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Supplementary appendix

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SUPPLEMENTARY METHODS

Expert Plaque Measurements from CCTA

In axial and multiplanar views, the expert reader placed a region of interest in the ascending aorta to define normal blood pool contrast attenuation and control points in the coronary artery lumen to define the centreline. Atherosclerotic lesions were defined as any tissue $\geq$1mm^2 within or adjacent to the lumen that could be discriminated from surrounding pericardial tissue, epicardial fat, or lumen, and identified in $\geq$2 planes. In coronary segments $\geq$1·5 mm within the 18-segment SCCT model of the coronary tree[1], the expert reader visually identified all lesions and manually defined their proximal and distal limits. Adaptive scan-specific Hounsfield Unit (HU) thresholds for plaque components were then automatically generated. Segmentation of the vessel wall and lumen were performed by a previously described algorithm[2], with manual adjustment as required. Plaque volume (mm^3) was calculated on a per-lesion level for the following components: total plaque, calcified plaque, noncalcified plaque, and low-attenuation plaque (fixed attenuation threshold <30 HU). The respective plaque burdens (%) were calculated as: plaque volume / analysed vessel segment volume × 100. Quantitative diameter stenosis (%) was calculated as the ratio of minimal lumen diameter to the mean of 2 (proximal and distal) non-diseased reference points[3].

IVUS Image Analysis

Vessel (external elastic membrane) and lumen contours were manually traced at every 1-mm cross-section. Minimal luminal area was measured at the site of the smallest lumen. Total plaque volume was calculated as the vessel volume minus lumen volume[4]. Matching of lesions between IVUS and CCTA was performed by an independent observer blinded to the results of the CCTA analysis. Stretched multiplanar reformatted CCTA images were compared with longitudinal reconstructed IVUS datasets using at least two orthogonal catheter angiography views. The proximal and distal limits of plaques were matched using anatomical landmarks, such as distance from the aorto-coronary ostium, target lesions, side branches, or calcifications[4].

Training the Deep Learning Model

CCTA image data were normalized using minmax normalization. We used a pre-trained DenseNet and Xavier initialization[5] as the initial weights of the model. Optimization was performed using the Adam method[6] to minimize the Dice Loss and implemented with the Monai library. The learning rate started at 1e-3 and was dynamically reduced as the validation loss plateaued. Early stopping was utilized to reduce overfitting. The performance of the DL model was evaluated in the internal validation dataset using the Dice coefficient which measures the overlap between the ground truth and predicted output image, with values ranging from 0 (no overlap) to 1 (complete overlap). The model configuration providing the best Dice coefficient for internal validation was then applied to the test set.

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Supplementary Table 1. Clinical characteristics of the overall study population (n=1,196)

Age (years)	65·2±9·8
Male sex	780 (65·2)
Diabetes mellitus	221 (18·5)
Hypertension	650 (54·3)
Dyslipidaemia	746 (62·3)
Smoking (current or former)	448 (37·4)
Family history of coronary artery disease	194 (16·2)
Prior coronary artery disease	393 (32·8)

Data are n (%) or mean ± standard deviation.

Supplementary Table 2. CT scan parameters for each study site

Cohort & Site	CT scanner	Detector rows	Voltage (kVp)	Matrix Size (pixels)	Pixel Size (mm)	Slice Thickness (mm)	Reconstruction
Training							
Cedars-Sinai I	Siemens Definition & Definition Flash	Dual source 128	100, 120	512 × 512	0·35 0·39	0·3	Filtered back projection Iterative reconstruction
MonashHeart	Canon Aquilion ONE	320	100, 120	512 × 512	0·37	0·25	Iterative reconstruction
Kusatsu Heart Center I	GE Lightspeed	64	120	512 × 512	0·39	0·6	Filtered back projection
Erlangen	Siemens Definition	Dual source 128	120	512 × 512	0·30	0·4	Filtered back projection
DIAMOND	Siemens Biograph mCT	128	120	512 × 512	0·36	0·5	Filtered back projection
PREFFIR - Aberdeen	GE Discovery 710	128	100, 120	512 × 512	0·40	0·6	Filtered back projection
PREFFIR - Manchester	Siemens Definition AS	64	100, 120	512 × 512	0·40	0·4	Filtered back projection
PREFFIR - Edinburgh	Siemens Biograph mCT	128	100, 120	512 × 512	0·32	0·5	Filtered back projection
Testing							
SCOT-HEART - Site 1	Phillips Brilliance	64	100, 120	512 × 512	0·40	0·4	Filtered back projection
SCOT-HEART - Site 2	Toshiba Aquilion ONE	320	100, 120	512 × 512	0·35	0·25	Filtered back projection Iterative reconstruction
SCOT-HEART - Site 3	Siemens Biograph mCT	128	100, 120	512 × 512	0·36	0·5	Filtered back projection
Cedars-Sinai II	Siemens Definition & Definition Flash	Dual source 128	100, 120	512 × 512	0·35 0·39	0·5	Filtered back projection Iterative reconstruction
Kusatsu Heart Center II	GE Lightspeed	64	120	512 × 512	0·39	0·6	Filtered back projection

CTA = computed tomography angiography. DIAMOND = Dual Antiplatelet Therapy to Reduce Myocardial Injury. ICA = invasive coronary angiography. PREFFIR = Prediction of Recurrent Events with 18F-Fluoride. SCOT-HEART = Scottish Computed Tomography of the Heart.

Supplementary Table 3. Performance of deep learning versus expert plaque measurements in the external validation cohort (1,081 lesions)

Plaque measurement	ICC (95% CI)	Spearman correlation
Total plaque volume (mm^3)	0·953 (0·946-0·959)	0·910
Noncalcified plaque volume (mm^3)	0·914 (0·901-0·926)	0·855
Calcified plaque volume (mm^3)	0·947 (0·939-0·954)	0·917
Low-attenuation plaque volume (mm^3)	0·827 (0·803-0·848)	0·808
Vessel volume (mm^3)	0·991 (0·990-0·992)	0·984
Diameter stenosis (%)	0·882 (0·861-0·901)	0·856
Total plaque burden (%)	0·813 (0·759-0·822)	0·787
Noncalcified plaque burden (%)	0·811 (0·772-0·829)	0·783
Calcified plaque burden (%)	0·936 (0·926-0·944)	0·883
Low-attenuation plaque burden (%)	0·808 (0·762-0·805)	0·779

CI = confidence interval. ICC = intraclass correlation coefficient.

Supplementary Table 4. Interobserver variability for expert reader plaque measurements

Plaque measurement	ICC (95% CI)	Spearman correlation
Total plaque volume (mm^3)	0.973 (0.963-0.981)	0.949
Noncalcified plaque volume (mm^3)	0.969 (0.957-0.978)	0.940
Calcified plaque volume (mm^3)	0.953 (0.935-0.967)	0.919
Low-attenuation plaque volume (mm^3)	0.915 (0.888-0.939)	0.843
Vessel volume (mm^3)	0.994 (0.993-0.995)	0.987
Diameter stenosis (%)	0.919 (0.885-0.942)	0.870
Total plaque burden (%)	0.835 (0.768-0.883)	0.795
Noncalcified plaque burden (%)	0.831 (0.762-0.880)	0.789
Calcified plaque burden (%)	0.955 (0.936-0.968)	0.914
Low-attenuation plaque burden (%)	0.824 (0.691-0.918)	0.791

CI = confidence interval. ICC = intraclass correlation coefficient.

Supplementary Table 5. Reproducibility of deep learning plaque measurements using coronary centrelines derived from different expert readers

Plaque measurement	ICC (95% CI)	Spearman correlation
Total plaque volume (mm^3)	1 (1-1)	1
Noncalcified plaque volume (mm^3)	0·998(0·997-0·998)	0.992
Calcified plaque volume (mm^3)	0·997 (0·995-0·998)	0.979
Low-attenuation plaque volume (mm^3)	0·990 (0·986-0·993)	0.976
Vessel volume (mm^3)	1 (0·999-1)	0.998
Diameter stenosis (%)	0·975 (0·965-0·982)	0.953
Total plaque burden (%)	0·979 (0·971-0·985)	0.946
Noncalcified plaque burden (%)	0·979 (0·970-0·985)	0.948
Calcified plaque burden (%)	0·984 (0·978-0·988)	0.964
Low-attenuation plaque burden (%)	0·986 (0·980-0·990)	0.973

CI = confidence interval. ICC = intraclass correlation coefficient.

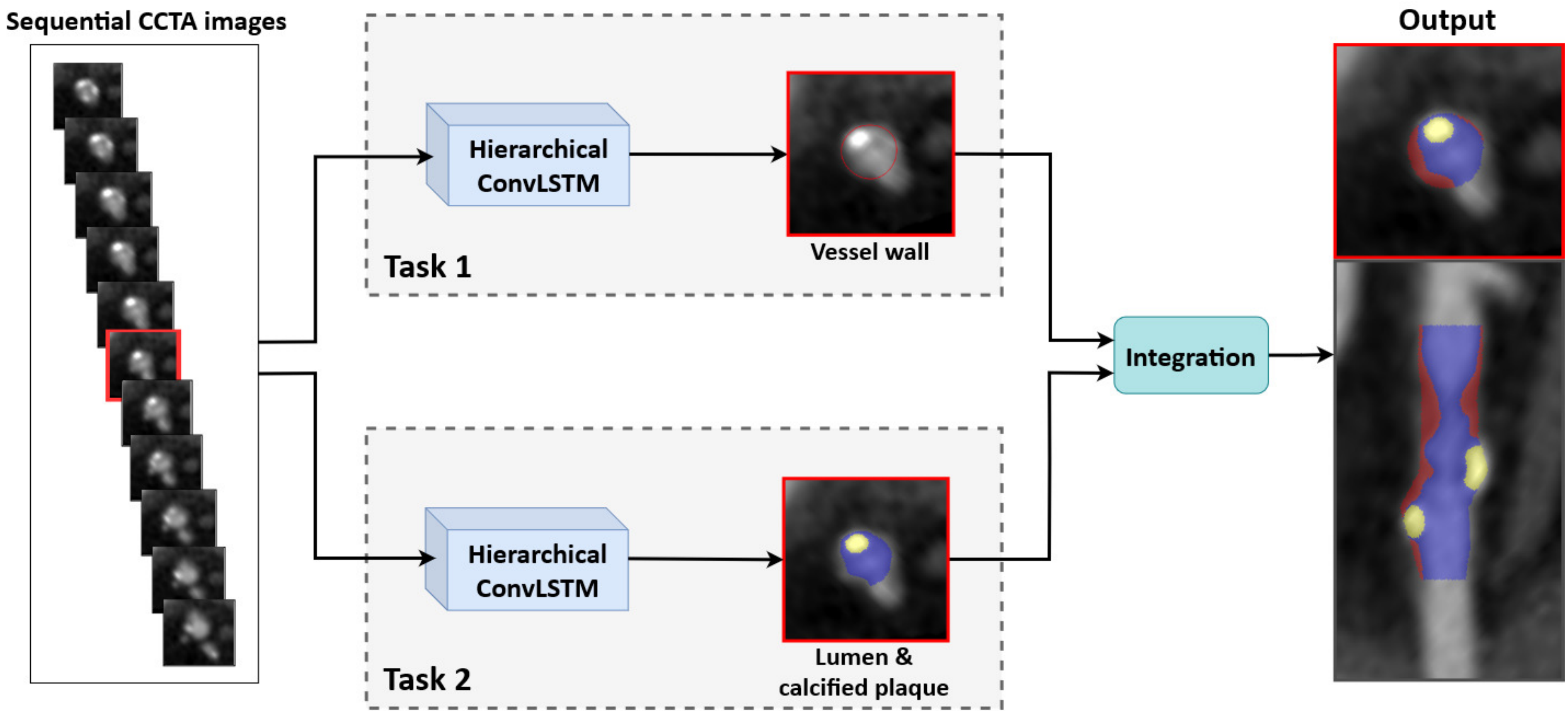
Supplementary Table 6. Diagnostic performance of deep learning for detection of significant stenosis

			Sensitivity	Specificity	PPV	NPV	Accuracy
Deep Learning vs Expert CCTA Interpretation	≥50%	Per-vessel	95·4 (84·2-99·4)	95·3 (89·4-98·5)	89·1 (77·7-95·1)	98·1 (92·9-99·5)	95·3 (90·6-98·1)
		Per-patient	100·0 (85·8-100·0)	88·5 (69·9-97·6)	88·9 (73·4-95.9)	100·0	94·0 (83·5-98·8)
	≥70%	Per-vessel	94·4 (72·7-99·9)	99·2 (95·9-99·9)	94·4 (70·6-99·2)	99·2 (95·1-99·9)	98·7 (95·3-99·8)
		Per-patient	100·0 (69·2-100·0)	97·5 (86·8-99·9)	90·9 (59·1-98·6)	100·0	98·0 (89·4-99·9)
Deep Learning vs Invasive Coronary Angiography	≥50%	Per-vessel	97·9 (88·9-99·9)	91·2 (83·9-95·9)	83·9 (73·7-90·7)	98·9 (93·0-99·9)	93·3 (88·1-96·8)
		Per-patient	100·0 (89·7-100·0)	68·8 (41·3-90·0)	87·2 (76·7-93·4)	100.0	90·0 (78·2-96·7)
	≥70%	Per-vessel	90·5 (69·6-98·8)	97·7 (93·4-99·5)	86·4 (67·2-95·1)	98·4 (94·4-99·6)	96·7 (92·4-98·9)
		Per-patient	90·0 (68·3-98·8)	96·7 (82·8-99·9)	94·7 (72·3-99·2)	93·6 (79·5-98·2)	94·0 (83·5-98·8)

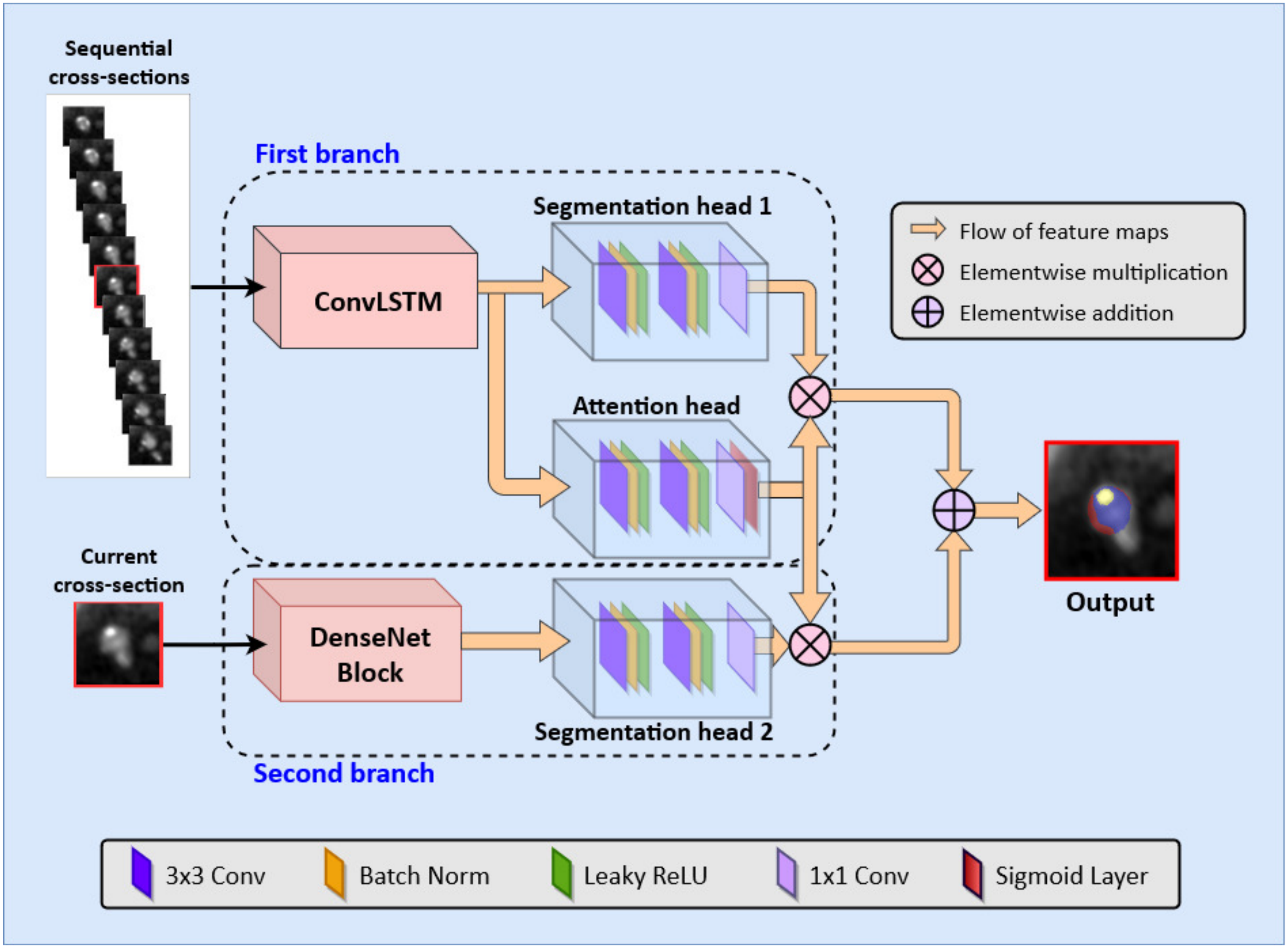
Data are percentage (95% confidence interval).
CCTA = coronary computed tomography angiography. NPV = negative predictive value. PPV = positive predictive value.

Supplementary Figure 1. Deep learning workflow for coronary segmentation

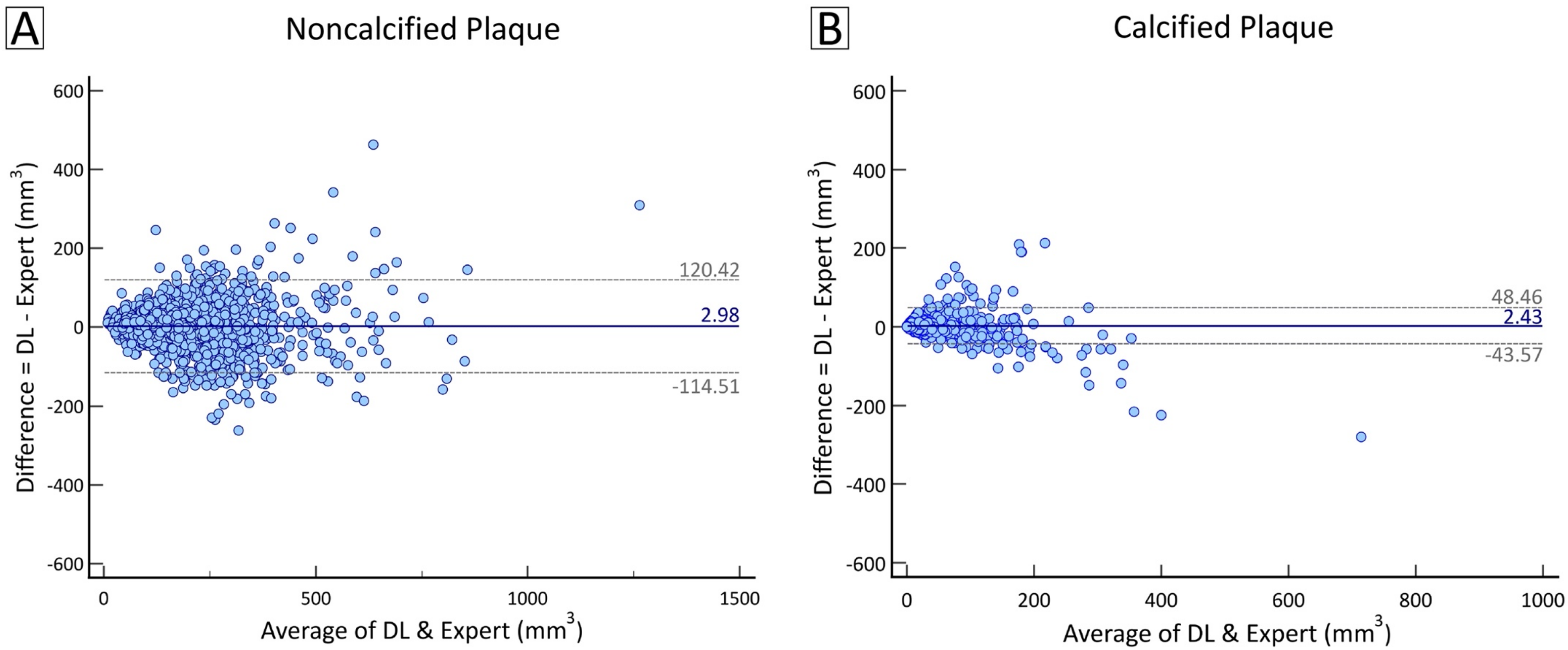
The Hierarchical convolutional long short-term memory (ConvLSTM) Network performed segmentation of coronary computed tomography angiography (CCTA) images in a multitask approach for: 1) vessel wall; and 2) lumen and calcified plaque (blue and yellow overlay, respectively). All remaining voxels between the vessel wall and lumen were defined as noncalcified plaque (red overlay).



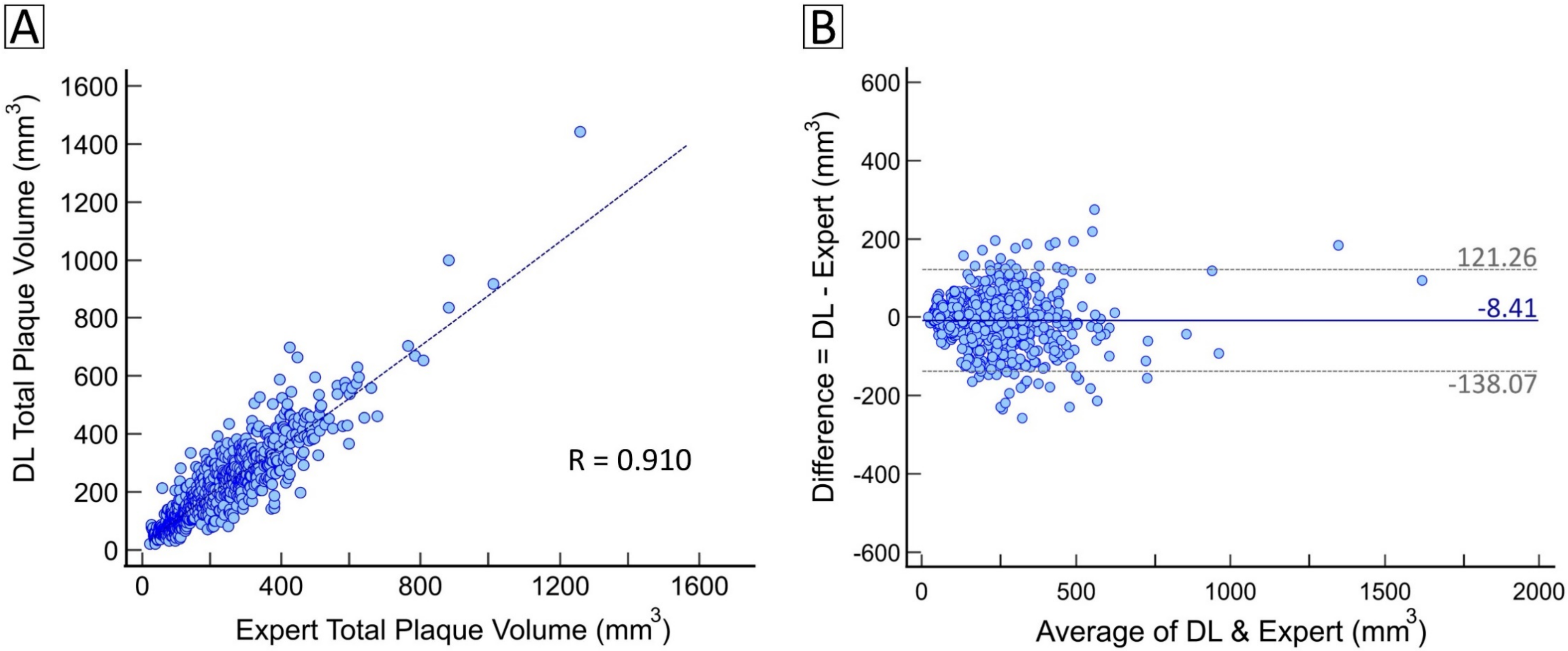
Supplementary Figure 2. Architecture of the Hierarchical ConvLSTM Network
The Hierarchical ConvLSTM Network had two branches, each containing a feature extractor and segmentation head. The first branch used a ConvLSTM to extract features from the current cross-section as well as five adjacent sections on either side. The second branch used a DenseNet block to extract features from the current vessel cross-section. The segmentation head in both branches performed semantic segmentation using convolutional layers (Conv), batch normalization (Batch Norm), and a Leaky Rectified Linear Unit (ReLU). An attention head combined the outputs of both branches.



Supplementary Figure 3. Noncalcified and calcified plaque volume measured by deep learning versus expert readers in the test set
Bland-Altman plots of **(A)** noncalcified and **(B)** calcified plaque volume measured by deep learning (DL) versus expert readers in 1,901 lesions from the overall test set.

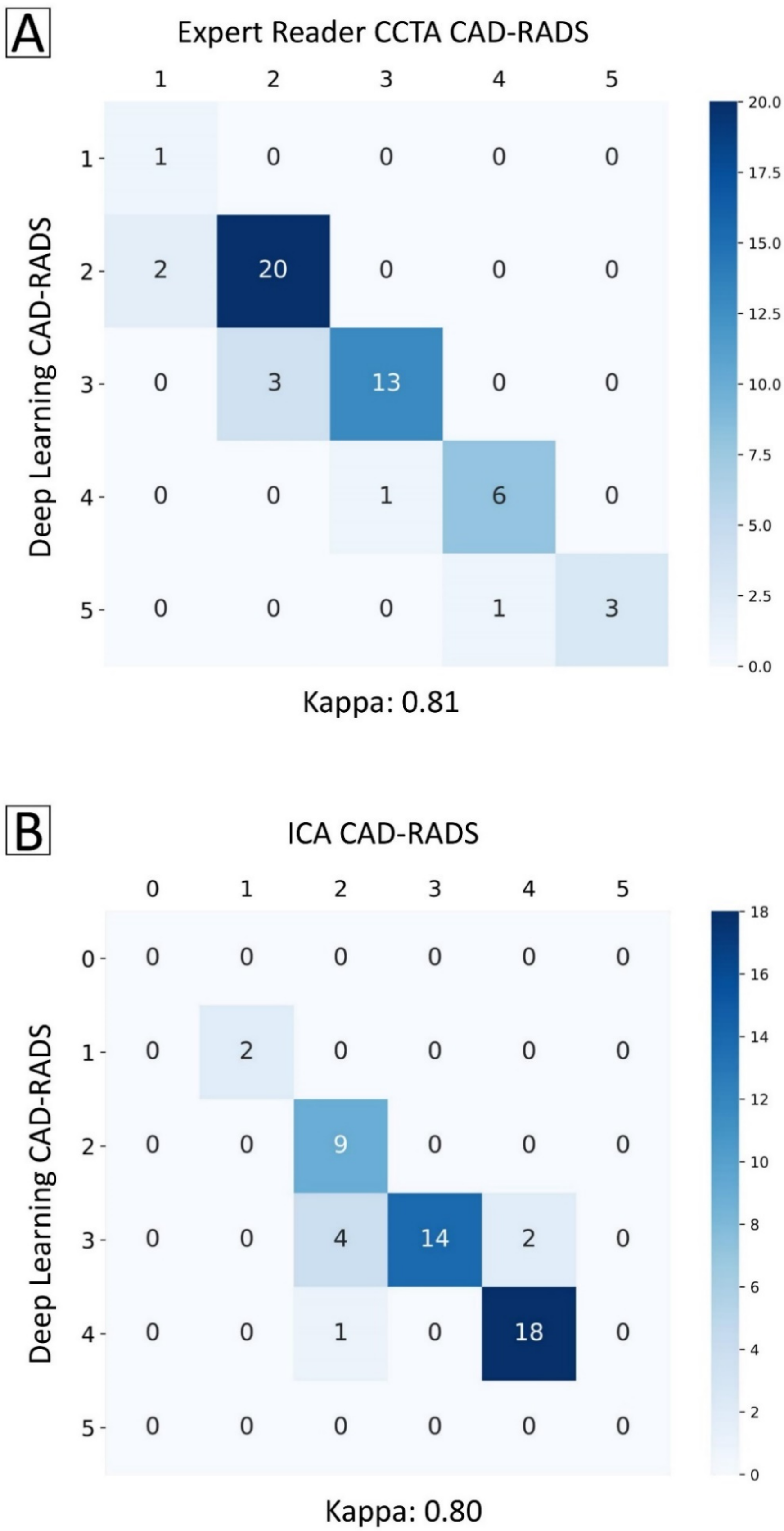


Supplementary Figure 4. Total plaque volume measured by deep learning versus expert readers in the external validation cohort
(A) Correlation and **(B)** Bland-Altman plots comparing total plaque volume measured by deep learning (DL) versus expert readers in 1,081 lesions from the external validation cohort.



Supplementary Figure 5. Per-patient CAD-RADS categorization by deep learning versus expert readers and invasive coronary angiography

Confusion matrices of deep learning versus **(A)** expert readers and **(B)** invasive coronary angiography (ICA) for the categorization of stenosis severity according to the Coronary Artery Disease Reporting and Data System (CAD-RADS).



Supplementary Figure 6. Prognostic value of deep learning-based low-attenuation plaque burden for myocardial infarction
Kaplan-Meier cumulative incidence curves of fatal or nonfatal myocardial infarction (MI) in patients from the SCOT-HEART trial stratified by low-attenuation plaque burden above or below 4%, the optimal cut-off determined by receiver operating characteristic curve analysis.