Peer Review File

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Reviewer A:

Comment 1: a major limitation is the small sample size

Reply 1: *We fully agree with this comment. We further emphasized this limitation in the abstract*

Changes in the text: *Please see page 4: "Our preliminary data show that…"*

Please see page 16: "Second, the number of finally included patients is rather low and results need to be confirmed in larger, prospective outcome studies."

Please see our conclusion on page 17: "Certainly, our preliminary results need to be confirmed in larger, prospective clinical outcome studies."

Comment 2: What was the rational to perform coronary CTA in patients with acute coronary syndrome? Would coronary CTA not delay cardiac catheterization and be associated with repeat contrast administration? Please describe the criteria used to decide about performance of coronary CTA including clinical presentation and results of high-resolution Troponin tests

Reply 2: *We agree in general with this comment. CT is not indicated in patients with ST-elevation or elevation of hs-troponin, which is also in line with our clinical approach in the ED. However, according to current recommendations CT can be performed in patients with indeterminate ECG findings and lab results improve triage of patients in the ED. Furthermore, we use to perform CT in patients who refuse to undergo invasive catheter angiography (ICA) as an "informed decision by the patient". For example, this was the case in the patient shown in figure 2. We now added further details for patient selection to our text.*

Changes in the text: *Please see page 7: "According to current recommendations, patients with indeterminate evaluation of ACS were referred to CPCT based on the clinical judgement of the emergeny department physician and the cardiologist on-call taking into account all available information (1, 2). Patients with ST-elevation in electrocardiography (ECG) or with clear elevation of cardiac biomarkers including high-sensitivity troponin were only referred to CPCT when the patient refused to undergo invasive coronary angiography (ICA) as an informed decision by the patient."*

Comment 3: Did the training of the algorithm include training for the high-risk plaque features?

Reply 3: *Thank you for your comment. The machine-learning based FFR_{CT} algorithm was trained on a large database of 12'000 synthetically generated coronary anatomies. However, the algorithm does not take into account the features of coronary plaques. This is certainly a limitation of the algorithm.*

Reviewer B:

Comment 4: The sample size of your study is small. In the abstract you should also emphasize that you report preliminary results.

Reply 4: *Thank you for that comment. We now emphasized this limitation in our abstract.*

Changes in the text: *Please see page 4: "Our preliminary data show that..."*

Comment 5: How and why were patients selected for chest pain CT, was this based on ED clinician judgement or a cardiologist? Was it based on troponin results or ECG changes?

Reply 5: *Thanks for this important comment. Indeed, patient referral to CT was based on the clinical judgement of the emergency department physician and the cardiologist on-call, taking into account all results available (including patient history, symptoms, laboratory and ECG results).*
Changes in the text: *Please see page 7: "According to current recommendations, patients with indeterminate evaluation of ACS were referred to CPCT based on the clinical judgement of the emergeny department physician and the cardiologist on-call taking into account all available information."*

Comment 6: Regarding the technical feasibility of CTFFR, please provide an analysis of CT attenuation values between feasible and not feasible CT examinations.
Reply 6: *We now provide an analysis of attenuation values for patients with and without feasibility of FFRCT. However, we did not find significant differences.*
Changes in the text: *Please see page 11: "There were no significant differences in the coronary Agatston score (median 167, IQR: 33-392 versus 156, IQR: 6-513; p=0.78) and attenuation value in the aortic root (353 ± 74 versus 343 ± 82; p=0.63) between patients with and without feasible* FFR_{CT} *analyses."*

Comment 7: The result that patients with plaque rupture should not undergo CTFFR evaluation is quite important as CTFFR cannot replace the anatomic evaluation. Is there any literature on this topic you could quote?
Reply 7: *Thank you for this remark. Currently there is only sparse literature on that topic. Chinnaiyan et al. (reference 25) reported of a patient who underwent CABG of a lesion showing disruptive plaque features on coronary CT angiography with a lesion-specific* FFR_{CT} *of 0.84, which somehow matches our results. However, in this patient no invasive catheter FFR was performed.*

Comment 8: Please further elaborate on the inherent shortcomings of your retrospective single-center study.
Reply 8: *Thank you for your suggestion. We further elaborated on this limitation on page 16.*
Changes in the text: *Please see page 16: "First, the retrospective study design has inherent shortcomings and our results may reflect local practice being not generalizable to other institutions. Moreover, differences in patient demographics in other hospitals may lead to different results."*

Reviewer C:
Comment 9: Material and Methods: Please provide more details of the ML algorithm. There should be enough detail for the reader to at least assess the quality of the approach. For instance, was transfer learning used? What are the dimensions of the layers? What preprocessing was performed on the images?
Reply 9: *Thank you for this valuable comment. We extended the description of the ML algorithm for the reader to assess the quality of the used ML-based approach.*
Changes in the text: *Please see page 9: " The machine learning algorithm was trained using a fully connected deep neural network architecture with four hidden layers on a large database of 12'000 synthetically generated coronary anatomies. The input layer had 28 neurons corresponding to the different features from the coronary tree and the hidden layers contained 256, 64, 16, and 4 neurons, respectively. The output layer had a single neuron with the linear activation function. Each layer was initially pretrained as an autoencoder. Subsequently, the model was validated in 87 patients against invasive FFR measurements and showed high accuracy. The preprocessing to generate an anatomical model of a patient's coronary tree is semiautomatic. The system automatically generates centerlines and afterwards luminal contours which can be interactively edited by the reader. In a third step the reader has to mark all coronary stenosis. Subsequently, features required for the machine learning-algorithm are automatically extracted from the reconstructed anatomical model. FFRCT values are computed at all locations in the coronary tree and the resulting values are color coded in the anatomical*

model."

Comment 10: Discussion, page 13: Difference between 81 and 67 bpm, in a group with median HR of 71, may not fully explain why 32% of the patients failed FFRct. What are other possible explanations?

Reply 10: *Thank you for this comment. As outlined above, we further analyzed our data to include also the coronary Agatston Score as well as the contrast attenuation in the aortic root at the level of the coronary ostia. Comparing patients with and without feasible FFR_{CT}, however, revealed no significant differences in these two parameters. Thus, other issues might have been the reason for this issue. Certainly, emergency department patients cannot be compared to a regular outpatient population not only regarding their heart rate and heart rate variability, but also regarding motion and anxiety potentially also hampering the quality of CPCT in these acute patients.*

Changes in the text: ***"****There were no significant differences in the coronary Agatston score (median 167, IQR: 33-392 versus 156, IQR: 6-513; p=0.78) and attenuation in the aortic root (353 ± 74 HU versus 343 ± 82 HU; p=0.63) between patients with and without feasible FFR_{CT} analyses."*

Comment 11: Time constraints are a function of hardware (CPU, GPU, RAM) specifications. Please state the hardware specifications used for this study.

Reply 11: *Thanks. We agree that time constraints are a function of hardware. However, the most time-consuming steps with this software tool is the creation of the anatomical model of the coronary anatomy in each patient with the need for repeated user interaction for checking/correcting centerlines and luminal contours as well as to define coronary stenosis. Once the coronary tree is defined for each patient, the computation of FFR_{CT} values is very fast. This is our experience as well as that stated in the literature (2.4 ± 0.44 seconds on a workstation with a 3.4-GHz Intel i7 8-core processor). We added details about the hardware we used for FFR_{CT} computations as well as the information mentioned above to our revised manuscript.*

Changes in the text: *Please see page 10: "… assessed FFR_{CT} on a dedicated workstation (Intel Xeon W-2125 CPU 4.00 GHz; 32.0 GB RAM)."*

Please see page 15: "The average time needed to accomplish the on-site machine learning algorithm used in our study was recently reported as 2.4 seconds on a workstation with a 3.4-GHz Intel i7 8-core processor. However, the need for repeated user interaction in the semi-automatic workflow to create a precise anatomical model of each patient's coronary tree was still time consuming (mean duration of 28 minutes in our study), which limits the routine clinical use of this new technique."

Comment 12: page 16, limitations: The final cohort included 75% male and 25% female. Please either list this imbalance as a limitation or explain why this ratio is not a limitation.

Reply 12: *Thank you for this comment. We believe that this represents the typical population encountered in emergency departments of Western countries with acute chest pain. Thus, our population should be representative of a common clinical scenario. Still, gender was not balanced and thus we added this issue to the limitation section of our manuscript.*

Changes in the text: *Please see page 16: Finally, the final study cohort showed a gender imbalance with only 25% women.*

Comment 13: Page 16, limitations: "The number of included patients is rather low." Suggest comparison with literature. Also suggest explanation of exclusion: why did only 7% of the patients meet the inclusion criteria? Is it a biased cohort (ie. does the hospital see a skewed population?)

Reply 13: *Thank you for this important comment. Our results were quite similar to those by Chinnaiyan et al (reference 25). In their study, the authors used similar inclusion criteria (stenosis ≥25%, no analysis of patients* *with occluded vessels) for FFR_{CT} analysis as we did in our study, resulting in 13% of patients being eligible for FFR_{CT} analysis. This is comparable to our results given that from 751 CPCTs only 218 CT studies were performed for the exclusion of ACS. Nevertheless, it remains correct that the overall number of patients is rather low needing confirmation in larger, prospective outcome studies.*

Changes in the text: *Please see page 16: "Second, the number of finally included patients is rather low and our results need to be confirmed in larger, prospective outcome studies."*

Comment 14: Figure 1: The numbers do not quite add up. 56+161 = 217, but this level of the cohort selection started with 218 patients.

Reply 14: *Sorry for this mistake. We corrected figure 1 accordingly.*

Changes in the text: *Please see figure 1.*

Reviewer D:

Comment 15: Introduction, last paragraph: "While most studies so far evaluated the accuracy and utility of FFR_{CT} in patients with chronic coronary syndrome, only one study – to our knowledge – showed the feasibility of FFR_{CT} in patients with acute chest pain undergoing coronary CT angiography." Authors should update the text and references, since a recent large (FFRCT group consisted of 297 patients) study evaluating CT-Derived Fractional Flow Reserve in the Emergency Department has been recently published (Ref. Chinnaiyan KM, Safian RD, Gallagher ML, et al. Clinical Use of CT-Derived Fractional Flow Reserve in the Emergency Department. JACC Cardiovasc Imaging. 2020 Feb;13(2 Pt 1):452-461. doi:10.1016/j.jcmg.2019.05.025). The final Discussion should be revised accordingly.

Reply 15: Thank you for this suggestion. At the time of our initial submission, we were not aware of this recent publication. We added this reference along with a discussion of this publication in the revised introduction and discussion section.

Changes in the text: *Please see page 6: "While most studies so far evaluated the accuracy and utility of FFR_{CT} in patients with chronic coronary syndrome, only few studies showed the feasibility of FFR_{CT} in patients with acute chest pain undergoing coronary CT angiography."*

Please see page 14: "This hypothesis is supported by the results of a recent study of Chinnaiyan et al showing a high feasibility rate of FFR_{CT} (97%) in patients with premedication of oral and/or intra-venous beta-blockers and a target heart rate <60 bpm for coronary CT angiography."

Please see page 15: "Chinnaiyan et al. applied a different, commercially available approach for FFR_{CT} having the drawback that median turnaround times were above 2.5 hours."

Comment 16: Methods: Patient Population. Please, provide the acute coronary syndrome (ACS) definition according to guidelines.

Reply 16: *Thank you for that suggestion. We added the ACS definition to our introduction.*

Changes in the text: *Please see page 5: Acute coronary syndrome (ACS) refers to a spectrum of conditions compatible with acute myocardial ischemia and/or infarction usually reflecting an abrupt reduction in coronary blood flow. Patients may present with ST-segment elevation having myocardial infarction (STEMI) or without ST-segment elevation having either unstable angina or non-ST-segment elevation myocardial infarction (NSTEMI).*

Comment 17: Methods: Patient Population. Authors should provide a better description of enrollment criteria, according to the presence/absence of diagnostic ischemic changes on the initial ECG, and initial troponin level. If possible, it could be interesting to provide a risk score for ACS (i.e. Thrombolysis in Myocardial Infarction (TIMI) score). Moreover, were patients with arrhythmia included?

Reply 17: *Thank you for this valuable comment. We extended the description of enrollment criteria of our study. Patients were included irrespective of their heart rate, heart rate variability (i.e. also with arrhythmia), which represents the real-life scenario in the emergency department. This certainly is one reason for the lower rate of* FFR_{CT} *feasibility in our study population. The TIMI score is a valuable tool for short-term outcome prediction in patients with unstable angina or NSTEMI. However, we did not include the TIMI score in our manuscript as the focus is centered towards imaging and we consider our study cohort to be too small for a meaningful comparison of* FFR_{CT} *with the TIMI score. We added this limitation to our revised manuscript.*
Changes in the text: *Please see page 7: "According to current recommendations, patients with indeterminate evaluation of ACS were referred to CPCT based on the clinical judgement of the emergeny department physician and the cardiologist on-call taking into account all available information. Patients with ST-elevation in electrocardiography (ECG) or with clear elevation of cardiac biomarkers including high-sensitivity troponin were only referred to CPCT when the patient refused to undergo invasive coronary angiography (ICA) as an informed decision by the patient. Patients with arrhythmia were not excluded from the study."*
Please see page 16: "In these studies the value of FFR_{CT} *analysis should be assessed in comparison to clinical risk scores such as the TIMI (Thrombolysis in Myocardial Infarction) score."*

Comment 18: Methods: CT evaluation. I suggest to describe in the text the CT definition of high-risk plaque features, including positive remodeling, low attenuation plaque, spotty calcification, and the napkin ring sign.
Reply 18: *Thank you. We added the definitions of high-risk plaque features to the revised methods section.*
Changes in the text: *Please see page 8/9: "The same reader also searched for the presence of high-risk plaque features with the following definitions: Positive remodeling (remodeling index >1.1); low attenuation plaque (plaque attenuation <30 Hounsfield Units); spotty calcification (calcified plaque comprising <90° of the vessel circumference and <3 mm in length); napkin ring sign (central low attenuation plaque with peripheral higher CT attenuation)."*

Comment 19: Results: Please, provide the median Calcium Score in Agatston units of the final included population to be added in Table 1.
Reply 19: *Done. We now provide the median coronary Agatston Score with inter-quartile ranges in table 1.*
Changes in the text: *Please see table 1.*

Comment 20: Did the authors find plaque rupture or high-risk plaque features in patients with zero Calcium Score? It is an interesting point to be addressed in the Results section.
Reply 20: *Thank you for this suggestion. Indeed, we found one patient with a calcium score of 0 showing plaque rupture. Another patient with a calcium score of 0 showed vulnerable plaque features. Thereafter, both of them underwent ICA with coronary revascularization.*
Changes in the text: *Please see page 11:"5 patients showed a coronary Agatston Score of 0 (9%). One of these patients showed acute plaque rupture (n=1/5; 20%) and another showed vulnerable plaque features (n=1/5; 20%). Thereafter, both of these patients underwent ICA with coronary revascularization."*

Comment 21: Discussion: It should be interesting to add the median Calcium Score of patients in whom FFRCT was not technically feasible, to understand the rejection rate for FFRCT analysis.
Reply 21: *Thank you for your suggestion. We added the comparison of the coronary Agatston Score for patients with and without feasibility of* FFR_{CT}*. However, we did not find a significant difference between groups.*
Changes in the text: *Please see page 11: "There were no significant differences in the coronary Agatston score (median 167, IQR: 33-392 versus 156, IQR: 6-513; p=0.78) and attenuation in the aortic root (353 ± 74 versus 343 ± 82; p=0.63) between patients with and without feasible* FFR_{CT} *analyses."*

Comment 22: Please, provide a separate section for the Limitations. Other important limitations of the study to be added in the text: only a per-patient analysis was performed, and not at per-vessel level (if correct, it is not specified in the text); quantitative analysis of plaque volume and components were not performed.
Reply 22: *We added a separate section heading for limitations and added the suggested limitations to our text.*
Changes in the text: *Please see page 16:" Fourth, we assessed the culprit lesions in a dichotomous way but did not analyze the presence, absence or degree of each individual vulnerable plaque features in more detail. Also, we did not assess quantitative measures of vulnerable plaque features since our patient cohort was too small for this purpose. Fifth, results were analyzed on a per-patient but not on a per-vessel level."*

Comment 23: Figures. For a better clarity, in the study flow-chart of Figure 1 the percentages of numbers should refer to the directly related subpopulation, and not to all subjects who underwent CT for chest pain, i.e., in the box "Study cohort", I suggest the authors to change the percentage into 26%; in the box "FFRCT technically not feasible", the percentage should be 32%", and so on.
Reply 23: *According to your suggestion, we changed the percentages accordingly.*
Changes in the text: *Please see figure 1.*

Comment 24: Figures 2 and 3 are of good quality and relevant to the subject. I only suggest zooming the colorimetric scale of the FFRCT values, because it is too small to read the numbers (Panel D of Figure 2 and Panel C of Figure 3).
Reply 24: *Thank you for that suggestion. We adapted both figures accordingly.*
Changes in the text: *Please see figure 2 and figure 3.*

Comment 25: Tables: For a better clarity and comprehension of the results, provide a Table illustrating stenosis assessment (graded as mild, moderate and severe), plaque rupture, and qualitative high-risk plaque features (positive remodeling, low attenuation plaque, spotty calcification, and the napkin ring sign), stratified by FFRCT results (<=0.8 and >0.8).
Reply 25: *Thank you for this suggestion. We now provide results of the CT evaluation stratified according to FFR_{CT} results in table 2.*
Changes in the text: *Please see table 2.*