Peer Review File

Article Information: https://dx.doi.org/10.21037/cdt-24-509

Reviewer A

Comment 1: This editorial attempts falls short in providing a clear, focused analysis of the study's strengths and limitations.

Firstly, the editorial lacks structure and coherence. Moreover, the editorial misses an opportunity to critically assess the practical relevance of the ML model for general cardiology practice. It should have raised questions about whether the model's high accuracy, achieved in a registry of expert operators, would translate effectively in everyday settings with less specialized teams.

Reply 1: *Thank you for your suggestion. We edited the text as shown below.*

Changes in the text:

(Manuscript)

Generally, ML models have a potential risk of increased computational time, overfitting, and reduced interpretability (15). To address these problems, the authors utilize the SHAP method to detect the effect that the predictors had on successful primary AW crossing in CTO-PCI. However, the generalizability of this ML system in CTO-PCI practice may be limited because the ML model in this paper is based upon observational registries and the operators in the PROGRESS-CTO registry are CTO PCI experts, and CTO lesions vary greatly in complexity. Nonetheless, the purpose of ML in this paper is to identify lesions which are easier to cross by AW within the data set from the more typical CTO-PCI operators. The features of CTO lesion contributing to their algorithm including occlusion length, the presence of stump, and vessel diameter are all identifiable by non-experts and not unique to CTO-PCI operators. This can make the algorithm of ML system more practical and utilizable for non-CTO experts. The prediction probability of AW success using the ML model can still be useful to evaluate and determine the primary CTO crossing strategy before attempting the CTO-PCI procedure.

Comment 2: Additionally, the editorial does not address the model's potential to support real-time decision-making, nor does it explore how ML could meaningfully reduce procedural time, contrast use, or patient risk in practice.

Reply 2: *Thank you for your suggestion. We edited the text as shown below.*

Changes in the text:

(Manuscript)

For example, the ML system may make it possible to do real-time decision-making before or during CTO-PCI. When the ML system indicates the highest chance of antegrade crossing success, operators can firstly choose AW strategy rather than other strategies such as retrograde wiring and ADR, which may decrease the procedural time. Moreover, in cases where the AW strategy is not working well during the procedure, other alternative strategies might be attempted earlier such as retrograde wiring based on the ML model prediction of occlusion length and presence of *interventional collaterals channels etc., saving radiation/contrast exposure and perhaps lowering procedural complications.*

Comment 3: In summary, this editorial lacks a focused, in-depth critique and fails to provide meaningful insights into the practical implications or limitations of using ML in CTO interventions. A well-structured editorial should offer a more balanced and detailed analysis.

Reply 3: *Thank you for your suggestion. We think that this comment is related to Comment 1. We have revised the text as below.*

Changes in the text:
(Manuscript)
Generally, ML models have a potential risk of increased computational time, overfitting, and reduced interpretability (15). To address these problems, the authors utilize the SHAP method to detect the effect that the predictors had on successful primary AW crossing in CTO-PCI. However, the generalizability of this ML system in CTO-PCI practice may be limited because the ML model in this paper is based upon observational registries and the operators in the PROGRESS-CTO registry are CTO PCI experts, and CTO lesions vary greatly in complexity. Nonetheless, the purpose of ML in this paper is to identify lesions which are easier to cross by AW within the data set from the more typical CTO-PCI operators. The features of CTO lesion contributing to their algorithm including occlusion length, the presence of stump, and vessel diameter are all identifiable by non-experts and not unique to CTO-PCI operators. This can make the algorithm of ML system more practical and utilizable for non-CTO experts. The prediction probability of AW success using the ML model can still be useful to evaluate and determine the primary CTO crossing strategy before attempting the CTO-PCI procedure. For example, the ML system may make it possible to do real-time decision-making before or during CTO-PCI. When the ML system indicates the highest chance of antegrade crossing success, operators can firstly choose AW strategy rather than other strategies such as retrograde wiring and ADR, which may decrease the procedural time. Moreover, in cases where the AW strategy is not working well during the procedure, other alternative strategies might be attempted earlier such as retrograde wiring based on the ML model prediction of occlusion length and presence of interventional collaterals channels etc., saving radiation/contrast exposure and perhaps lowering procedural complications.

Reviewer B

Thank you for the opportunity to review your editorial "Can Machine Learning Predict Successful Chronic Total Occlusion Crossing With Primary Antegrade Wiring?". As a practicing cardiologist, I consider the research question of machine learning risk prediction of CTO success to be of importance.
Despite the development of angiographic-based algorithms, determining lesion suitability for CTO PCI and selecting the best approach remains challenging. Machine learning (ML) has emerged as a potential tool to predict AW success, utilizing lesion characteristics to guide clinical decisions.
I offer the following points to consider:

Comment 1: Introduction: Reference for the first part (line 3) "Chronic total occlusions are found in approximately one quarter of patients undergoing diagnostic angiography and are defined as 100% occlusion of a coronary artery of greater than or equal to 3 months duration" (DOI: 10.4244/EIJ-D-23-00749).

Reply 1: *Thank you for your suggestion. We have added the reference to the text as shown below.*

Changes in the text:
(Manuscript)
References

1. Galassi AR, Vadala G, Werner GS, et al. Evaluation and management of patients with coronary chronic total occlusions considered for revascularisation. A clinical consensus statement of the European Association of Percutaneous Cardiovascular Interventions (EAPCI) of the ESC, the European Association of Cardiovascular Imaging (EACVI) of the ESC, and the ESC Working Group on Cardiovascular Surgery. EuroIntervention. 2024;20:e174-e84.

Comment 2: Make abbreviations and acronyms consistent throughout the text: average area under the receiver operating characteristic curve or antegrade wiring (line 90, page 5).

Reply 2: *Thank you for pointing them out. We have made abbreviations and acronyms consistent throughout the text as below.*

Changes in the text:
(Manuscript)
Abbreviations:
AW = antegrade wiring
CTO = chronic total occlusions
LD-CTO = long-duration chronic total occlusion
ML = machine learning
PCI = percutaneous coronary intervention
ROC = receiver-operating characteristic
SD-CTO = short-duration chronic total occlusion

(Manuscript)
Extreme gradient boosting was the best performing ML model with an average area under the receiver-operating characteristic (ROC) curve of 0.775 (± 0.010). After hyperparameter tuning, the average area under the ROC curve of the extreme gradient boosting model was 0.782 in the training set and 0.780 in the testing set.

(Manuscript)
From the PROGRESS CTO registry, Rempakos, et al. showed that proximal cap ambiguity (odds ratio [OR]: 0.52; 95% confidence interval [CI], 0.46-0.59), side branch at the proximal cap (OR: 0.85; 95% CI, 0.77-0.95), blunt/no stump (OR: 0.52; 95% CI: 0.47-0.59), longer lesion length (OR [per 10 mm increase]: 0.79; 95% CI, 0.76-0.81), moderate to severe calcification (OR: 0.73; 95%

CI, 0.66-85 0.81), moderate to severe proximal tortuosity (OR: 0.67; 95% CI, 0.59-0.75), bifurcation at the distal cap (OR: 0.66; 95% CI, 0.59-0.73), left anterior descending artery CTO (OR [vs right coronary artery]: 1.44; 95% CI, 1.28-1.62) and left circumflex CTO (OR [vs right coronary artery]: 1.22; 95% CI, 1.07-1.40), non-in-stent restenosis lesion (OR: 0.56; 95% CI, 0.49-0.65), and good distal landing zone (OR: 1.18; 95% CI, 1.06-1.32) were independently associated with primary AW crossing success, using multivariable logistic regression analysis (2).

Comment 3: I would describe a little better the objective of the study, the population, the methods.

Reply 3: *As you recommended, we have modified the text as below.*

Changes in the text:
(Manuscript)
In the article entitled "Predicting Successful Chronic Total Occlusion Crossing With Primary Antegrade Wiring Using Machine Learning", published on JACC: Cardiovascular Interventions, the authors analyzed the data of CTO-PCI using primary AW. The objective of this study was to develop and validate the ML model with high predictive capacity for successful primary AW in CTO-PCI (1).

(Manuscript)
The authors utilized the data from 12,136 primary AW cases performed between 2012 and 2023 at 48 U.S. and non-U.S. centers in the PROGRESS CTO registry (Prospective Global Registry for the Study of Chronic Total Occlusion Intervention; NCT02061436) to create 5 ML models. The 14 lesion characteristics were used for the prediction of successful CTO crossing using primary AW. They were as follows; blunt/no stump, occlusion length, vessel diameter, aorto-ostial lesion, proximal cap ambiguity, in-stent restenosis, side branch at proximal cap, bifurcation at distal cap, poor distal landing zone, interventional collateral channels, calcification, tortuosity, target vessel, and prior attempt to open CTO.

Comment 4: The transitions between paragraphs could be smoother. For example, the transition from the ML model results to the pathological studies is a bit abrupt. Also a connecting sentence explaining in the introduction that a lot of importance has been given to AI and machine learning in cardiology but perhaps their use in CTOs is less clear (consider https://doi.org/10.1093/eurheartj/ehae465 and DOI: 10.2459/JCM.0000000000001664)

Reply 4: *As you indicated, we have revised the text and added the references as shown below.*

Changes in the text:
(Manuscript)
To investigate the microstructure in CTO lesions, all clinical studies have a crucial limitation that the resolution of current imaging technologies including intravascular ultrasound, optical

coherence tomography and coronary computed tomography angiography are not as precise as histology. Previous pathological studies analyzing CTO lesions lend support for the use of this ML model (12-14) as a predictive for CTO-PCI success. From the pathological point of view, CTO lesions are classified into the short-duration CTO (SD-CTO) lesions or the long-duration CTO (LD-CTO) lesions based on the differences of structural constituents.

(Manuscript)
Machine learning (ML) encompasses several different algorithmic models and statistical methods to solve problems without specialized programming. Although a lot of importance has been given to artificial intelligence and ML in cardiology (2,3), their use in CTO-PCI has not been elucidated so far. The use of ML models may be helpful in determining the suitability of specific lesions for AW approaches.

(Manuscript)
References
2. Lüscher TF, Wenzl FA, D'Ascenzo F, et al. Artificial intelligence in cardiovascular medicine: clinical applications. Eur Heart J. 2024;45:4291-304.
3. Madaudo C, Parlati ALM, Di Lisi D, et al. Artificial intelligence in cardiology: a peek at the future and the role of ChatGPT in cardiology practice. J Cardiovasc Med (Hagerstown). 2024;25:766-71.

Comment 5: The paper emphasizes extreme gradient boosting as the best-performing algorithm, but more insights into why this model performed better than others and how specific features influence decision-making could strengthen the discussion. It would also be useful to explore limitations in the model's generalizability across different patient populations, given that CTOs vary greatly in complexity. Moreover, the lack of a more detailed comparison between traditional risk models and ML-driven approaches leaves the reader with unanswered questions about the true added value of AI in this setting. Exploring these points could deepen the understanding of how ML enhances decision-making in CTO interventions and clarify its potential clinical utility. Learn more about this topic in the discussion.

Reply 5: *We have revised the text as shown below according to your suggestions.*

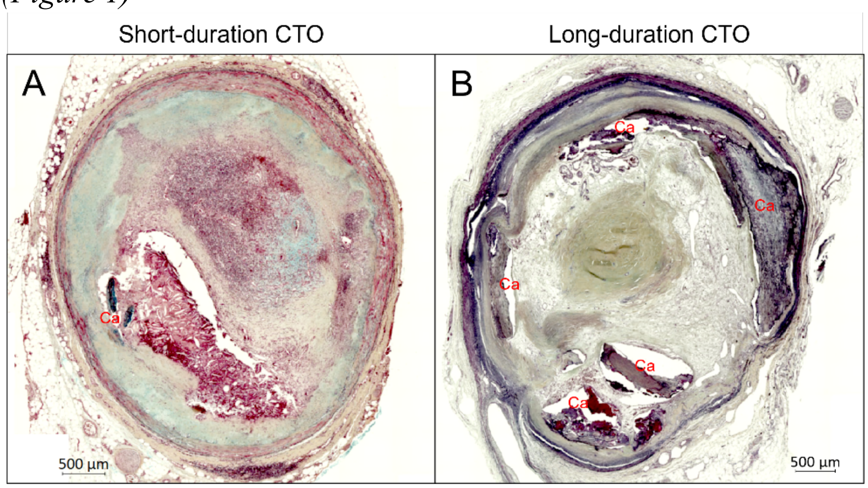
Changes in the text:
(Manuscript)
Generally, ML models have a potential risk of increased computational time, overfitting, and reduced interpretability. To address these problems, the authors utilize the SHAP method to detect the effect that the predictors had on successful primary AW crossing in CTO-PCI. However, the generalizability of this ML system in CTO-PCI practice may be limited because the ML model in this paper is based upon observational registries and the operators in the PROGRESS-CTO registry are CTO PCI experts, and CTO lesions vary greatly in complexity.

Comment 6: I'm not convinced by the figure, as clear and explanatory as it is of the text, I would rather have a figure that comments on the JACC study that the editorial deals with.

Reply 6: *Figure 1 shows that a long-duration CTO (LD-CTO) lesion has more calcification, compared to a short-duration (SD-CTO) lesion, which suggests that the unsuccessful AW occurs more frequently in LD-CTO lesions, compared to SD-CTO lesions. We have revised Figure 1, figure legends and the text as below.*

Changes in the text:
(Manuscript)
Representative figures of SD- and LD-CTO lesions are shown in Figure 1. Figure 1 shows that the LD-CTO has more calcification than the SD-CTO. Previous studies have shown that LD-CTOs had longer lesions, more blunt/no stump lesions, more calcification, smaller vessel diameter, and more proximal cap ambiguity, compared to SD-CTOs (9, 10).

(Figure 1)



(Figure legends)
Figure 1. Representative pathological images of CTO sections. (A) A short-duration CTO is defined as a lesion including principally proteoglycan, which is shown by the green or blue staining in MP, and fibrin. (B) A long-duration CTO is defined as a lesion consisting of type 1 collagen, shown by the green or gray stain in MP. Note that (B) long-duration CTO has more calcification, compared to (A) short-duration CTO. Ca = calcification. CTO = chronic total occlusion. MP = Movat and Pentachrome. A, B: MP stains.

Reviewer C

Comment 1: Line 46 "symptoms of angina and thus not uncommonly performed". This sentence sounds awkward (small grammatical correction)

Reply 1: *Thank you for your suggestion. We corrected the text as below.*

Changes in the text:
(Manuscript)
CTO revascularization has been shown to significantly improve patients' quality of life and reduce symptoms of angina.

Comment 2: Line 77-78 "Although the PCI techniques used to recanalize CTO lesions have been developed substantially over the past two decades along with the retrograde approach and antegrade dissection". Another awkward sentence. Perhaps something more like, "Although CTO-PCI techniques have advanced substantially, with retrograde approach and antegrade dissection re-entry (ADR) being performed by select operators, AW crossing remains the most common primary approach in CTO-PCI."

Reply 2: *Thank you for your suggestions. We have revised the text as shown below.*

Changes in the text:
(Manuscript)
Although CTO-PCI techniques have advanced substantially, with retrograde approach and antegrade dissection re-entry (ADR) being performed by select operators, AW crossing remains the most common primary approach in CTO-PCI.

Comment 3: Line 107: I would emphasise that the short- vs long-duration refers to chronological duration, not lesion length as this is not a common classification.

Reply 3: *Thank you for your suggestion. We have added the following sentence to the revised text.*

Changes in the text:
(Manuscript)
From the pathological point of view, CTO lesions are classified into the short-duration CTO (SD-CTO) lesions or the long-duration CTO (LD-CTO) lesions based on the differences of structural constituents. The short- or long-duration refers to chronological duration, not lesion length.

Comment 4: Line 108 "lesions based on the differences of structural constituents" Again, poorly phrased but not inaccurate. Needs reworking.

Reply 4: *Thank you for your suggestion. We have revised the text as below.*

Changes in the text:
(Manuscript)

From the pathological point of view, CTO lesions are classified into the short-duration CTO (SD-CTO) lesions or the long-duration CTO (LD-CTO) lesions based on the differences in plaque characteristics.

Comment 5: I would reconsider the statement, "Because the ML model in this paper is based upon observational registries and the operators in the PROGRESS-CTO registry are CTO PCI experts, the applicability of this ML system to general CTO PCI practice may be limited". The purpose of ML in this context is to identify lesions which are easier to cross antegrade, and are thus within the skillset of the more typical Interventionalist. The features contributing to their algorithm (stump presence, lesion length, diameter, ISR, etc.) are all identifiable by non-experts and not unique to CTO operators. I would argue this makes the algorithm MORE utilisable by non-CTO experts. The following statement on lines 128-130 holds true - "using the ML model can still be useful to evaluate and determine the primary CTO crossing strategy before attempting the CTO PCI procedure."

Reply 5: *Thank you for your suggestion. We have revised the text as below.*

Changes in the text:
(Manuscript)
However, the generalizability of this ML system in CTO-PCI practice may be limited because the ML model in this paper is based upon observational registries and the operators in the PROGRESS-CTO registry are CTO PCI experts, and CTO lesions vary greatly in complexity. Nonetheless, the purpose of ML in this paper is to identify lesions which are easier to cross by AW within the data set from the more typical CTO-PCI operators. The features of CTO lesion contributing to their algorithm including occlusion length, the presence of stump, and vessel diameter are all identifiable by non-experts and not unique to CTO-PCI operators. This can make the algorithm of ML system more practical and utilizable for non-CTO experts. The prediction probability of AW success using the ML model can still be useful to evaluate and determine the primary CTO crossing strategy before attempting the CTO-PCI procedure.