

Peer review file

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Reviewer A

Comment 1:

The first sentence is wrong, preventive aortic surgery is not performed clinically because aortic aneurysm is asymptomatic. Emergency surgery is performed clinically. Ligne 40, The authors should write “..., preventive surgery is the sole option in case of large aneurysm”.

Reply 1: Thanks for your suggestions. We feel sorry for the improper wording. We have used “..., preventive surgery is the sole option in case of large aneurysm” as you suggested.

Changes in the text: “In order to prevent the occurrence of aortic adverse events in ascending thoracic aortic aneurysm patients, preventive surgery is the sole option in case of large aneurysm” (see Page 2, lines 32-33)

Comment 2:

Ligne 42, “Absolute diameter is ineffective”...but rapid aortic expansion rate is a good predictor, it should be precised.

Reply2: Thank you very much for your suggestion. In order to make our expression more precise, we have corrected it.

Changes in the text: “Absolute diameter measured after a single imaging examination, which has been used as the predictive indicator for decades, has been proved to be ineffective for risk stratification in moderately dilated aorta.” (see Page 2, lines 35-36)

Comment 3:

Ligne 52, The authors don't demonstrate anything in a review, they “highlight that the algorithm...”.

Reply 3: Thanks for your suggestions. We feel sorry for the improper wording. We have used “highlight” as you suggested.

Changes in the text: “We also highlight that the algorithm obtained by combining multiple indicators may be a better choice compared with single indicator, but this still requires more evidence.” (see Page 3, line 46)

Comment 4:

Ligne 53, “of its higher sensitivity and specificity”to be removed, it is wrong and the authors didn't discuss this point in the manuscript.

Moreover, these last two remarks have to be modified in the conclusion.

A new algorithm should be evaluated in a control population.

Reply 4: Thank you very much for your suggestion, the content about the algorithm obtained by combining multiple indicators is really misleading. What we want to express is that different morphological indicators can be combined to more comprehensively evaluate the morphology of the aorta. On page 11 of the revised manuscript, we mentioned two new algorithms created by combining the length and diameter of the aorta. Wu J et al. (Ref 6) took the arithmetic sum of diameter and aortic length as a new indicator called aortic height index (AHI). The AUC for the diameter- and AHI-based logistic models are 0.783 and 0.810, respectively ($p = 0.08$). Therefore, the AHI-based model has better discrimination than the diameter-based model in distinguishing the AAAs risk. Meanwhile, Tobias Krüger (Ref 7) proposed a score that combines aortic length and diameter to predict the risk of AAAs. The score defines a diameter ≥ 55 mm as 2 points, a diameter between 45 and 54 mm as 1 point, and a centerline length ≥ 120 mm as 1 point. When the total score is greater than 2 points, preventive surgery is recommended. The score was positive in 23.5% of the pre-TAA patients (sensitivity = 0.24) and would have identified at least twice as many pre-TAA patients compared with the diameter alone. The above evidences showed the superiority of algorithm obtained by combining multiple indicators, therefore, we suggest that more studies can combine imaging indicators in order to better assess the risk of ATAA. In order to better clarify our point of view, we have made the following changes in the article:

Changes in the text:

“We also highlight that the algorithm obtained by combining multiple indicators may be a better choice compared with single indicator, but this still requires more evidence.” (see Page 3, lines 45-47)

“We also highlight that the algorithm obtained by combining multiple indicators may be a better choice compared with single indicator, but this still requires more evidence.” (see Page 4, lines 69-71)

“At least 23.5% of pre-TAA patients had a positive score (sensitivity = 0.24), and the identifiable pre-TAA patients were at least twice as many as when diameter alone is used as a risk indicator. The above evidences showed the superiority of algorithms obtained by combining multiple indicators, and the establishment and proof of these algorithms may become the future research direction.” (see Page 15, lines 325-329)

“We also highlight that the algorithm obtained by combining multiple indicators may be a better choice compared with single indicator, but this still requires the support of more evidence.” (see Page 17, lines 368-370)

Comment 5: *It should be clearly stated that you won't talk about syndromic aortic disease in the abstract.*

Reply 5: This is a very good suggestion and we have already emphasized in the summary.

Changes in the text: “Due to the particularity of syndromic aortic disease, whether these new indicators can be used for its risk stratification is still uncertain. Therefore,

the scope of this manuscript does not include this kind of disease.” (see Page 2, lines 47-50)

Comment 6: *Ligne 102, reference 13 should be added with references 9-11.*

Reply 6: We feel sorry for our carelessness. We have corrected it and we also feel great thanks for your point out.

Changes in the text: [Ref 12](#)(see Page 5, line 100)

Comment 7: *Ligne 103, “heterogenity among studies” ...but just one reference of a single center experience.*

Probably the author should add these two references:

-Kay-Hyun Park et al. Eur J Cardiothorac Surg 2017 ;51 :959-964.

-Min Hao Guo et al. JAMA Network Open 2018;1(4):e181281. doi:10.1001/jamanetworkopen.2018.1281

Reply 7: As suggested by the reviewer, we have added more references to support this idea(Kay-Hyun Park et al. Eur J Cardiothorac Surg 2017 ;51 :959-964; Min Hao Guo et al. JAMA Network Open 2018;1(4):e181281. doi:10.1001/jamanetworkopen.2018.1281)

Changes in the text: [Ref 16](#); [Ref 17](#)(see Page 5, line 105)

Comment 8: *Ligne 104, “most studies”... but just one reference.*

Reply 8: We sincerely appreciate the valuable comments. We have checked the literatures carefully and added more references (Wu J et al. J Am Coll Cardiol. 2019;74(15):1883–94; Coady MA et al. Ann Thorac Surg. 1999;67(6):1922–6; Davies RR et al. Ann Thorac Surg. 2002;73(1):17–28.)

Changes in the text: [Ref 6](#), [18](#),[19](#)(see Page 5, line 108)

Comment 9: *Ligne 105, “previous studies”...but just one reference*

The authors should clearly say that the data in the literature are very rare. We have only a few single center series in the case of moderate aortic aneurysm follow-up. Use the singular if you have just one reference.

Reply 9: Thank you for your reminding. There is indeed very little data on this topic. According to your suggestion, we have explained this situation in the article.

Changes in the text: “..., and there are few studies comparing the aortic diameter before and after the occurrence of AAEs. Previous study reported an increment of at least 32% in the average mid-ascending aortic diameter after AD occurrence, with a value of 13±7 mm” (see Page 5, lines107-110)

Comment 10: *Ligne 119: add a reference after “centerline method measurement*

technique, which usually obtains lower aortic diameter”.

Reply 10: We sincerely appreciate the valuable comments. We have checked the literatures carefully and added more references (Rengier F et al. Am J Roentgenol. 2009;192(5):255–63; Han SM et al. J Vasc Surg [Internet]. 2017;66(4):1184–91.)

Changes in the text: [Ref 28,29\(see Page 6, line 122\)](#)

Comment 11: Ligne 120, “many studies”...references 24 and 25 are talking about the same registry.

Reply 11: Thanks for your help. We feel really sorry for our carelessness. We have modified the corresponding content in the article

Changes in the text: [“Furthermore, there is also a method of calculating the diameter based on the circumference to minimize the influence of the non-circular aorta.”](#) (see [Page 6, line 123-124](#))

Comment 12: *Ligne 142, aortic diameter is also modulated in case of syndromic or non syndromic disease aortic disease, in patients with bicuspid valve. Sleep apnea is probably the major trigger of aortic root dilatation.*

Reply 12: We feel great thanks for your professional suggestion. We have checked the literatures carefully and added more actors affecting the aortic diameter.

Changes in the text: [“Aortic diameter is modulated by several personalized parameters such as height, gender, age, lifestyle, body size, hypertension, genetic factors, bicuspid aortic valve \(BAV\) and sleep apnea \(Ref 6,23,25,35–44\).”](#) (see [Page 7, line 145-147](#))

Comment 13: *Ligne 151, Ref 29 is not appropriate, this article is talking about surface area and aortic size*

Reply 13: Thanks for your help. We feel really sorry for our carelessness. Ref29 really shouldn't be cited here, we have already deleted it.

Changes in the text: [see Page 8, line 155](#)

Comment 14: *Ligne 229, Ref 46 is not appropriate, it should be precised :Prognosis of women suffering from aortic dissection is worse than men*

Reply 14: We are very sorry for the problem with our expression. In order to more accurately express the difference in prognosis between men and women, we have deleted the citation 46

Changes in the text: [see Page 11, line 234](#)

Comment 15: *Ligne 238, remove the word systolic.*

Reply 15: Thanks for your correction. As blood pressure is often encountered in daily practice, we decided to discuss the possibility of combining it with aortic diameter as a

risk predictor more systematically. Therefore, we have added a section "hypertension" to the article

Changes in the text:

“Hypertension

It was traditionally considered that hypertension would accelerate the rupture of elastin fibers in the aorta, causing the proximal aortic dilation (Ref 70,71). However, as previous studies have shown, compared with the diameter prediction model established by height, body size, age, and gender, the incremental effect of hypertension is much smaller (Ref 39,72–74). Another study divided patients with hypertension into four subgroups, including prehypertension, systolic–diastolic, isolated diastolic and isolated systolic. However, there were no significant difference in aortic root diameter between the subgroups and normotensive individuals after adjusting age and BSA (Ref 36). As whether hypertension will cause aortic dilatation is still unclear, no studies have proposed the revision of risk stratification thresholds for hypertension patients.”(see Page 12, line 256-265)

Comment 16: *Title: remove the word “comprehensive”.*

Reply 16: It is really a giant mistake to the whole quality of our article. We feel sorry for our carelessness. We have corrected it and we also feel great thanks for your point out.

Changes in the text: “New Indicators For Systematic Assessment of Aortic Morphology: A Review” (see Page 1, line 1)

Comment 17: *In the conclusion, it could be precised that all the new index are available with the CT-angiogram performed in the clinical management.*

Reply 17: Thank you for your suggestion. We agree that adding content about parameter measurement methods in the article will make the content of the article more precise.

Changes in the text: “At present, the acquisition of these 3D indicators is mostly processed by 3D post-processing technology based on computer tomography angiography (CTA). (Ref 75, 76)” (see Page 13, lines 271-273)

“Meanwhile, a previous study also showed that the length of the AAEs aorta processed from 3D reconstruction based on CTA is significantly larger than the non-AAEs aorta.” (see Page 14, lines 294-296)

“In addition, the continuous advancement of CTA-based 3D reconstruction technology makes it possible to quantify the aortic arch tortuosity. (Ref 76)”(see Page

16, lines 342-343)

Comment 18: *Some illustrations could help readers to understand the different index evoked in this review.*

Reply 18: Thank you for your suggestion. We also agree that adding pictures to the article will make readers understand the parameters more clearly

Changes in the text: [see Page 14, line 297 and Page 16, line 334](#)

Reviewer B

Comment 1: *This is not a “A Comprehensive Review” for these reasons: firstly, some parameters were not discussed (such as genetic factors, impact of systolic pressure, etc., despite they are clinical factors that are often encountered in daily practice; secondly in my opinion other studies should be cited and discussed which I indicate below (see points 4,6)*

Reply 1: Sorry for our mistake, this is indeed not a comprehensive review. We have revised the title, and we think that adding genetic factors and the impact of blood pressure is a very good suggestion, so we have made the following changes.

Changes in the text: [“New Indicators for Systematic Assessment of Aortic Morphology: A Review”](#) (see Page 1, line 1)

[“Non-syndromic ATAA](#)

[It has been reported that 20% of TAA patients have a first- degree relative whose thoracic aorta is dilated, which shows the important role of genes in TAA. \(Ref 35\) In contrast to syndromic ATAA, some families exhibit abnormalities limited to the cardiovascular system without physical features of connective tissue disorders. \(Ref 63\) These conditions are called non-syndromic ATAA include familial thoracic aortic aneurysm and dissections \(FTAAD\), familial thoracic aortic aneurysm and BAV with aneurysm. \(Ref 63\) The non-syndromic ATAA related genes included ACTA2, MYH11, MYLK and PRKG1, which encode components of the smooth muscle contractile apparatus. \(Ref 64–67\)](#)

[It has been reported that non-syndromic ATAA tend to grow at a higher rate even compared with MFS patients, which highlights the need for different risk stratification thresholds for non-syndromic ATAA patients. \(Ref 35\) Previous studies have focused on assessing relationships between candidate genes and ATAA to facilitate daily monitoring of the aorta, early intervention of aortic disease and family cascade screening. \(Ref 68,69\) As technology advances and the cost of DNA sequencing continues to decrease, the use of ATAA-related genetic testing is expected to gradually increasing clinical practice.](#)

[Hypertension](#)

[It was traditionally considered that hypertension would accelerate the rupture of elastin](#)

fibers in the aorta, causing the proximal aortic dilation.(Ref 70,71) However, as previous studies have shown, compared with the diameter prediction model established by height, body size, age, and gender, the incremental effect of hypertension is much smaller.(Ref 39,72–74) Another study divided patients with hypertension into four subgroups, including prehypertension, systolic–diastolic, isolated diastolic and isolated systolic. However, there were no significant difference in aortic root diameter between the subgroups and normotensive individuals after adjusting age and BSA. (Ref 36) As whether hypertension will cause aortic dilatation is still unclear, no studies have proposed the revision of risk stratification thresholds for hypertension patients.” (see Page 11, lines 239-265)

Comment 2: *The authors reported that in the review there is an algorithm obtained by combining multiple indicators which may be a better choice because of its higher sensitivity and specificity compared with single indicator. However, in the manuscript I found an Interesting discussion about new indicators of ATAA, but these novel factors are discussed and explained singly, and there is not an algorithm that considers them all together. The authors recommended to evaluate these indicators (but one by one)*

Reply 2:

Thank you very much for your suggestion, the content about the algorithm obtained by combining multiple indicators is really misleading. What we want to express is that different morphological indicators can be combined to more comprehensively evaluate the morphology of the aorta. On page 11 of the revised manuscript, we mentioned two new algorithms created by combining the length and diameter of the aorta. Wu J et al. (Ref 6) took the arithmetic sum of diameter and aortic length as a new indicator called aortic height index (AHI). The AUC for the diameter- and AHI-based logistic models are 0.783 and 0.810, respectively ($p = 0.08$). Therefore, the AHI-based model has better discrimination than the diameter-based model in distinguishing the AAEs risk. Meanwhile, Tobias Krüger (Ref 7) proposed a score that combines aortic length and diameter to predict the risk of AAEs. The score defines a diameter ≥ 55 mm as 2 points, a diameter between 45 and 54 mm as 1 point, and a centerline length ≥ 120 mm as 1 point. When the total score is greater than 2 points, preventive surgery is recommended. The score was positive in 23.5% of the pre-TAD patients (sensitivity = 0.24) and would have identified at least twice as many pre-TAD patients compared with the diameter alone. The above evidences showed the superiority of algorithm obtained by combining multiple indicators, therefore, we suggest that more studies can combine imaging indicators in order to better assess the risk of ATAA. In order to better clarify our point of view, we have made the following changes in the article:

Changes in the text:

“We also highlight that the algorithm obtained by combining multiple indicators may be a better choice compared with single indicator, but this still requires more evidence.” (see Page 3, lines 45-47)

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be a better choice compared with single indicator, but this still requires more evidence.” (see Page 4, lines 69-71)

“At least 23.5% of pre-TAD patients had a positive score (sensitivity = 0.24), and the identifiable pre-TAD patients were at least twice as many as when diameter alone is used as a risk indicator. The above evidences showed the superiority of algorithms obtained by combining multiple indicators, and the establishment and proof of these algorithms may become the future research direction.” (see Page 15, lines 325-329)

“We also highlight that the algorithm obtained by combining multiple indicators may be a better choice compared with single indicator, but this still requires the support of more evidence.” (see Page 17, lines 368-370)

Comment 3: *English language phrasing could be improved. For example:*

a) *“Meanwhile, when combining three-dimensional parameters to formulate risk stratification thresholds, not only can the aortic risk morphology be more accurately characterized, but also the accuracy of aortic adverse events prediction is improved.”*

Lines 47-49 (who performs the action?)

b) *lines 107-110: maybe, the authors mean the size of ATAA to prevents AAEs was probably lower.....”*

c) *line 310: diverse?*

d) *etc..*

Reply 3: Thanks for your suggestions. We feel sorry for our poor writing; however, we do invite a friend of us who is a native English speaker help polish our article. Due to our friend’s help, the article was edited extensively. And we hope the revised manuscript could be acceptable for you.

Changes in the text:

“Meanwhile, combining three-dimensional parameters to formulate risk stratification thresholds not only may characterize the aortic risk morphology more precisely, but also predict aortic adverse events more accurately.” (see Page 2, line 40-42)

“As a result of this AD primed aortic dilatation, the aortic diameter, which should be recommended as risk stratification threshold, may be less than 5.5 cm”(see Page 5, line 110-111)

“Meanwhile, the anatomical sites that measure arch tortuosity are not the same between different studies and no protocols have been validated in a robust fashion” (see Page 16, line 345-346)

“Meanwhile, combining three-dimensional parameters to formulate risk stratification thresholds not only may characterize the aortic risk morphology more precisely, but also predict aortic adverse events more accurately. These new indicators may provide more systematic assessment methods of patients’ risk, formulate more personalized intervention strategies for ascending thoracic aortic aneurysm patients, and also provide a basis for researchers to develop more accurate and effective risk thresholds.” (see Page 2, line 40-47)

“Therefore, for high-risk ATAA patients, preventive surgery is often performed before AAEs occur and in such cases the mortality rate drops to 3–9%.” (see Page 2, line 57-58)

“..., this may be due to heterogeneity among the studies of measurement methods used to confirm the threshold of 5.5 cm.” (see Page 4, line 99-100)
etc...

Comment 4: *About aortic size paradox, the authors should explain it better. I recommend to add and comment these Interesting studies*

a) *Aortic Size Distribution in the General Population: Explaining the Size Paradox in Aortic Dissection. Paruchuri V, Salhab KF, Kuzmik G, Gubernikoff G, Fang H, Rizzo JA, Ziganshin BA, Elefteriades JA. Cardiology. 2015;131(4):265-72. doi: 10.1159/000381281. Epub 2015 May 14.*

b) *Indications and imaging for aortic surgery: size and other matters. Elefteriades JA, Ziganshin BA, Rizzo JA, Fang H, Tranquilli M, Paruchuri V, Kuzmik G, Gubernikoff G, Dumfarth J, Charilaou P, Theodoropoulos P. J Thorac Cardiovasc Surg. 2015 Feb;149(2 Suppl):S10-3. doi: 10.1016/j.jtcvs.2014.07.066. Epub 2014 Aug 4.*

Reply 4: Thank you very much for your suggestion. These two articles do provide a very good explanation of the aortic size paradox, so we added and comment these interesting studies.

Changes in the text: “On the one hand, the phenomenon is probably due to the bell-shaped curve of the aortic diameter distribution in the general population. Specifically, the number of people with aortic diameters less than 5.5 cm is much larger than that of people with a diameter greater than 5.5 cm (Ref 13,14)” (see Page 5, lines 100-103)

Comment 5: *Lines 128-130: please, explain better: are there statistically significant differences or “substantially overlapping”?*

Reply 5: Thank you for underlining this deficiency. This section was revised and modified according to the information showed in the work suggested by the reviewer.

Changes in the text: “Firstly, when comparing the median diameters of non-AAE, post-AAEs and pre-AAEs aortas, the diameter ranges of these three groups substantially overlap, which explains why there is suboptimal discrimination between non-AAEs and AAEs aortas based on diameter alone.” (see Page 6, line 132-135)

Comment 6: *I recommend to explain better the concepts about AHI, arch tortuosity and ASI and I think some figures should be added. Moreover, the authors should explain how to evaluate these parameters at echocardiography (to make them more usable). For AHI see also “Height alone, rather than body surface area, suffices for risk estimation in ascending aortic aneurysm” Zafar et al,*

The Journal of Thoracic and Cardiovascular Surgery c May 2018

Reply 6:

Thank you for your suggestion. Our expressions of 3D indicators are really not clear enough. In order to make it more understandable, we use pictures to describe it. At the same time, although there are very few articles on how to use echocardiography to measure 3D indicators, this direction is very meaningful, so we have added this content. Meanwhile, we think this article is very interesting, already cited.

Changes in the text: “Meanwhile, echocardiography, which has high repeatability and no nephrotoxicity from contrast agents, has been proven to have the potential to measure 3D parameters (Ref 79). Previous study measured length from aortic annulus to the most cranial part of visible aorta with transthoracic 2D echocardiography (Ref 80). Another study also proposed an algorithm for aortic root 3D modeling based on 2D echocardiography by a computer-aided design software (Ref 81). Such technological progress makes 3D indicators expected to be widely used.” (see Page 13, line 276-282)

Comment 7: 7) Lines 292-293: please, explain the concept of volume (possibly through a figure)

Reply 7: Thank you very much for pointing out this problem. After discussion, we believe that the concept of volume is not appropriate here. Since the aorta is not a regular cylinder, it is not appropriate to describe volume as a combination of diameter and length. After discussion, we decided to delete this part.

Changes in the text: Remove “Another way to combine length and diameter is volume, which also shows good predictive power, with sensitivity sevenfold higher than diameter. Together, these findings prove the feasibility of combining length and diameter to develop thresholds for preventive surgery.”