

Peer review file

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Reviewer A

Comment 1: Ln 41 There are 2 values listed for removal rate. It is unclear what the difference is here, although reading through the results section of the paper, one can determine the difference. Please clarify

Reply 1: Thanks for your comment, we are very sorry for our negligence of the “Abstract”, the latter data should be “Effective rate”, this mistake has already been corrected. (See page2 Ln39-43)

Change in the text: Line 39-42 “Analysis of efficacy revealed that stability rate was 41.12% (95% CI, 34.85%-48.52%), and the removal rate is 40.74%(95% CI, 34.92%-47.53%) and 75.49%(95% CI, 70.89%-80.39%).” was corrected as “ A total of 395 patients from 8 studies were included in this study, revealing that the stability rate was 41.12% (95% CI, 34.85%-48.52%) of Dumon stenting. Further, a curative rate of 40.74%(95% CI, 34.92%-47.53%), and efficacy of 75.49%(95% CI, 70.89%-80.39%) were obtained from this study.”

Comment 2: Please clarify what is meant as a remedy for surgery. Do you mean an alternative to surgery? If so, that would contradict the initial statement that “the Dumon stent for benign tracheal stenosis appears unsatisfactory.”

Ln 225 please define what is meant by “remedy.” Do you mean alternative, last resort for non-surgical patients, etc? Understanding this conclusion is key to the analysis. Please clarify

Reply 2: We truly appreciate the reviewer’s suggestion, after our careful consideration, we deleted this statement in the “Abstract” and main text. (See page2 Ln47-48 and page 11 Ln 241)

Change in the text: Line 48-49 “The Dumon stent is recommended as a remedy for surgery or for alleviating dyspnea before surgery.” and line 224-225 “the silicone stent is thus only recommended as a remedy to surgery.” were deleted.

Comment 3: Ln 64 please list the “strict indications” for better clarity

Reply 3: It is really true as Reviewer suggested that we should describe the striction of surgery in detail. So we rewritten this part to make clear that fewer than 10%

tracheal stenosis patients can undergo tracheal surgery, we also describe the relationship between surgery complication and mortality risk. (See page3 Ln66-69)

Change in the text: Line 63-64 the statement “However, this type of surgery has strict indications.” was rewritten as “ However, less than 10% patients with tracheal stenosis are operable and resectable, since the surgery treatment has been limited by the high risks associated with anaesthesia and surgery, the length of the tracheal resection and the extent of the lesion. In addition, surgery-related deaths could increase thirteen-fold for patients with risk factors for anastomotic complications (diabetes, long-segment stenosis, previous tracheal surgery, et al) .”

Comment 4: Ln 64-65 elaborate what are “typical symptoms”

Reply 4: As Reviewer suggested, we list 2 “typical symptoms” and rewrote this part to explain the importance of interventional bronchoscopy. (See page3 Ln72-74)

Change in the text: line 64-65 the statement “For patients with inoperable stenosis or typical symptoms, interventional bronchoscopy can be the method of choice.” was rewritten as “Thus, timely interventional bronchoscopy might contribute to the preferred approach for patients with inoperable stenosis, hyoxemia or related-respiratory failure”

Comment 5: Spelling and grammatical error

Reply 5: Thank you very much for pointing out spelling and grammatical errors. We have corrected spelling and grammatical errors. The English presentation have been improved in the revised manuscript.

Change in the text: we do not list the changes here but marked in red in revised paper.

Reviewer B

Comment 1: The entire manuscript requires rigorous grammatical and editorial revision.

Reply 1: Thank you for pointing our spelling and grammatical errors. We have corrected spelling and grammatical errors. The English presentation have been improved in the revised manuscript.

Change in the text: Revised and polish portion are marked in red in the paper.

Comment 2: Authors' message becomes unclear as they use confusing terminology to gauge the success of the stent. "Removal" rate being referred at success rate is confusing. Stent may need to be removed for complications as well. Best they stick with terms" success, failure and complication rates

Reply 2: It is true as reviewer suggested that “removal” may mislead reader, so we used “curative rate” to describe the rates of patients who had their stents successfully removed without symptomatic restenosis in 1 year.

Change in the text: Revised and polish portion are marked in red in the paper.

Comment 3: A rate of 75%, in my opinion is good rate of success among patients who cannot undergo surgical correction; unless authors can offer an alternative. Most of these patients will otherwise require tracheostomy. As stated by the authors, metallic stent is not an option for these patients.

Reply 3: Thanks for the reviewer’s comment. We adjusted our conclusion that the efficacy of Dumon stent is moderate, but complication still needs to be proceeded with caution. (See page 11 Ln 222-225 and Page 14 Ln 305-307)

Change in the text: Line 202-203 “This means that the efficacy and safety of the Dumon stent is good but unsatisfactory” was corrected as “The current study showed Dumon stent has 75.49% effective rate and approximately 20% incidence of complications (migration, granulation, and mucus retention) indicating that Dumon stent had moderate efficacy and safety for airway stenosis.”

line 279-281 “The present study has shown that the efficacy of the Dumon stent for the treatment of benign tracheal stenosis is still unsatisfactory, with a quite high incidence of complications.” was corrected as “Dumon stent has a moderate efficacy for treating benign tracheal stenosis with middle incidence of complication, regular bronchoscopy follow-up should be conducted. .”

Comment 4: All the figures, especially figure 4 - are confusing and requires better legends and reorganization. You may consider, placing the figures as online supplement.

Reply 4: It is really true as Reviewer suggested that the figures are hard to understand. We redo the figures and delete insignificant content. For Figure 4, only subgroup analysis of effective rate has significant statistical difference, so we put other part of

figure in supplement material, only reveal curative rate in Figure 4. (See Figure 4 and Page 19 Ln 448)

Change in the text: Figure 4 was revised and Legend of Figure 4 was rewrite as “Forest plots for subgroup meta-analysis of curative rate based on median follow-up”

Reviewer C

Comment 1: I wonder why the authors focused on Dumon stent, despite the variety of stents. For example, the hybrid stent (AERO stent) is also a removable stent. Have you assessed whether Dumon stent has more or less complications than other stents?

Reply 1: Thank you for your question, here are some reasons for why we focus on Dumon stent. It has been 40 years since Dumon stent was first reported, but Dumon stent is still the most widely used silicone stent(over 90% of stent placement), and there is still no clinical trials of Dumon stent with a large size sample to figure out its efficacy and safety. On the other hand, other kind of silicone stent has different design, placement of stent and postoperative care are different either, which will lead to a pretty high heterogenicity. We assessed the efficacy and safety of Montgomery T-tube which was designed as both a tracheal stent and a tracheotomy tube. But we didn't figure out any significant differences. And the most important point is that there are only a few studies about silicone stent other than Dumon stent, which is insufficient for meta-analysis.

Comment 2: Clinicians encounter the airway stenosis due to malignant disease more frequently than benign disease. Why don't you analyze the airway stent placement to airway stenosis caused by malignant disease? The metallic stent(Spiral Z etc) stents are often used for malignant diseases.

Reply 2: Thank you for your comment. We do need to explain why we chose this main theme. In adults, 90% of malignant tracheal stenosis are caused by squamous cell carcinoma, the first-line treatment is tracheal resection with end-to-end anastomosis, unless the tumor involves more than 50% of trachea, invades mediastinal structures and lymph nodes, or metastasizes to distant sites or the mediastinum. For this situations, patients do not undergo surgery but receive palliation with interventional bronchoscopy. (Airway stent, Clin Chest Med. 2010 Mar;31(1):141-50) Stent placement for malignant tracheal stenosis has a quite

different aim, thus, which has different endpoint in study. Comprehensive analysis benign and malignant tracheal stenosis in one study may confuse readers. Our more concern point is the curative effect of stent instead of the palliative effect, so we focused on benign tracheal stenosis and conduct this study.

As we describe in text, the FDA sent a warning against the use of metallic stents in benign airway obstruction, we didn't include metallic stent in this research. But as Reviewer suggested that metallic stent has advantage in treatment of malignant diseases, which is worthy of further study.

Comment 3: The forest plots (Figure 2, 3, 4) are very difficult to see and understand. Please try to simplify the figure or make each plot easy to understand.

Reply 3: Thank you for your comment. We do apologize for our perifix forest plots, which has been simplified by delete insignificant content. (See Figure 2,3,4)

Comment 4: I'm not sure what the authors want to say in Figure 5.

Reply 4: Thanks for the reviewer's concern. The funnel plot is a method to assess the potential role of publication bias, which is a part of meta-analysis according to PRISMA guidelines and the Cochrane Handbook. The closer the funnel plot is to a pyramid shape, the weaker the publication bias. Normally, >10 included studies are needed to conduct a funnel plot, due to insufficient included studies (this meta-analysis only included 8 studies), this funnel plot didn't show a typical pyramid shape. But in the light of Egger linear test (a statistic method of publication bias), there is no publication bias in this meta-analysis.

Response to Reviewer D

Comment 1: The authors doesn't detail in the results and discussion if they have seen any difference between the 2 type of stenosis (post intubation or post-operative)

Reply 1: It is really true as Reviewer suggested that 2 different type of stenosis should undergo a subgroup analysis, but some studies mixed up 2 type of stenosis to study benign tracheal stenosis, we didn't have sufficient data to group included patients by etiology. This is a limitation of our study. So, we discussed the different between

post-intubation tracheal stenosis and post-tracheostomy tracheal stenosis (Respirology. 2017 Apr;22(3):513-520.) (See page 13 Ln 282-286)

Change in the text: We add “Shin et al report clinical significant difference in efficacy between post-intubation tracheal stenosis (PITS) and post-tracheostomy tracheal stenosis (PTTS).” at line 280

Comment 2: Moreover, in the limits, the authors should maybe add that why in articles the reason of non surgical solution haven't been report and why authors decided to use a Dumon stent because in some cases the stenosis could be more complex than other and it could lead to bias.

Reply 2: Thank you for your comment. We have added this part in the limitations according to your suggestion. About why authors of included studies decided to use Dumon stent, all studies followed the therapeutic algorithm of benign tracheal stenosis, and confirmed the indication of Dumon stents, which may not cause bias in this meta-analysis.

Change in the text: We add the statement “Moreover, the current study did not investigate the other non-surgical treatment (i.e. balloon-dilation or laser ablation) in pre-and postoperative care, which might affect the prognosis of stent treatment.” at line 286

Comment 3: The Incidence of efficacy indexes could be change and define in the methods part not in Results and maybe the term “Effective Rates” could be modify?

Reply 3: Thank you for your comment. It is true that we should not define the indexes in “Result”, we have revamped this part to “Method”. But I am afraid there is no better term than “Effective rate” to describe the efficacy of Dumon stent. (See page 7 line 151-157)

Change in the text: Line 163-166 the description of efficacy indexes was removed to Line 149-155 and revised as “Four indexes were chosen to evaluate the efficacy of Dumon stent for benign tracheal stenosis; 1) the curative rates (defined as the number of patients who had their stents successfully removed without symptomatic restenosis in 1 year); 2) the stability rates (defined as the number of patients who maintained stable stent placement); 3) the effective rates (defined as the sum of curative and stability rates added together) and 4) the restenosis rates.”

Comment 4: Please modified page 2 line 49: alleviating to alleviating

Reply 4: Thank you for your comment. Sorry for our mistake spell, we have rewritten Conclusions of Abstract in page 2 Ln 47-50

Change in the text: The statement which contain mistake spell “The efficacy and safety of the Dumon stent for benign tracheal stenosis appears unsatisfactory. Multicenter and prospective studies are needed to fully evaluate its effect. The Dumon stent is recommended as a remedy for surgery or for alleviating dyspnea before surgery.” was rewritten as “Dumon stent has a moderate efficacy for treating benign tracheal stenosis with approximately 20% incidence of complication, regular bronchoscopy follow-up should be conducted.”

Comment 5: Please put in all text and table Dumon with a “D capital”.

Reply 4: Thank you very much for your point out. We have made correction according to the Reviewer’s comments.

Change in the text: Revised and polish portion are marked in red in the paper.

Reviewer E

Comment 1: Silicone airway stents needs expertized skill and long-term experience, therefore, I myself feel better result nowadays, compared to 10 years ago. Therefore, bronchoscopist factor should be added in discussion and conclusion.

Reply 1: Thank you for your question. It has been 40 years since Dumon stent was first reported, but the shape and placement procedure didn’t change. And all Dumon stent were implanted by skilled bronchoscopists. We also underwent a cumulative meta analysis(defined as the performance of an updated meta-analysis every time a new trial appears) for evaluating the results as a continuum. In 1996 to 2017, the effective rate of Dumon stent don’t have significant change. So we could draw a conclusion that there is little bronchoscopist factor affect the efficacy of Dumon stent.

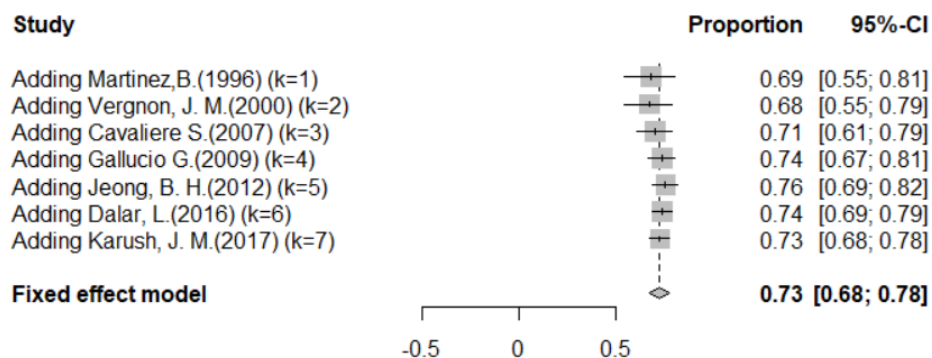


Figure: Cumulative meta analysis for effective rate

Comment 2: Also, patients' etiologies are too variable to analyze in one analysis, thus subgroup analysis is needed, as authors described in limitation. I think the conclusion of below paper should be added in discussion part. "Respirology. 2017 Apr;22(3):513-520. Clinical significance of differentiating post-intubation and post-tracheostomy tracheal stenosis. "

Reply 2: We are appreciate for this comment, and conclusion of this article was added in discussion part to discuss the different between post-intubation tracheal stenosis and post-tracheostomy tracheal stenosis. (See page 13 Ln 282-286)

Change in the text: We add "Shin et al report clinical significant difference in efficacy between post-intubation tracheal stenosis (PITS) and post-tracheostomy tracheal stenosis (PTTS). " at line 282.

Comment 3: late complications are bothersome, but could be usually handled by bronchoscopy and at least less complicated compared to tracheostomy. Therefore, further research should be needed to develop advanced airway stents resulting less complications.

Reply 3: It is really true as reviewer suggested that surveillance bronchoscopy can manage most of complication (See page 13 Ln 275-277). But we still need further research to reduce complications like customized stents or tissue-engineering stent.

Change in the text: We add the statement "Regular bronchoscopy follow-up should be conducted after Dumon stenting for early identification and management of related complications.." at line 275.

Reviewer F

Special thanks to you for your valuable comments, all of these modifications helped to elevate the quality of our article.

Comment 1: When stating that surgery obtains 90% of success, the authors do not indicate that only a few patients with tracheal stenosis are operable and stenosis resectable, accounting for less than 10% of the candidates.

Reply 1: Special thank for this excellent comment, as the reviewer suggested, we rewrote this part of Introduction to show the strict indication of tracheal resection and end-to-end anastomosis. (See page3 Ln66-72)

Change in the text: Line 63-64 the statement “However, this type of surgery has strict indications.” was rewritten as “However, less than 10% patients with tracheal stenosis are operable and resectable, since the surgery treatment has been limited by the high risks associated with anaesthesia and surgery, the length of the tracheal resection and the extent of the lesion.”

Comment 2: The authors do not communicate mortality associated with surgery and do not consider “granulation tissue and fibrous scar,” as they mention for bronchoscopic procedures

Reply 2: It is really true as reviewer suggest that we should list the complications of surgery and show that occurrence of complication will significant increase the risk of mortality. (See page 3 Ln 69-72)

Change in the text: We add “In addition, surgery-related deaths could increase thirteen-fold for patients with risk factors (diabetes, long-segment stenosis, previous tracheal surgery, et al) for anastomotic complications.” at Line 69.

Comment 3: Other misleading statements are “interventional bronchoscopy CAN be the method of choice” (line 65), when in reality, IS the method of choice.

Reply 3: Thank you very much for your comment. We are very sorry for our misleading statement. This statement has been rewritten as reviewer’s suggestion. (See page 3 Ln 72-74)

Change in the text: Line 64-65 the statement “For patients with inoperable stenosis or typical symptoms, interventional bronchoscopy can be the method of choice.” was correct as “Thus, timely interventional bronchoscopy might contribute to the preferred approach for patients with inoperable stenosis, hypoxemia or related-respiratory failure .”

Comment 4: Not to mention lines 86-88: “In the light of these palliative effects, the silicone stent is always to be considered as a temporary treatment before surgery.” That is wrong and cannot be published in a serious journal.

Reply 4: Thanks for your comment. We do realize our incorrect statement. This sentence has been deleted.

Change in the text: Line 86-88 “In the light of these palliative effects, the silicone stent is always to be considered as a temporary treatment before surgery.” was deleted.

Comment 5: On the other hand, it seems not convenient to add personal experience in a meta-analysis

Reply 5 : Thank you for your comment. As reviewer suggested, we deleted this part in our revised manuscript.

Change in the text: Line 223 “This finding supports experts’ consensus and our clinical experience of about 100 cases of benign stenosis in 4 years, compared with an over 90% cure rate for surgery;” was deleted

Comment 6: Also in the discussion, to mention the Oki stent as a possible solution to the Dumon limitations reflects that the authors have not considered the customized stents or the new experiments with drug-eluting stents for fibrosis.

Reply 6: Thank you for your comment. We are sorry for our inadequate consideration. Patient-specific stent and drug-eluting stents are important research direction of airway stents. We have added a brief discussion in the revised manuscript. (See page 14 Ln 298-303)

Change in the text: Line 298, “Advances in materialogy have increased interest in study of customized stents. Gildea et al. reported the application of 3D patient-specific stent in the treatment of Wegener’s granuloma. Drug-eluting stents have been designed for treating airway infections and granulation.” was added.

Comment 7: And on top, the authors cannot keep repeating that 75.49% of effective rate of not surgical candidates is unsatisfactory.

Reply 7: Thank you very much for the valuable comment. We are very sorry for our misleading statement. This conclusion is pessimistic and subjective. After careful consideration, we objectively draw a conclusion that Dumon stent has a good efficacy in benign tracheal stenosis, and reduction of complications will be the future research direction of silicone stents. (See page 10 Ln 222-225 and Page 14 Ln 305-307)

Change in the text: Line 202-203 “This means that the efficacy and safety of the Dumon stent is good but unsatisfactory” was corrected and rewritten as “The current study showed Dumon stent has 75.49% effective rate and approximately 20% incidence of complications (migration, granulation, and mucus retention) indicating that Dumon stent had moderate efficacy and safety for airway stenosis”

line 279-281 “The present study has shown that the efficacy of the Dumon stent for the treatment of benign tracheal stenosis is still unsatisfactory, with a quite high incidence of complications.” was corrected as “Dumon stent has a moderate efficacy for treating benign tracheal stenosis with approximately 20% incidence of complications, regular bronchoscopy follow-up should be conducted.”