

Peer Review File

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Response to Reviewer A:

We appreciate the constructive comments provided by the Reviewer and have made all changes in the text, accordingly.

Comment 1: Authors described “Clinically relevant echo-attenuation was defined as an attenuation length $\geq 5\text{mm}$ with a maximum angle $\geq 180^\circ$.” However, the definition was the high risk plaque of microvascular obstruction (MVO) by using contrast-enhanced cardiac magnetic resonance imaging (CE-CMR) in ST-segment elevation myocardial infarction (STEMI) patient who underwent stent implantation. Therefore, Authors could not apply the definition in this study. The authors should replace it by another appropriate definition.

Response: We fully agree with reviewer and the clinically relevant echo-attenuation is redefined as an attenuation with classical anatomical cut-offs (MLA=4.0mm² and PB=70%) for the vulnerable plaque deriving from the PROSPECT trial(1). (Page 2, line 13, line 17, line 22; Page 7, line 6-7; Page 9, line 18; Page 10, line 19-20; Page 11, line 3; Table 2; Figure 5).

Comment 2: Attenuation length and angle cut-off value from the receiver operating characteristic (ROC) analysis for predicting QFR ≤ 0.80 should be shown.

Response: The ROCs and cut-offs of attenuation parameters in predicting QFR ≤ 0.80 have been added to Figure 4.

Comment 3: MLA and DS cut-off value from the receiver operating characteristic (ROC) analysis for predicting QFR ≤ 0.80 should be shown.

Response: The cut-offs of anatomical parameters for predicting QFR ≤ 0.80 have been presented in Figure 4 accordingly. However, IVUS-derived area stenosis (AS) might be a more suitable anatomical reference than DS, as the intrinsic bias might occur when using QCA-derived DS to predict the QCA-derived QFR.

Comment 4: Relating to the above, the authors should compare the cut-off value of these parameters for predicting QFR ≤ 0.80 .

Response: The ROCs of the IVUS parameters for predicting QFR ≤ 0.80 were compared using the Delong method (R software) (Page 8, line 8-9, line 21-23; Page 9, line 1-3; Page 10, line 7-12) and a comment was added to the Discussion (Page 12, line 13-16).

Comment 5: Previous studies have demonstrated that positive remodeling in coronary artery was defined as a remodeling index of > 1.05 . On the other hand, the present study applies the definition as a remodeling index of > 1.0 . Why is the reason of this discrepancy?

Response: We agree with the reviewer and the percentages of positive remodeled lesions have been corrected accordingly (Page 7, line 1; Table 2).

Comment 6: Page 9/Line 9-10; DS% \rightarrow DS, AS% \rightarrow AS, and PB% \rightarrow PB

Response: The acronyms have been corrected accordingly. (Page 9, line 14-15).

Response to Reviewer B:

We appreciate the valuable suggestions from the reviewer and add additional data into the manuscript.

Comment 7: The reviewer wonders whether analyzed lesions received PCI or non-culprit lesions.

Response: The percentages of lesions received PCI and non-culprit lesions were added to the Table 2.

Comment 8: How much percentage of subjects received a statin at the index of the procedure?

Response: The percentages of statin usage were added to the Table 1.

Response to Reviewer C:

We appreciate the valuable comments and careful revision from the reviewer, and have address all the comments point-by-point.

Comment 9: QFR was measured with a system not available outside China and with single centre validation. Furthermore you measured retrospectively and this probably means few of the angiographic acquisition were optimized for orthogonal views elongating the vessel and avoiding overlapping. Hard to believe that an index that is a surrogate of the real thing (the proper pressure derived index) can be considered a gold standard for a validation study.

Response: We agree with reviewer and have added these caveats into Discussion section (limitations) (Page 14, line 11-15)

Comment 10: Echo attenuation with IVUS is certainly of possible prognostic value but lacks the prospective data of NIRS-IVUS and OCT

Response: The caveat was added to the discussion (limitation) accordingly (Page 14, line 7-11).

Comment 11: As expected, the best correlation IVUS and QFR is with measurements of lesion severity (MLS, %AS) rather than morphological characteristics

Response: We agree with the reviewer and a new comment was added to the discussion (Page 12, line 13-16).

Comment 12: Figure 4, despite the significant p-value, shows an extremely poor AUC of 0.695. Does it justify the final statement on clinical implications at the end of the Discussion? “Importantly, our study showed that $QFR \leq 0.88$ was predictive for clinically relevant echo-attenuation in intermediate coronary lesions, supporting a new utility of QFR assessment in detecting vulnerable plaques. Further prospective studies are warranted to examine if deferred intervention of intermediate lesions with $QFR \leq 0.88$ could pose residual risk of adverse clinical events as a result of progression/rupture of attenuated plaques and then rigorous secondary therapeutic prevention is required.”

Response: We agree with the reviewer. Both the final statement and conclusion have been modified according to the reviewer's comments. (Page 13, line 17-22; Page 14, line 1-2, line 18-21)

Specific comments:

Comment 13: Page 4: would be of important clinical values: rephrase (“of great clinical importance”)

Response: The sentence has been rephrased accordingly (Page 4, line 9).

Comment 14: Page 4, and needless use of adenosine: rephrase!

Response: As requested, this sentence has been rephrased (Page 4, line 14).

Comment 15: received IVUS examination were consecutively enrolled.: maybe: “receiving IVUS examination or examined with IVUS” were enrolled

Response: As requested, this sentence has been corrected (Page 5, line 5-6).

Comment 16: Page 5: Patient's clinical characteristics: without “ ’s” after patient

Response: This word has been corrected (Page 5, line 12-13).

Comment 17: Page 5: and automatically pull back: pulled-back

Response: This word has been corrected (Page 5, line 22).

Comment 18: Page 7: that was in the absence of calcification: without “that was”

Response: The sentence has been corrected accordingly (Page 7, line 2).

Reference:

1. Stone GW, Maehara A, Lansky AJ, et al. A prospective natural-history study of coronary atherosclerosis. N Engl J Med 2011;364:226-35.