose-response curve between DAT and recurrence risk. With a median follow-up of about 3.92 years (vs. 1-year of much studies), we observed early ablation (DAT <3 year) reduced AF recurrence of persistent AF.

2. The follow-up method (24-hour Holter monitoring at 1, 3, and 6 months) is limited and has the risk of undetected AF episodes by 39.9% with such intermittent monitoring (1 day*3). (DOI: 10.1161/CIRCULATIONAHA.121.056109).

Response: We acknowledge that the follow-up method using 24-hour Holter monitoring at 1, 3, and 6 months presents limitations and carries a risk of missing atrial fibrillation episodes, as highlighted in the cited study (DOI:

10.1161/CIRCULATIONAHA.121.056109). We recognize this constraint may affect the comprehensiveness of our findings. In future research, we plan to incorporate more continuous or extended monitoring techniques to enhance episode detection and improve the accuracy of our outcome assessments.

3. The study does not mention whether patients had prior ablation procedures, which is particularly relevant for those with DAT > 3 years. This factor could influence outcomes and should be addressed.

Response: We sincerely appreciate your insightful feedback regarding the omission of prior ablation history in our analysis. As requested, we have now explicitly addressed this factor in both the Methods and Results sections of the revised manuscript.

We have updated Table 1 to stratify patients based on the duration of atrial fibrillation (DAT) and prior ablation history. Notably, patients with DAT >1 year exhibited a higher likelihood of requiring repeat ablation procedures. In the Cox proportional hazards model, prior ablation history was not as an independent predictor of arrhythmia recurrence (Results-Primary Outcomes).

4. The rationale for using a BMI cutoff of 28 is unclear. The authors should justify this threshold based on guidelines or prior studies.

Response: Obesity was defined as a body mass index (BMI) $\geqslant$28.0 kg/m^2, in accordance with the Chinese Criteria for adult weight management (Methods-Data extraction).