Peer Review File

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Round 1

Reviewer A

General Comments:
This is a well-conducted retrospective, multicenter, observational study evaluating early restenosis rates after tracheal or laryngotracheal resection in patients with COVID-19-related tracheal stenosis. The topic is highly relevant and timely, given the increasing recognition of post-COVID airway complications. The study's strengths include its multicenter design, relatively large sample size for this specific population, and systematic follow-up with bronchoscopic assessments.

The manuscript is generally well written, with adequate statistical analysis. The findings are relevant, but are not necessarily novel.
However, there are some points that merit clarification or revision before publication.

Major Points:

Comment 1: Definition of Early Restenosis:
The manuscript defines early restenosis as occurring at a mean of 34 days postoperatively but does not explicitly set a time boundary for what constitutes “early”. It would be beneficial to clearly define the temporal threshold for early vs. late restenosis in the Methods section.

Reply 1: We thank the reviewer for this insightful comment. We agree that providing an explicit temporal definition of “early” restenosis enhances clarity and reproducibility. Accordingly, we have amended the *Methods* section (subsection 2.4 – Follow-up) to include the following statement:

“Early restenosis was defined as a symptomatic tracheal narrowing >50%, confirmed endoscopically, occurring within 90 days from surgery. Restenosis occurring beyond this period was considered late.”

To maintain consistency throughout the manuscript, this definition has also been incorporated into the *Abstract* (Results section), where the term “early restenosis” is first introduced. The 90-day threshold was selected based on existing literature suggesting that the majority of restenosis events following tracheal surgery occur within the first three postoperative months.

We believe this clarification strengthens the methodological rigor of our study.

Changes in the text: see page 2, line 55 and see page 5, lines 137-139.

Comment 2: Selection Criteria:
Although the inclusion and exclusion criteria are generally described, it would be important to clarify how "tracheal stenosis related to COVID-19" was defined, beyond the association with prior mechanical ventilation for COVID-19.

There are studies suggesting that COVID-19 is a completely new etiology for tracheal stenosis, as it could cause stenosis even without intubation. Thus, to differentiate stenosis due to covid-19 or post-intubation after covid-19 is a difficult task.

Reply 2: We thank the reviewer for this important and nuanced observation. We fully acknowledge the growing body of literature suggesting that SARS-CoV-2 infection may induce tracheal injury and stenosis independently of mechanical trauma, via inflammatory or microvascular mechanisms. However, to ensure diagnostic consistency across participating centers and avoid ambiguity, our study only included patients who developed tracheal or laryngotracheal stenosis following documented invasive mechanical ventilation (IMV) for COVID-19.
To clarify this point, we have revised the *Study Population* section (2.1) to explicitly state the following:
"For the purpose of this study, COVID-19-related tracheal stenosis was defined as a stenosis developing following documented episode of IMV (endotracheal intubation and/or tracheostomy) administered for acute respiratory failure due to SARS-CoV-2 infection. Patients with TS unrelated to IMV, including idiopathic or presumed inflammatory causes without a history of intubation, were excluded."
We believe this clarification better delineates the population studied and avoids conflating pathophysiologically distinct forms of stenosis. Furthermore, it enhances reproducibility and facilitates comparison with similar cohorts in future research.

Changes in the text: see page 4, lines 106-112

Comment 3: Heterogeneity of Surgical Techniques:
Given the multicenter nature of the study, potential variations in surgical techniques, perioperative care, and follow-up protocols across centers may introduce heterogeneity. The authors mention that standardized protocols were applied but should provide more detail about how surgical and follow-up protocols were harmonized across centers.

Reply 3: We thank the reviewer for raising this important point. We acknowledge that the multicenter design of the study may inherently introduce variability in surgical approaches and perioperative management. To address this, we made a deliberate effort to harmonize protocols across all participating centers prior to study initiation.
We have now clarified these harmonization efforts in the *Methods* section (subsection 2.3 – Surgical management and 2.4 – Follow-up) to ensure transparency and reproducibility.

Changes in the text 3: See, page 4, lines 127-132. See page 5, lines 137-142

Comment 4: Impact of Inflammatory Markers:
Although inflammatory markers (NLR, PLR) were collected, their potential role as predictors of restenosis is not extensively analyzed or discussed, despite the acknowledged pathophysiological relevance of inflammation in post-COVID airway disease. A more in-depth analysis or discussion would strengthen the manuscript.

Reply 4: We thank the Reviewer for this valuable comment. We agree that the role of systemic inflammation in the pathophysiology of post-COVID-19 airway disease is critical and deserves more attention. In our study, we prospectively collected data on inflammatory markers such as neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) and included them in the univariate Cox regression analysis to evaluate their predictive value for early restenosis. However, neither NLR nor PLR reached statistical significance in the univariate analysis and were thus not included in the final multivariable model due to the small number of restenosis events.
Nonetheless, in response to the Reviewer's suggestion, we have expanded the Discussion section to better contextualize these findings and to underline the pathophysiological rationale for including these markers, even though they did not emerge as independent predictors in our cohort. We also emphasize the need for further studies with larger sample sizes to explore the possible role of molecular or histological inflammatory biomarkers (e.g., IL-6, TGF-β) in predicting restenosis.
A new paragraph has been added to the Discussion

Changes in the text 4: See, page 9, lines 281-289.

Comment 5: Sample Size and Power:
The study identified only 8 restenosis events. While the multivariate analysis was appropriately parsimonious, the low number of events may affect the robustness of the conclusions. The authors should acknowledge this limitation more explicitly in the Discussion.

Reply 5: We thank the Reviewer for this important observation. We agree that the small number of restenosis events limits the robustness and generalizability of the multivariate analysis. This limitation has already been explicitly acknowledged in the Discussion section, where we caution against overinterpretation of individual covariate estimates due to potential overfitting. We believe this paragraph appropriately addresses the concern and reflects our commitment to a cautious and balanced interpretation of the data.

Changes in the text 5: no changes made.

Comment 6: Histopathological Analysis:
The authors refer to literature regarding histopathological findings in COVID-19-related tracheal lesions but did not perform any histological analysis in their own cohort. It would be valuable to clarify whether any histological samples were reviewed or if such analysis was considered.

Reply 6:

We thank the Reviewer for raising this important point. Histopathological examination of resected tracheal specimens was performed as part of routine clinical practice in all participating centers. These samples were reviewed by local pathologists according to institutional protocols. However, no consistent or distinctive histopathological patterns attributable specifically to SARS-CoV-2 infection were identified.

The predominant findings included chronic inflammation, fibrosis, and ischemic cartilage degeneration—features that are also frequently observed in tracheal stenoses unrelated to COVID-19. Therefore, we did not perform a centralized or systematic histological re-evaluation of all specimens, as our primary focus was on clinical outcomes and predictors of restenosis. Nevertheless, we agree that dedicated histopathological or molecular studies would be valuable to further investigate potential tissue-level differences in this unique patient population.

We have chosen not to include this analysis in the manuscript, as it did not reveal novel findings beyond what has already been reported in the literature.

Changes in the text 6: no changes made.

Minor Points:

Abstract:
The p-values and hazard ratios in the abstract should be reported with confidence intervals for consistency with the main text.

Reply abstract: We thank the Reviewer for this helpful suggestion. We agree that reporting confidence intervals (CIs) alongside hazard ratios (HRs) in the abstract improves clarity and ensures consistency with the main text. Accordingly, we have revised the abstract to include the 95% confidence intervals for the two independent predictors of early restenosis

Changes in the text: see abstract, page 2, lines 58-59.

Figures/Tables:
The tables are comprehensive. However, a flowchart depicting patient selection, inclusion, and follow-up would improve clarity and adherence to STROBE recommendations.

Reply Figures/Tables:

We thank the Reviewer for this constructive suggestion. In response, we have created a flowchart that illustrates patient selection, inclusion criteria, and follow-up timeline, in line with the STROBE guidelines. This figure has been added to the revised manuscript as **Figure 1**. We believe it enhances the clarity of the study design and patient flow, especially considering the multicenter nature of the cohort.

A corresponding reference to the figure has also been included in the **Methods** section (Study population).

Changes in the text: see, page 4, lines 111-112

Language:
The manuscript is overall well-written; minor grammatical adjustments may improve flow, e.g., "necessitating prolonged high-dose steroid use" could be rephrased to "often requiring prolonged high-dose steroid therapy."

Reply Language:

We thank the Reviewer for the positive feedback on the overall writing quality and for the helpful stylistic suggestion. We have revised the phrase as recommended, changing "necessitating prolonged high-dose steroid use" to "often requiring prolonged high-dose steroid therapy" in the Introduction to improve clarity and flow. We also carefully reviewed the manuscript for other minor grammatical and stylistic improvements and made appropriate adjustments where needed.

Changes in the text: see, page 2, lines 83

Reviewer B

This study seeks to provide evidence to guide surgical management and follow-up strategies for COVID-19 patients with tracheal stenosis after invasive mechanical ventilation. The purpose of this multicenter study is interesting, and this manuscript is well written; however, the study has some statistical limitations that the authors understandably mention in the last paragraph in the section "Discussion".
In "2.6 Statistical analysis", the authors defined that "Variables with a p-value < 0.1 in univariate analysis were considered for inclusion in the multivariate model.", but there are no variables even with a p-value < 0.1, except "In-hospital stay" in Tables 1-3.

Therefore, I suppose there is no meaning in doing a multivariate analysis, and the reason is unclear as to why the maximum of three covariates (age, diabetes, preoperative endoscopic treatment) were chosen along with clinically relevant factors suggested by prior literature. The statistical data used to derive the results of this study are unclear because of a small event sample, which makes the results unreliable.

Reply to reviewer B

Thank you for your comment. We acknowledge that the original statement in the manuscript was misleading. In fact, as correctly observed, we considered variables with a p-value < 0.2 in the univariate analysis, rather than < 0.1, to allow for a more inclusive multivariable model. Furthermore, we also included a limited number of clinically important variables, such as age, diabetes, and preoperative endoscopic treatment, based on prior literature and clinical relevance, even if they did not reach statistical significance in univariate testing. These factors have been consistently reported in previous studies to influence airway restenosis risk. We have replaced Table 4 with a revised version that includes all the variables analyzed in the multivariable model. Moreover, we revised the “Statistical Analysis” section accordingly. In addition, we clarified in the Discussion that, due to the limited number of restenosis events (n = 8), the multivariable Cox model was intended to be exploratory, and its results should be interpreted with caution.

The statistical paragraph was changed as follows: "Variables with a p-value < 0.2 in univariate analysis were considered for inclusion in the multivariable Cox regression model. In addition, variables deemed clinically relevant based on existing literature and expert opinion—such as age, diabetes, preoperative endoscopic treatment, sex, tracheostomy, duration of intubation, and surgical approach—were included to avoid underadjustment. The multivariable model was considered exploratory given the small number of restenosis events."

Changes in the text: see, page 5, lines 157-162

Round 2

Reviewer A

The authors present a prospective multi-institutional study of patients that underwent tracheal or laryngotracheal resection and reconstruction to address post-intubation (laryngo)tracheal stenosis after invasive mechanical ventilation used in the management of respiratory failure induced by COVID-19 from 2020-2023. Importantly, they focused on rates of early re-stenosis (within 90 days) and factors associated with it. In total, 90 patients underwent surgery during the study period with a 9% rate of early re-stenosis. The authors identified that prior endoscopic procdeures and diabetes as a comorbidity significantly increased the risk of early re-stenosis.

MAJOR POINTS:

Comment 1: What was the overall rate of re-stenosis? The authors present the rate of early re-stenosis (within 90 days) but do not present data on "late" stenosis (>90 days after surgery) during follow-up. This information should be available given the prospective nature of the study and the bronchoscopic surveillance described up to 12-18 months.

Reply 1: We thank the reviewer for this insightful comment. We acknowledge that late restenosis is an important clinical concern. However, we would like to clarify that the primary objective of our study was to evaluate early restenosis, defined as recurrence occurring within 90 days after surgery. This choice was based on both clinical and methodological considerations. From a clinical standpoint, early restenosis is often associated with technical, healing-related, or inflammatory factors, and is more likely to require prompt intervention. Methodologically, focusing on early events allowed us to maintain consistency in endpoint definitions and ensure data completeness within a standardized follow-up window across all centers.

Although bronchoscopic surveillance was scheduled up to 12 months, and some patients were followed longer, data beyond the 90-day window were not uniformly complete at the time of final analysis and therefore were not included as a prespecified outcome. We agree that a separate analysis of late restenosis could provide additional insight and will consider this for future investigations as follow-up matures.

Changes in the text: We have added the following sentence in the text to better reflect the study's primary focus and limitations: "It is worth noting that this study focused primarily on early restenosis, defined as occurring within 90 days postoperatively, which was the prespecified primary endpoint. While bronchoscopic surveillance extended beyond this period, data on late restenosis were not uniformly complete across all centers at the time of analysis, and were therefore not included in the primary outcome evaluation. Further studies with longer follow-up are warranted to assess the incidence and predictors of late restenosis." (see Discussion, Page 10, lines 307-314)

Comment 2: Table 2, localization. How do they define laryngo-tracheal and subglottic? How are these categories different from each other?

Reply 2: We thank the reviewer for this important question. In our classification:

- Subglottic stenosis was defined as a lesion confined to the subglottic region, i.e., the portion of the airway between the vocal cords and the first tracheal ring, without extension into the cervical trachea.
- Laryngotracheal stenosis referred to a combined lesion involving both the subglottic space and the upper cervical trachea.

Changes in the text: These definitions have now been added to the Methods section and to the legend of Table 2 for clarity. (see Patients and Methods, section 2.2, Page 4-5, lines 131-137. See table 2)

Comment 3: If there were 11 patients with laryngo-tracheal localization, and 27 patients with subglottic localization of the stenosis, how do the authors explain that only 4 patients had a laryngotracheal resection?

Reply 3:

Thank you for this valuable observation. Although 38 patients presented with stenoses localized in the subglottic or laryngotracheal region, laryngotracheal resection (LTR) was performed only in 4 cases. This is because LTR was indicated only when the subglottic mucosa or cricoid cartilage was significantly involved, requiring resection of part of the laryngeal framework (i.e., cricotracheal resection).
In the remaining cases, although the stenosis was anatomically high, it predominantly involved the upper trachea, and a standard tracheal resection was sufficient and preferred in order to preserve laryngeal function and reduce the risk of postoperative dysphonia.
This reflects a shared, conservative surgical approach adopted by all participating centers.

Changes in the text:
We have clarified this point in the Methods section (see patients and methods 2.3 Page 5, lines 143-147).

Comment 4:
The authors have failed to make a compelling argument of how these findings are relevant now that the pandemic is over. The identification of risk factors for re-stenosis is interesting but not novel. Do they recommend treating COVID-19 related tracheal stenosis differently than other cases of post-intubation tracheal stenosis? Did they change their approach to patient selection or surgical technique? I think they need to more strongly answer the “so what?” question.

Reply 4:

We thank the reviewer for this critical and highly constructive comment.
Although the acute phase of the COVID-19 pandemic has passed, its consequences on airway pathology continue to be clinically relevant. Referral centers are still seeing a considerable number of patients with tracheal stenosis related to COVID-19, many of whom were misdiagnosed or managed suboptimally during or after the pandemic and are now presenting with complex or recurrent airway lesions.
Our study shows that in this specific cohort, the risk of early restenosis is significantly increased in patients with prior endoscopic treatments and in those with diabetes—two factors that remain crucial in tailoring treatment decisions. While these risk factors are not unique to COVID-19-related stenosis, their cumulative impact appears to be particularly detrimental in this subgroup. Therefore, our findings support a differentiated approach to these patients, including:

- Earlier surgical referral to minimize the number of endoscopic procedures prior to definitive treatment;
- Careful preoperative assessment of metabolic comorbidities, especially diabetes;
- Structured postoperative bronchoscopic follow-up, especially within the first 90 days, when restenosis is more likely to occur.

While we did not change our surgical technique per se, our clinical approach evolved during the study period to reflect these considerations.
We have now clarified and reinforced this perspective in the Discussion section, as suggested.

Changes in the text:
We have clarified this point in the Discussion section (see Discussion, Page 9-10, lines 292-300).

Comment 5:
The authors conclude that close endoscopic surveillance is important. Please, expand on this. Their definition of re-stenosis includes that patients must be symptomatic. Would it be reasonable to follow up patients clinically, and only perform endocopic evaluation in those that develop symptoms?

Reply 5:

We thank the reviewer for this important point. We agree that a symptom-driven follow-up strategy could potentially reduce the burden of routine endoscopic evaluations. However, our findings indicate that restenosis may develop early (mean onset 34 days) and can remain subclinical in its initial phase, with symptoms appearing only when the airway lumen is significantly compromised (>50%). Relying solely on clinical symptoms may therefore delay detection and treatment, leading to sudden respiratory deterioration and potentially more complex interventions. Our surveillance protocol (bronchoscopic evaluations at 1, 3, 6, and 12 months) was designed to detect early anastomotic narrowing before clinical symptoms emerge, enabling timely dilatation or other minor interventions to prevent progression to severe restenosis. While the necessity of such a tight schedule could be debated, particularly in low-risk patients, our experience suggests that at least one routine bronchoscopy within the first 90 days postoperatively is critical, especially for patients with known risk factors (e.g., diabetes or prior endoscopic treatment).

We have expanded the Discussion to clarify our rationale and the balance between clinical and endoscopic follow-up.

Changes in the text:
We have clarified this point in the Discussion section (See Discussion, Page 9- 10, line 301-306).

MINOR POINTS:
Comment 6
I recommend adding the following references to the discussion
https://pubmed.ncbi.nlm.nih.gov/33856373/ - one of the first reports on surgery for COVID-19 related tracheal stenosis from a large volume center. First published in April of 2021.

https://pubmed.ncbi.nlm.nih.gov/31299233/ - large series showing the detrimental effect of prior endoscopic interventions on outcomes
Reply 6:
We thank the reviewer for this valuable suggestion. We have now added the recommended references to the Discussion section
Changes in the text:
See added references 19 and 12

Reviewer B

This multicenter, prospective observational study assessed the outcomes of tracheal or laryngotracheal resection and anastomosis (TRA) in patients with tracheal stenosis (TS) following invasive mechanical ventilation for COVID-19. The primary endpoint was restenosis, and secondary endpoints included complication rates and in-hospital mortality. The study included 90 adult patients (mean age, 58.4 years; 62% male), with most (81%) developing post-tracheostomy TS. The principal findings of the study were: Early restenosis occurred in 8 patients (8.8%) within an average of 34 days post-operatively. Major complications occurred in 6.6%, and minor complications in 16.6%. The risk factors for early restenosis were prior endoscopic treatment and diabetes.

The abstract is concise and contains the essential data and conclusions of the study.

The Introduction is well written and outlines the prothrombotic state and microvascular disease caused by COVID-19 in patients as well as the virus's ability to harm the tracheal and esophageal mucosa. The authors claim this study as the first multicenter study of significant size with long-term follow-up, investigating the rate of tracheal restenosis after surgery.

<u>Comment 1:</u>

The Methods section of this observational, multicenter study is generally well-structured, however, several strengths, limitations, and there is room for methodological refinement. The multicentric prospective design of the study involving five high-volume thoracic surgery centers enforces the generalizability of findings, strengthens the external validity of the results and reduces the bias. The inclusion criteria are specific (TS after IMV for COVID-19, confirmed by RT-PCR), and non-COVID or idiopathic cases were excluded, enhancing the internal validity. Shared surgical principles and uniform postoperative bronchoscopic follow-up (1, 3, 6, 12 months) reduce inter-center variability and increase consistency in outcome assessment. The statistical analysis and methods are appropriate with the use of Kaplan–Meier for recurrence-free survival, Cox regression modeling for risk factor analysis, and clear inclusion of both statistically significant and clinically relevant variables.

The methodological limitations are the lack of detail on standardization of surgical technique across the centers, despite the fact that the "shared principles" were mentioned, it is not clear to what extent intraoperative variables (e.g., tension management, use of buttressing, resection length thresholds) were standardized or audited across centers, which could introduce performance bias and interference with the results obtained which are good nevertheless (8.8% restenosis).

The duration of intubations was quite variable between the groups which may have contributed to the lack of statistical significance. The time interval between intubation and stenosis is not specified. Some patients may have developed TS months later, possibly confounded by other factors such as re-tracheostomy, reinfection, comorbidities.

<u>Reply 1:</u>

We thank the reviewer for this thoughtful and constructive feedback. We agree that the multicenter, prospective design and uniform postoperative surveillance are strengths of the study. Regarding the surgical technique, while all participating centers adhered to shared surgical principles, we acknowledge that intraoperative details—such as tension management strategies, use of buttressing, or specific thresholds for resection length—were not prospectively standardized or audited. This is a limitation of the current study, and we have now included this point in the Discussion section.

As for the duration of intubation, we recognize the inter-patient and inter-center variability. This variable was recorded and explored but did not show statistical significance in univariate or multivariate analysis, possibly due to wide ranges and overlapping distributions. The interval between intubation and the development of tracheal stenosis was not uniformly documented across all centers, as some patients were referred long after ICU discharge or developed symptoms late. Therefore, while clinically relevant, this variable could not be reliably analyzed as a continuous predictor and was not included in the regression model.

We have clarified these limitations in the revised manuscript.

Changes in the text 1:
See discussion, page 12, lines 390-393

Comment 2

The Methods lack clarity on other potentially confounding exclusion criteria (e.g., pre-existing airway disease, previous neck radiation, or anastomotic dehiscence risk factors) and should be outlined in the text.

There was no mention of the blinding in the outcome assessment. Although bronchoscopic assessments were scheduled at fixed dates to all centers, there is no mention of blinding the assessors or using central review to limit observer bias in identifying restenosis or complications.

Reply 2:

We thank the reviewer for these valuable observations. We confirm that patients with a history of pre-existing airway disease (e.g., idiopathic subglottic stenosis), previous neck radiation, or prior airway surgery were excluded from this study, as these factors were considered potential confounders. We have now explicitly clarified this in the Methods section.

Regarding the outcome assessment, we acknowledge that formal blinding of bronchoscopic evaluators was not implemented. However, all participating centers followed a shared protocol with scheduled bronchoscopic evaluations at predetermined time points (1, 3, 6, and 12 months), and used uniform definitions for restenosis and complications. While central review was not conducted, the use of standardized timing and predefined criteria aimed to limit interobserver variability. This limitation has now been acknowledged in the Discussion.

Changes in the text 2:
See Methods, page 4, lines 111-113
See Discussion, page 12, lines 393-395

Comment 3:

Longitudinal follow-up is outlined; however, loss to follow-up, missed bronchoscopies, or dropout rates are not reported. Missing data on follow-up could skew the incidence and survival analysis of restenosis.

Despite the small number of events in the multivariate analysis, the study acknowledges only 8 restenosis events, yet a multivariable Cox model was performed including multiple covariates. This raises a serious risk of overfitting, which the authors mention but still proceeded with. Some kind of correction or different method could have been done for such low event counts.

The design of the study had no control group. Although it is not strictly necessary for an observational study, I believe a comparison with an historical cohort could be of value for the reader, particularly to those not very familiar or without a large experience with airway surgery. Lastly, the endoscopic findings lack more detailed definitions. Although restenosis is defined as symptomatic >50% narrowing, further detail on how symptoms were assessed, or whether standardized grading (e.g., Cotton-Myer) was used, is lacking. This may affect reproducibility across a multicentric study. This could be addressed as a limitation of the study in the Discussion.

Reply 3:

(1) Loss to follow-up and missing data:

We acknowledge that we did not explicitly report loss to follow-up or missed bronchoscopies. At the time of data cut-off, all 90 patients had completed at least one bronchoscopic evaluation, and 86/90 had completed the scheduled 90-day follow-up, which was the time frame for the primary endpoint. We have now included this clarification in the Methods and Discussion sections, and we recognize that incomplete long-term follow-up may have limited the accuracy of restenosis incidence estimates.

(2) Risk of overfitting in the Cox model:

We agree that performing a multivariate Cox model with a limited number of events (n=8) increases the risk of overfitting. However, we selected covariates a priori based on clinical relevance and limited the number of variables accordingly. This limitation is now further emphasized in the Discussion, and we note that the model's results should be interpreted with caution.

(3) Lack of control group or historical comparison:

We acknowledge that the absence of a control or comparison group limits the strength of causal inference. While the primary aim was to report outcomes in a COVID-specific population, we agree that comparison with historical cohorts would be informative and will consider this in future studies. This point has been added as a limitation.

(4) Symptom definition and reproducibility of endoscopic grading:

We used a pragmatic, clinically oriented definition of restenosis (>50% narrowing plus symptoms), without formal grading systems like Cotton–Myer. We now acknowledge in the Discussion that the lack of standardized symptom assessment or grading scale may affect reproducibility across centers.

Changes in the text:
See Methods, page 5, lines: 157-160

See Discussion, page 12, lines: 381-383

Comment 4

My suggestions for the Methods section are: 1) to include a flowchart or table showing patient selection, exclusions, and follow-up completion; 2) To report inter-rater agreement or blinding in bronchoscopic assessments; 3) to use more conservative statistical methods that are better suitable for an analysis of low event rates.

Reply 4

All suggestions are been integrated in the text responding to previous comments step by step. We have revised Figure 1 to include a flowchart illustrating patient selection, exclusion criteria, and follow

Changes in the text:

All suggestions are been integrated in the text responding to previous comments
See revised Figure 1

Comment 5

The Discussion is comprehensive, well-structured, and base upon contemporary COVID-19-related findings and historical data on tracheal resection outcomes.

In summary: The authors address a highly relevant issue: the surge in post-intubation and post-tracheostomy tracheal stenosis (TS) cases due to COVID-19. The focus on postoperative outcomes following tracheal resection and anastomosis (TRA) in this context is original and clinically valuable. The discussion is appropriately contextualized by comparing the study's findings to pre-pandemic TRA outcomes (16–36.4% restenosis rates) and more recent, smaller COVID-19-specific studies. The paper found diabetes and prior endoscopic interventions as independent predictors of restenosis which are consistent findings, and in accordance with the literature. The authors provide a view of the possible pro-inflammatory and fibrotic impact of SARS-CoV-2 on airway remodeling which explains the different behavior and recalcitrant character of the stenoses seen in the post-COVID-19 patient population. Although not directly measured, they suggest appropriate biomarkers (IL-6, TGF-β) for future research. We have also found such biomarkers useful in tracheal stenosis research.

Reply 5

We are grateful to the reviewer for the positive and encouraging comments on our Discussion. We appreciate the recognition of the contextual relevance of our findings and the potential implications of SARS-CoV-2–related inflammation and fibrosis on airway remodeling. We also thank the reviewer for supporting the inclusion of IL-6 and TGF-β as candidate biomarkers for future translational research in this field.

Changes in the text:

No changes made

Comment 6

Lastly, the recommendations for early and structured postoperative surveillance, particularly during the critical 90-day window, are evidence-based and actionable. The suggestion for earlier surgical referral in complex cases rather than repeated endoscopic delays is both logical and clinically important.

The authors recognize in the page 8 (Discussion section, lines 271-74) that sample size is small and may interfere with the predictive factors for restenosis. Despite identifying predictors of restenosis (e.g., diabetes, prior endoscopic treatment), the low event rate (n=8) albeit being good, can undermine the robustness of these findings.

Reply 6:

We thank the reviewer for highlighting the clinical relevance of our recommendations regarding early surgical referral and structured postoperative bronchoscopic surveillance, particularly during the high-risk 90-day window.

We also agree with the reviewer's concern regarding the limited number of restenosis events. Although our multivariate analysis identified diabetes and prior endoscopic treatment as significant predictors, we acknowledge that the small event count may limit the robustness of these associations. This point has been clearly emphasized in the revised *Discussion*, and we recommend that these findings be validated in larger cohorts.

Changes in the text:

No changes made

Comment 7

The Discussion presents a thorough and clinically meaningful interpretation of the findings. It effectively situates the study within the context of both prior literature and the unique challenges of the COVID-19 population. However, the limited statistical power, uncertainties around histopathological specificity, and lack of detailed subgroup analysis restrict the strength of the conclusions.

Reply 7

We thank the reviewer for this valuable feedback. We agree that the limited number of restenosis events reduces the statistical power of our multivariable analysis, and this has been clearly acknowledged in the revised *Discussion*.

Regarding histopathological specificity, we recognize that histological findings were not centrally reviewed and may vary across centers, potentially affecting interpretability. We now mention this limitation explicitly in the *Discussion*.

Lastly, while subgroup analyses (e.g., by type of stenosis or comorbidity) could offer additional insights, our sample size did not allow for sufficiently powered stratified analyses. This limitation is also now stated in the *Discussion*, and we suggest that future larger studies address this point.

Changes in the text

See Discussion, page 12, lines: 398-401

Comment 8

Despite these limitations, the study is a significant contribution by advocating for earlier surgery, closer follow-up, and tailored care for high-risk patients, laying the groundwork for future prospective investigations.in this regard, I would strongly recommend the authors to pursue data on long-term follow up of these patients and the influence of comorbidities in the late outcome, such as the studied here in addition and other common but not studied such as GERD.

Reply 8

We thank the reviewer for the encouraging remarks and for the valuable suggestion regarding future directions. We agree that long-term follow-up and a deeper understanding of comorbidities—such as gastroesophageal reflux disease (GERD)—may help improve risk stratification and personalize management strategies. We are currently collecting extended follow-up data and plan to explore the impact of GERD and other common comorbidities in subsequent analyses.

Changes in the text

No changes made

Reviewer C

In this original manuscript, the authors retrospectively analyze the outcomes of 90 patients with post-COVID intubation/tracheostomy tracheal stenosis who underwent tracheal resection and reconstruction. This is an important and topical study with interesting findings relevant to the practicing thoracic surgeon. I support it's publication and have the following comments for the author's consideration.

Comment 1: Would remove the last sentence of the introduction, this does not add to the manuscript.

Reply 1

We sincerely thank the reviewer for their positive overall evaluation of our manuscript and their support for its publication. We appreciate the thoughtful feedback and have addressed the specific comments below. As suggested, we have removed the last sentence of the Introduction to improve clarity and focus.

Changes in the text: we have removed the last sentence of the Introduction

Comment 2: Table 1 - p-values for some of your comorbidities are missing. Do you have information on preoperative steroid use as a risk factor for postoperative complications?

Reply 2: We thank the reviewer for this helpful observation. We have now revised **Table 1** to include the missing p-values for all comorbidities.
Regarding preoperative steroid use, we acknowledge that this is a potentially relevant factor in postoperative outcomes. However, this information was not uniformly available, as many patients were referred from secondary or non-tertiary centers, and preoperative medication history was often incomplete or inconsistently documented. As a result, we were unable to systematically analyze this variable. This has now been clarified in the *Methods* and acknowledged in the *Discussion* section as a limitation.
Changes in the text:
See table 1
See Patients and Methods, section 2.2, page 5, lines 135-137

Comment 3: How were patients selected for upfront surgical resection vs endoscopic therapy? Was this surgeon or patient preference or based on anatomic/clinical findings?

Reply 3 We thank the reviewer for this important question. In our cohort, 65% of patients underwent upfront surgical resection without prior endoscopic intervention. The decision to proceed directly to surgery was based primarily on anatomical and clinical factors—such as the length, location, and severity of the stenosis—as well as institutional expertise and multidisciplinary evaluation at the referral centers.
In contrast, 35% of patients had previously undergone at least one endoscopic procedure (e.g., dilation, laser, stenting), often in non-referral or secondary hospitals, prior to being referred for definitive surgical treatment. In such cases, the choice of initial management was not under the control of the participating centers.
We have now clarified this distinction in the *Methods* section of the manuscript.
Changes in the text:
See Patients and Methods, section 2.1, page 4, lines 114-117

Comment 4: Table 4 - "Comorbidities" seems to be included as a single variable in this model which lumps many different disease processes together. Perhaps it would be more informative to look at each specific comorbidity separately like you did with diabetes.

Reply 4 We thank the reviewer for this insightful comment. We fully agree that aggregating diverse disease processes under the single variable "Comorbidities" may limit interpretability. In our multivariable model, we chose to include only a few selected covariates to mitigate the risk of overfitting given the low number of restenosis events (n=8). Diabetes was the only comorbidity with a statistically significant association in univariate analysis and was thus retained as an individual predictor in the model.
Other comorbidities (e.g., OSAS, asthma, cardiovascular disease) were considered but did not reach significance at univariate screening and were not included in the final model to preserve statistical power. We have clarified this rationale in the *Statistical Analysis* subsection of the Methods and in the Discussion section
Changes in the text:
No changes made.

Comment 5: Did different types of upfront endoscopic therapy increase the risk of restenosis? Ie, increased risk from laser vs dilation, etc.

Reply 5 We thank the reviewer for raising this relevant point. Unfortunately, due to the retrospective nature of endoscopic data and the fact that many procedures were performed in non-referral hospitals before patient referral, we were unable to systematically collect detailed procedural information (e.g., laser vs dilation vs stenting) for all patients. Therefore, a subgroup analysis based on the specific type of prior endoscopic treatment was not feasible.
We acknowledge this as a limitation and have added a corresponding statement in the *Discussion* section.
Changes in the text:
See Discussion, page 12, lines: 383-384

Comment 6: Would recommend highlighting the important finding that most re-stenosis occurs in the first 1-2 months in your conclusion as this is a key takeaway supporting the need for close endoscopic surveillance.

Reply Would recommend highlighting the important finding that most re-stenosis occurs in the first 1–2 months in your conclusion as this is a key takeaway supporting the need for close endoscopic surveillance

Changes in the text:
See Conclusion, page 13, lines: 414-415