**Response letter**

Dear Editor and Reviewers,

Thank you for your efforts and for giving us the opportunity to revise our manuscript titled 'HAGMN-UQ: Hyper Association Graph Matching Network with Uncertainty Quantification for Coronary Artery Semantic Labeling' for publication in the *Medical Image Analysis* journal.

**Editors’ comments:**

Please discuss the comments from Reviewer #2 -- Associate Editor

**Reviewer #2**:  I partially agree with Reviewer 2's comments. Semantic labeling can indeed be divided into two components: semantic segmentation and classification. The former involves pixel-wise classification of X-ray angiographic images into foreground (coronary arteries) and background regions, while the latter further classifies the identified foreground regions into different vascular segments. The authors of this article obtained semantic segmentation results using a manual method, primarily focusing on the subsequent classification task. As noted in Reviewer 2's comment 2, this approach does affect the robustness and usability of the entire semantic labeling process. However, the precise semantic segmentation of coronary arteries is a hot research topic in its own right and deserves to be addressed in the future work of this article.

A. Thank you for your comments. We agree that the proposed algorithm involves multiple steps, including vascular tree extraction, centerline generation, and graph matching for coronary artery semantic labeling, which relies on pixel-wise classification of X-ray angiography into foreground and background regions. However, even with a binary mask of the coronary artery, accurately classifying coronary arterial branches remains challenging due to the morphological similarities among different types of arteries, as well as the variability in anatomical structures and arterial anatomy under different projection view angles.

While building an end-to-end model for coronary artery semantic segmentation may seem more straightforward—since it directly provides pixel-to-pixel semantic mapping—there are inherent challenges. As described in the introduction and discussion sections, coronary artery topology and anatomy vary significantly between patients, while pixel intensities remain similar across different types of arteries. This makes it difficult for CNN-based end-to-end models to reliably distinguish individual arteries. As a result, most existing studies focus primarily on major artery semantic segmentation [1–3]. In contrast, our model is capable of extracting multiple artery branches simultaneously, providing a comprehensive understanding of the coronary artery vasculature and offering more detailed information for clinical applications.

The binary segmentation results may influence the performance for semantic labeling using the proposed HAGMN-UQ, however, the influence is limited. In our manuscript, we designed multiple experiments to demonstrate the robustness of the proposed model through several robustness tests:

1. In Section 4.5, we conducted both uni-site and cross-site experiments. The uni-site experiments confirmed that the proposed HAGMN-UQ delivered impressive performance on our multi-center datasets. The cross-site experiments demonstrated that while using a cross-template may slightly lower model performance, the proposed HAGMN-UQ still achieved an average accuracy above 0.83.
2. In Section 4.6, we performed multiple robustness tests. We evaluated the model’s performance on arteries of different lengths, its graph-matching capabilities using incomplete trees, and its performance on ICAs with incorrect inlet points. These experiments indicate that even without using a perfect graph generated by manual or automated annotation of the arterial tree, the proposed HAGMN-UQ still achieved impressive performance with an accuracy above 0.84.
3. We also employed our previously modified ZORRO [4,5] method to explain the graph-matching model. The explanation revealed that topological features, as well as arterial positional features, were significantly more important in graph matching than pixel-based features. This result further validated our hypothesis: recognizing the significance of topology in arterial identification, we were motivated to transform arteries and their interconnections into graph structures. Therefore, incorporating both topological and positional features for coronary artery semantic labeling is both practical and reasonable. And graph matching model is robust and suitable for this task.

While we acknowledge these advantages, we also recognize that the proposed approach is not without challenges. One of the primary concerns is the method's sensitivity to the quality of pre-processing steps. During ICA binary segmentation, human intervention is sometimes required to adjust the binary contours. Several recently published papers [2,6,7] on binary coronary artery segmentation using ICAs have the potential to be incorporated into our work to further improve artery semantic segmentation. In the future, more precise coronary artery binary segmentation algorithms/models will need to be developed.

We modified the Section 5. Limitation and Future Work in the revised manuscript.

(Section 5. Limitation and Future Work)

However, despite these advantages, the proposed approach is not without its challenges. One of the primary concerns lies in the sensitivity of the method to the quality of pre-processing steps. Although the robustness experiments demonstrate the robustness of HAGMN-UQ using corrupted graphs, its performance still decreases. During the ICA binary segmentation, human intervention is required to adjust the binary contours if needed. In the future, more precise coronary artery binary segmentation algorithms/models [2,6,7] have the potential to be incorporated into our work to further improve artery semantic segmentation. For ICA graph generation, hyperparameters are required to adjust the length of the arterial segment and the radius threshold of the arterial segment to preprocess the arterial skeleton. Thus, we developed our in-house software for image preprocessing, as shown in Figures S1 and S2. Compared to an end-to-end approach, such as image semantic segmentation using CNN, the proposed approach contains multiple steps, meaning that subsequent steps may be influenced by preceding ones.

**Reference**

[1] Jun TJ, Kweon J, Kim Y-H, Kim D. T-Net: Nested encoder–decoder architecture for the main vessel segmentation in coronary angiography. Neural Networks. 2020 Aug;128:216–233.

[2] Zhang H, Gao Z, Zhang D, Hau WK, Zhang H. Progressive Perception Learning for Main Coronary Segmentation in X-ray Angiography. IEEE Transactions on Medical Imaging. 2022;1–1.

[3] Xian Z, Wang X, Yan S, Yang D, Chen J, Peng C. Main Coronary Vessel Segmentation Using Deep Learning in Smart Medical. Huang C, editor. Mathematical Problems in Engineering. 2020 Oct 21;2020:1–9.

[4] Funke T, Khosla M, Rathee M, Anand A. ZORRO: Valid, Sparse, and Stable Explanations in Graph Neural Networks. IEEE Trans Knowl Data Eng. 2023;1–12.

[5] Zhao C, Xu Z, Jiang J, Esposito M, Pienta D, Hung G-U, Zhou W. AGMN: Association graph-based graph matching network for coronary artery semantic labeling on invasive coronary angiograms. Pattern Recognition. 2023 Nov;143:109789.

[6] Khan SS, Khan M, Khan RS. Automatic Segmentation and Classification to Diagnose Coronary Artery Disease (AuSC-CAD) Using Angiographic Images: A Novel Framework. 2023 18th International Conference on Emerging Technologies (ICET) [Internet]. Peshawar, Pakistan: IEEE; 2023 [cited 2024 Oct 8]. p. 110–115. Available from: https://ieeexplore.ieee.org/document/10374634/

[7] Wang G, Zhou P, Gao H, Qin Z, Wang S, Sun J, Yu H. Coronary vessel segmentation in coronary angiography with a multi-scale U-shaped transformer incorporating boundary aggregation and topology preservation. Phys Med Biol. 2024 Jan 10;69(2). PMID: 38200403