

Peer Review File

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First Round of Peer Review

Reviewer A:

Major:

Comment 1. The definition of ISR is not provided. Moreover, how does this relate to the amount of prior PCI/CABG? How was the outcome ‘myocardial infarction’ defined, and was this assessed per specific lesion?

Response: I am sorry to bother you. I added the definition of ISR in “Method section” (Page 9, Line 136-137). Furthermore, I forgot to add additional exclusion criteria. In the present study, in-stent restenosis (ISR) with previous PCI history (≥ 2) was excluded (Page 7, Line 96).

As you point out, I forgot to add prior PCI and CABG data, too. So, I really thank you for your valuable suggestion. I added these data in Table 1.

In addition, according to your suggestion, we evaluated the relationship of ISR with prior PCI, but they did not have any relationship. Therefore, I added this result in “Result section” (Page 10, Line 166 and 167).

Furthermore, I added the additional definition regarding the outcome ‘myocardial infarction’ in “Method section” (Page 8, Line 128-129 and Page 8-9, Line 130-135).

Comment 2. The current study combines both target lesion outcome (TLR) and patient outcome (myocardial infarction and death). It is unclear for the reader if survival analyses were performed based on lesion or on patient level. This should be mentioned explicitly. How many patients did the TLR events (n=18) encompass?

Response: I am sorry to bother you again. To make it clear, I added “based on patient level” and “based on lesion” in Figure 1. Furthermore, I explained these definitions in “Definition section” (Page 9, Line 138-140). In the present study, 18 patients had 18 TLR. Hence, regarding this data, I added it in “Result section”. (Page 11, Line 170-172).

Comment 3. Figure 1 only includes only a panel with all-cause death data. The Kaplan-Meier curve x-axis seems to show days instead of years of follow-up, although it is titled 'Years of follow-up'. In addition, please provide the patients at risk for the Kaplan-Meier curves.

Response: I am sorry to bother you again. I modified everything according to your suggestion. Thank you so much for your valuable suggestions.

Comment 4. The main conclusion of the study is drawn from multivariable Cox-regression analysis. The authors included all predictors that had a $p < 0.10$ in univariable analysis, resulting in a final model of 5 factors. The event rate ($n=17$) is too low for this number of factors. The final model should exclude those factors not significantly contributing to the model. How did the factors found in other studies (line 204-207) predict TLR in your study? Moreover, sensitivity analyses for sex, patients with only FFR > 0.80 , and possibly also study center, will enhance the methodology.

Response:

Thank you for your good suggestion. According to your valuable suggestion, I re-analyzed our data with exclusion of factors not significantly contributing to this study in "Statistics section and Result section" (Page 10 Line 152-154; Page 12, Line 189-191) Furthermore, in "Discussion section", we added our discussion regarding previous TLR factors which ended up failing to be predictors for TLR in "Discussion section" (Page 13 and Page 14, Line 210-236).

Finally, I analyzed sensitivity analyses for sex (Page 10, Line 154-155; Page 12, Line 191-192).

I hope that these changes meet your demand.

Comment 5. The reliability of FFR values during acute coronary syndrome is under debate. Clinical presentation during baseline FFR should be incorporated accordingly in the survival analyses.

Response:

I really appreciate your valuable comment. I totally agree with you. Therefore, according to your suggestion, I added Kaplan-Meier curve based on clinical presentation in Figure

2. Furthermore, I added statistical sentences and our discussion regarding this topic in “Statistical section”, “Result section” and “Discussion section” (Page 9, Line 147-149, Page 11, Line 182-184 and Page 14, Line 227-236). Once again, thank you for your valuable question and I hope that these changes meet your demand.

Comment 6. The discussion shows other factors that have been found to predict TLR, but do not discuss how these results together with the current results should be interpreted. (Line 204-211). For example, the association between SYNTAX score and FFR values has been reported before (10.1016/j.jacc.2015.12.053). References based on lesion specific and patient level outcome are mixed (such as 10.1161/JAHA.119.014458, line 207). More elaboration on the current findings in the current era of coronary diagnostics is expected (line 253-254).

Response: I really appreciate your valuable comment, too. Honestly, we did not have definite reasons why other factors that have been found to predict TLR did not become predictors for TLR in the present study. However, I added as much explanation about these regard as possible in “Discussion section” (Page 13 and Page 14, Line 210-236). In addition, as for the association between SYNTAX score and FFR value, to strengthen our result, I added some sentences in “Discussion section” by using the report you mentioned (Page 15, Line 240-241 and Page 15, Line 243-246) and added it as one of valuable references in “Reference section”. I hope these changes meet your demand.

Minor:

Comment 1. Abbreviations are not consistently used and explained when first used in the Abstract: line 42, 49, 51. The authors may want to consider to add Hazard ratios and 95% confidence intervals of the predictors to the Abstract.

Response: I am sorry to bother you. I revised abbreviations you pointed out and added Hazard ratio and 95% CI in “Abstract section”.

Comment 2. The clinical data used for the SYNTAX score should be reported in Table 1 or 2. Was SYNTAX score I or II calculated?

Response: Thank you for your suggestion. We calculated SYNTAX score by SYNTAX

score I. I added this explanation in “Method section” (Page 7 and 8, Line 113-114).

Comment 3. What was the main reason coronary intervention was deferred in lesions with FFR <0.80?

Response: Thank you for your question. Actually, in the present study, the decision making on the defer was performed according to local institutional guidelines. On top on that, since the present study was retrospective, we could not elucidate the main deferral reasons for coronary intervention.

However, in one of the biggest studies performed in Japan, the CVIT-DEFER Registry, 506 out of 3857 lesions were enrolled as FFR<0.80, consistent with the present study results. Anyway, since the present study is a real-world study, we must acknowledge this as one of limitations. Therefore, I added this regard in “Limitation section” (Page 17, Line 282-286)

Comment 4. The statistical method used with the Kaplan-Meier survival curves is not reported in the ‘Statistical analysis’ section.

Response: I am sorry to bother you. I deleted the cumulative incidence curve and added some sentences about Kaplan-Meier curves in “Statistical analysis section” (Page9, Line 145-146)

Comment 5. Information on prior PCI and CABG, and rate of incident myocardial infarction is missing.

Response: Thank you for your valuable suggestion. According to your advice, I added information on prior PCI and CABG in Table1. In addition, the incidence rate of myocardial infarction was added in “Result section” (Page11, Line 172).

Comment 6. What was the timeframe of inclusion and follow-up? Did follow-up time have an effect on the study results? Did all patients have a follow-up of 3 years or until death? Providing the median time of TLR and elaboration thereon adds additional information to the reader. Specifically because it looks almost all events occur within 6 months after initial FFR in Figure 1. How is outcome visualized for ISR and the SYNTAX score?

Response: Thank you for your valuable suggestion. This study was retrospective, so to be honest, we are not sure what kind of effect this follow-up time had on the present study results. However, according to your suggestion, I provided the median time of TLR and median time of follow-up in the “Result section” (Page 11, Line 171 and Page 10, Line 161). Finally, I added the information about ISR cases with ischemia-driven TLR (Page 11, Line 175-176)

Comment 7. The authors could comment on an optimal cut-off for FFR and SYNTAX score in the study population, such as based on AUC analysis of ROCurves. This could provide more data for a clinical perspective.

Response: Thank you for your good suggestion. According to your suggestion, I performed a ROC curve analysis to identify the SYNTAX score cutoff value for predicting an ischemia-driven TLR in deferral lesions (Page 10, Line 150-152 and Page 12, Line 193-194). Furthermore, as you point out, we totally agree that it is crucial to decide cut-off value, incorporating the anatomical complexity of the coronary artery into a functional evaluation such as FFR. Therefore, I added this regard in “Limitation section” (Page 17, Line 289-290).

I hope that this change meets your demand.

Reviewer B:

Interesting idea , though no practical conclusion. For example we cannot conclude whether the cutoff value of FFR 0.8 (which is currently proposed from the ESC guidelines) should be trusted or not. The manuscript proposes the idea " the higher , the better" , though fails to support it . It is important that the authors highlight the point that they don't conclude to a new cutoff value, and that clearly don't question the FFR cutoff value, as there is no randomisation.

Response: Thank you so much for your valuable feedback.

As you point out, the present study is not prospective randomized study. So we did not aim to decide FFR cut-off value. We thought we would rather decide factors influencing TLR along with FFR value. I revised our manuscript according to the valuable suggestions from another reviewer. I would appreciate your understanding.

Second Round of Peer Review

Comment 1.

Please specify the relevant dates when the data was collected in the Methods.

Response) Thank you for your valuable suggestion. It slipped my mind. I am so sorry. I added the relevant dates when the data was collected (Page 6, Line 90-92)

Comment 2.

Please check through the tables again to keep the same decimal places of each mean \pm SD value.

Response) Thank you for your valuable suggestion. I looked through the table again and modified the decimal places of mean \pm SD value regarding “Minimal lumen diameter” in Quantitative coronary analysis result to keep the same decimal places. However, as you know, since FFR values need to be calculated to two decimal places, I only denoted values including two decimal places.