

Review

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Applications of artificial intelligence-based models in vulnerable carotid plaque

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Abstract

Carotid atherosclerotic disease is a widely acknowledged risk factor for ischemic stroke, making it a major concern on a global scale. To alleviate the socio-economic impact of carotid atherosclerotic disease, crucial objectives include prioritizing prevention efforts and early detection. So far, the degree of carotid stenosis has been regarded as the primary parameter for risk assessment and determining appropriate therapeutic interventions. Histopathological and imaging-based studies demonstrated important differences in the risk of cardiovascular events given a similar degree of luminal stenosis, identifying plaque structure and composition as key determinants of either plaque vulnerability or stability. The application of Artificial Intelligence (AI)-based techniques to carotid imaging can offer several solutions for tissue characterization and classification. This review aims to present a comprehensive overview of the main concepts related to AI. Additionally, we review the existing literature on AI-based models in ultrasound (US), computed tomography (CT), and Magnetic Resonance Imaging (MRI) for vulnerable plaque detection, and we finally examine the advantages and limitations of these AI approaches.

Keywords: Cardiovascular imaging, carotid, AI, vulnerable plaque



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INTRODUCTION

Cardiovascular disease is a prominent contributor to disability and premature mortality worldwide^[1-3]. In the context of carotid atherosclerosis, a systematic review revealed that approximately 21.1% [95% confidence interval (CI) 13.2-31.5] of individuals aged 30 to 79 years worldwide have carotid plaques^[4]. Notably, a considerable portion of ischemic strokes, ranging from 8% to 15%, are caused by large artery atherosclerosis in the carotid arteries. This condition can lead to embolism and hypoperfusion resulting from vascular stenosis^[5]. Beyond the degree of carotid artery stenosis, plaque morphology and composition have shown a crucial role in terms of plaque vulnerability or stability^[6,7], and are strongly associated with cardiovascular complications^[8,9]. Early identification of carotid atherosclerotic disease is a mainstay to reduce the healthcare burden and improve patient outcomes. In this scenario, non-invasive carotid imaging modalities, including ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI), have proven their efficacy in assessing and characterizing plaque features that serve as predictors of future cardiovascular events, directing patient stratification and management^[10].

Artificial intelligence (AI) encompasses a wide range of computer science techniques that enable machines to perform tasks resembling human intelligence. Within the field of cardiovascular imaging, AI has seen significant advancements and progress in recent years^[11-18]. AI models have demonstrated their utility in different carotid imaging areas, including the assessment of plaque morphology and composition^[15].

This review aims to provide a comprehensive overview of the key concepts related to AI. Furthermore, we will discuss the current literature on AI-based models in US, CT, and MRI for the detection of vulnerable plaques. Finally, we will examine the advantages and limitations of these AI models.

NOTIONS OF AI

AI is a generic term including a diverse range of techniques enabling machines to acquire knowledge from experience and emulate human cognitive processes^[11,12,15,16,19]. The discipline of AI contains several subfields, such as Machine Learning (ML). ML is an AI technique that solves problems by extracting patterns from raw data without explicit programming. In ML, features are vital inputs to the algorithms and are typically task-specific. However, determining the necessary features in advance for a given task can pose a complicated hurdle. Deep Learning (DL) is a branch of ML that has evolved by allowing the algorithms to learn and extract pertinent features autonomously^[12,20] [Figure 1]. This ability to automatically extract features, without the need for human intervention or explicit guidance, has led to a shift away from traditional processing methods towards the adoption of deep artificial neural networks (DNN). The architecture of a DNN consists of input, hidden, and output neurons organized into multiple layers. Neurons within the same layer and across different layers are interconnected. During the learning process, if the network achieves the desired outcome, the connections between neurons responsible for that achievement are strengthened. Conversely, if the desired outcome is not reached, the connections are weakened. This iterative mechanism allows the algorithm to refine itself automatically until a high level of accuracy or performance is attained.

Categorization of ML tasks

ML algorithms can be categorized into different classes depending on the type of data used for training, including supervised, unsupervised, and hybrid paradigms such as semi-supervised learning, weakly supervised learning, and self-supervised learning^[20].

Supervised learning

In supervised learning, the learning algorithms are trained with labeled data, where each sample in the

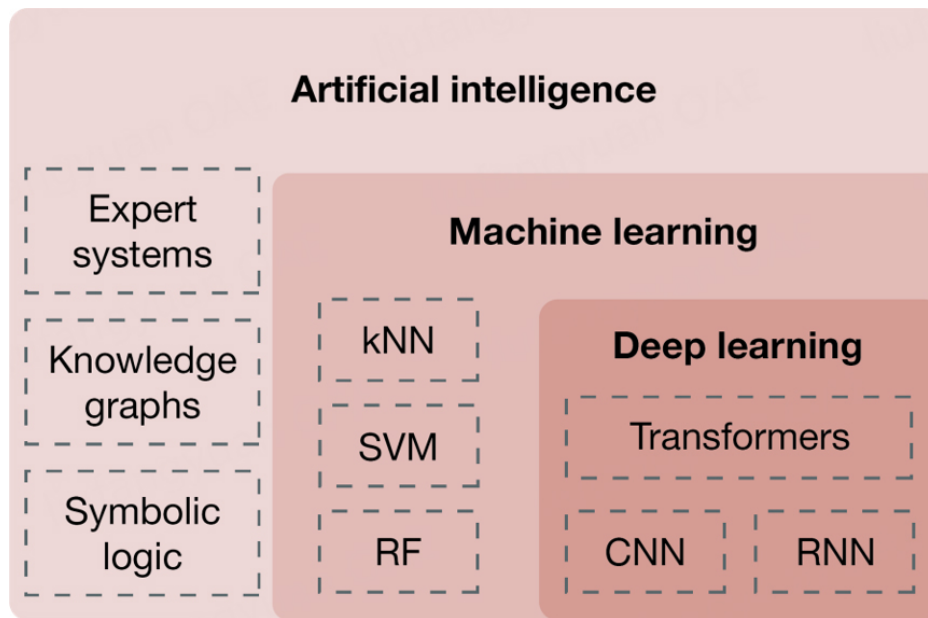


Figure 1. Hierarchical taxonomy of artificial intelligence methodologies. The taxonomy outlines the progressive relationship of artificial intelligence, machine learning, and deep learning, featuring specific algorithmic examples within each category. kNN: k-nearest neighbors; SVM: support vector machines; RF: random forests; CNN: convolutional neural networks; RNN: recurrent neural networks.

dataset is associated with a specific output. These labels enable the algorithms to learn the mapping between the input data and the corresponding output labels. During the training process of a supervised learning algorithm, the learned parameters are iteratively adjusted to minimize the difference between the predicted output and the true output. This iterative update aims to align the algorithm's predictions as closely as possible with the provided labels in the training data. Once the training is completed, the accuracy is evaluated using test data that was not seen during the training stage. Some examples of supervised learning algorithms are linear regression models, support vector machines, and tree-based and nearest-neighbor algorithms.

Unsupervised learning

In unsupervised learning, algorithms are presented with vast amounts of data without any accompanying labels or ground-truth information. The objective of unsupervised learning is to extract meaningful patterns, structures, or representations from the data itself.

Hybrid paradigms

Hybrid paradigms that bridge the gap between supervised and unsupervised learning encompass semi-supervised, weakly-supervised, and self-supervised learning approaches. Semi-supervised learning combines labeled and unlabeled data during the training process. By leveraging labeled data, the algorithm learns from explicit examples and gains insights from them. Additionally, the utilization of unlabeled data helps in capturing supplementary information and enhancing the algorithm's generalization capabilities. In weakly-supervised learning, the training data contains partial or noisy labels, rather than complete and accurate labels. The algorithms are designed to learn from this limited label information and make predictions or classifications based on it. In self-supervised learning, only unlabeled data is accessible, and the learning task is derived or generated from the data itself. The algorithm constructs its own learning task by creating surrogate tasks from the input data. By solving these surrogate tasks, the algorithm learns meaningful representations or features that can then be used for downstream tasks. [Figure 2](#) summarizes the taxonomy of ML models according to the nature of supervision.

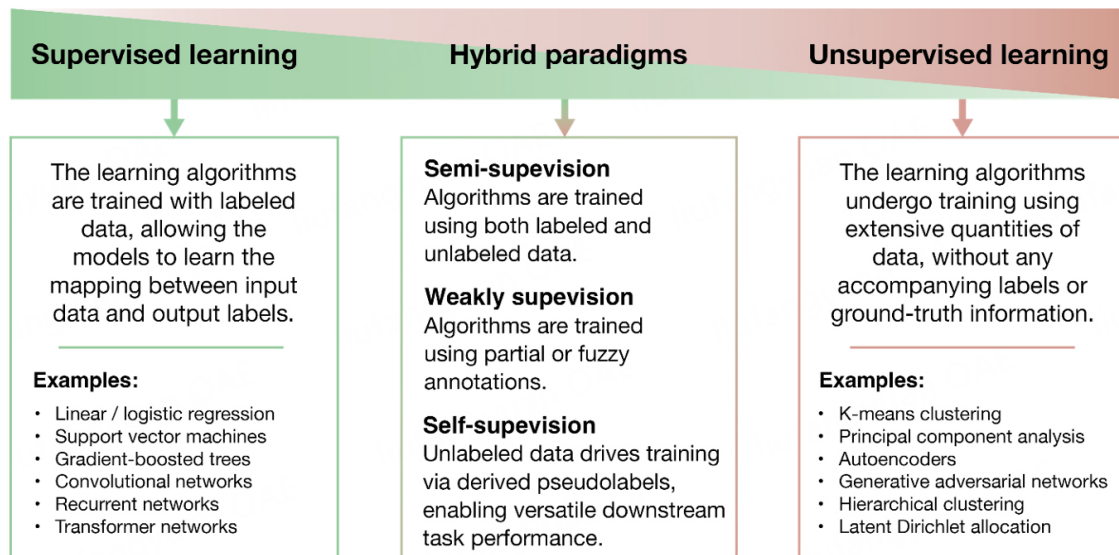


Figure 2. Taxonomy of Machine Learning (ML) tasks categorized by the nature of supervision. The taxonomy showcases the categorization of ML tasks based on their supervision types, outlining their defining characteristics and representative examples.

Convolutional neural networks in diagnostic imaging

Deep learning methodologies applied to medical image analysis often rely heavily on convolutional neural networks (CNNs). CNNs are a specific type of artificial neural network designed to excel in interpreting visual data, particularly images and videos. The architecture of a CNN comprises multiple interconnected layers, primarily including convolutional layers. These convolutional layers play a pivotal role in enabling the network to learn incrementally abstract and complex hierarchical features from the input data. In essence, a CNN processes input data through a series of convolutional and pooling layers, which collectively extract features of varying complexities. The convolutional layers apply filters to the input data, capturing distinctive patterns and features. Subsequent pooling layers downsample the data, reducing its spatial dimensions while retaining relevant information. This hierarchical feature extraction allows the network to discern both low-level features, such as edges and textures, as well as high-level semantic features, such as complex structures and shapes^[21]. For different tasks, the architecture of the final layers of a CNN varies. In classification tasks, the final layer typically consists of one or more fully connected layers followed by a softmax activation function, enabling the network to output class probabilities. In object detection tasks, the final layer often combines classification and bounding box regression, generating predictions for both the presence of objects and their spatial locations. In segmentation tasks, the final layers consist of convolutional layers that produce dense pixel-wise predictions, assigning each pixel to a specific class. Lastly, for regression tasks, the output layer typically comprises a single neuron with an appropriate activation function, providing continuous numerical predictions.

In 2015, Ronneberger *et al.* introduced U-Net, a segmentation network rooted in Fully Convolutional Networks and tailored explicitly for medical image segmentation^[22]. Since its inception, the U-Net architecture has solidified its position as one of the most extensively employed segmentation architectures within the medical domain^[22]. Originally, the U-Net architecture was deployed for segmenting plaque morphology^[23]. The hallmark of the U-Net architecture, alongside its variations, is its distinct U-shaped design comprising two interconnected pathways. The first path, known as the contracting pathway, is dedicated to extracting progressively abstract and intricate features while preserving both local and global contextual information. The second path, referred to as the expanding path, entails upsampling the image back to its original spatial resolution through the incorporation of skip connections. This dual-path

approach enables the network to learn localized classification information and enhances the output's spatial resolution^[24].

However, the original U-Net architecture was not immune to certain limitations, such as challenges with over-segmentation and under-segmentation. To overcome these issues, diverse optimization strategies have been employed to U-Net on various fronts, including network architecture, loss function design, heuristic rules, and preprocessing techniques^[23]. Among the extension of UNet architectures adopted in the field of segmentation, no-new-net UNet (nnU-Net stands out as the state-of-the-art framework. Differing from previous DL architectures, nnU-Net is an automated DL-driven segmentation framework that automatically adapts its configurations, including preprocessing, network architecture, training, and postprocessing^[25]. It demonstrates the capability to adapt to new datasets without requiring manual intervention, consistently outperforming many previous methods^[25]. In the realm of imaging analysis, transformers are emerging as a popular approach^[26]. Dosovitskiy *et al.* introduced the vision transformer (ViT) method, which considers image patches as the fundamental units of information in an image patch, as opposed to individual pixels^[27]. ViT embeds image patches into a common space and acquires the relationships between these embeddings through self-attention modules^[27]. The utilization of transformers, such as the U-shaped CSWin transformer, has been recently proposed in carotid arteries segmentation, showing promising results^[28].

Explainable and interpretable AI models

The interpretability of AI-based models is crucial for the application of these models, particularly in healthcare. Building confidence in systems is challenging when their decision-making process remains enigmatic. Some AI models are characterized by a "black box" nature, alluding to algorithms so intricate that human comprehension is not immediate. Addressing the substantial challenges posed by such "black box" models, a growing body of literature focuses on crafting AI models that are both explainable and interpretable^[29,30].

The terms "interpretability" and "explainability" delineate two distinct concepts. Interpretability denotes the capacity to discern cause and effect within an AI model. In essence, an interpretable algorithm is one that a human can apprehend clearly^[29,30]. Conversely, explainability pertains to the ability to elucidate an AI algorithm's decision-making mechanism using language intelligible to humans. This empowers individuals to grasp why a model generates a specific outcome^[29,30].

In the context of vulnerable carotid plaque, an explainable AI model might involve well-established features of plaque instability as input data, rather than employing "raw" images. In contrast, interpretability could be achieved by utilizing histology specimens as ground truth, enabling the validation of model inferences against well-established pathological characteristics.

IMAGING FEATURES OF PLAQUE VULNERABILITY

Atherosclerosis is a multifactorial disease that stems from the interaction of genetic and environmental factors and is a well-established risk factor for ischemic stroke^[31-34]. Histopathological studies have provided evidence that specific types of carotid plaques have a significantly increased likelihood of causing ischemic stroke and thrombotic complications, irrespective of the degree of stenosis. Carotid plaque imaging can detect some biomarkers of vulnerability. The main imaging determinants of carotid plaque vulnerability described in the literature are intraplaque hemorrhage (IPH), thinning or rupture of the fibrous cap (FC), lipid-rich necrotic core (LRNC), plaque burden, surface morphology, plaque inflammation, plaque neovascularization, and calcifications^[10,35-38]. See [Figure 3](#). Mainstream non-invasive measurements of

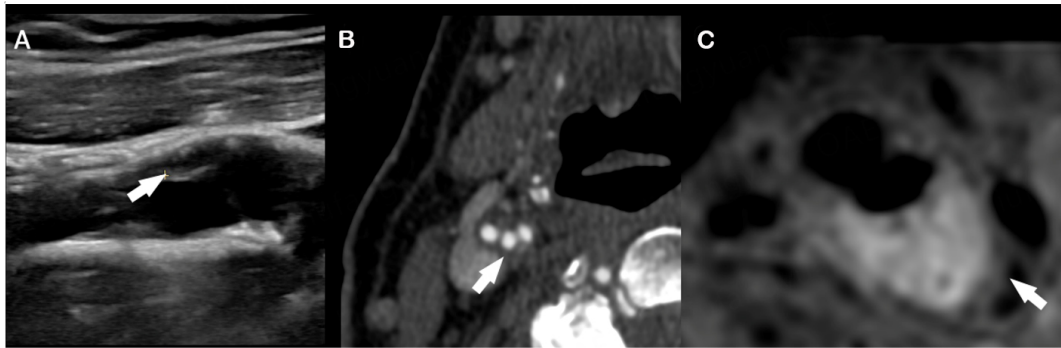


Figure 3. Multimodality imaging features of vulnerable plaques. (A) depicts a hypoechoic plaque at the carotid bulb, revealing a lipid necrotic core with a thin fibrous cap on B-mode ultrasound imaging. (B) an ulcerated plaque is evident through computed tomography. (C) showcases intraplaque hemorrhage as observed in MRI images.

carotid atherosclerotic plaque include US, CT, and MRI. These imaging techniques, with different pros and cons, provide valuable information about plaque composition and morphology as well as a characterization of luminal stenosis.

Plaque burden

The relevance of plaque size in determining the risk of clinical events, often referred to as atherosclerotic “burden” [i.e., maximum wall thickness (MWT) plaque volume, total plaque area, and normalized wall index (NWI)] has been widely recognized^[39]. In “real life” clinical practice, US is the preferred initial imaging modality for evaluating carotid plaque burden due to its wide availability and practicality^[35,40,41].

Plaque surface morphology

Plaque surface characteristics, either irregularities or ulceration, represent an important determinant of vulnerability associated with the occurrence of cerebrovascular events^[42]. Carotid plaques are typically classified as smooth, irregular, or ulcerated^[43]. Plaque surface evaluation can be performed using US, CT, and MRI^[10,44]. CT with iodinated contrast agent administrations serves as the benchmark non-invasive imaging method for assessing plaque ulcerations, which is defined as contrast material that protrudes from the vascular lumen into the plaque, typically covering a distance of at least 1 mm^[8,9]. This imaging technique encounters limitations due to plaque calcifications, leading to subsequent beam-hardening artifacts. However, this limitation could be addressed through photon-counting scanners, enabling the elimination of calcified plaque components from the lumen^[45-47].

Plaque composition

Beyond plaque morphology, plaque composition plays a crucial role in determining plaque vulnerability. Plaque composition refers to the types and distribution of various components within the plaque, such as LRNC, fibrous tissue, calcifications, IPH, and inflammation. MRI has proven to be highly accurate in the detection of features of vulnerability in carotid plaques. By employing a multi-sequence protocol (including T1-weighted, T2-weighted, proton density, and TOF sequences) along with a specialized carotid coil, MRI can effectively identify significant characteristics such as the presence of a LRNC, thinning or rupture of the fibrous cap, and intraplaque hemorrhage IPH^[8,40,48]. The characterization of different plaque compositions can also be evaluated with US and CT. Carotid plaque composition was traditionally assessed qualitatively using US based on grayscale values, taking into account echogenicity and heterogeneity. However, this qualitative information can be further enhanced by incorporating quantitative analyses, specifically grayscale median^[8,49]. Nonetheless, US lacks the ability to effectively differentiate between IPH and LRNC, thereby constraining its utility in the characterization of carotid plaques^[8]. In CT imaging, the

differentiation of carotid atherosclerotic plaque components relies on Hounsfield unit (HU) densities. Carotid plaques are categorized into three main types based on their HU values, namely fatty (< 60 HU), mixed (60-130 HU), and calcified (> 130 HU)^[50]. The main limitation of CT techniques is a substantial overlap of HU values among LRNC, fibrous tissues, and IPH. Additionally, certain artifacts, such as beam-hardening, edge-blur, and halo effect artifacts, further restrict the CT's capability to evaluate plaque composition^[8]. Promising results in plaque characterization are emerging with the introduction of photon-counting computed tomography technologies, which can generate quantitative maps depicting the spatial distribution of particular atomic elements within a plaque^[45-47].

General imaging techniques limitations

Beyond the individual constraints of each imaging modality in detecting vulnerable plaques, it is essential to understand the overall limitations of the techniques employed. Specifically, the utilization of US is constrained by the sonographers' experience, plaque calcifications, and anatomical considerations^[51]. CT limitations encompass exposure to ionizing radiation and potential adverse responses to iodinated contrast agents. Moreover, CT faces limitations in effectively distinguishing some plaque subcomponents according to the HU^[8]. Finally, MRI limitations include extended acquisition periods, a requirement for specialized hardware like carotid coils to achieve high-resolution images, and constrained availability^[9].

AI-BASED MODEL FOR AUTOMATIC CAROTID PLAQUE SEGMENTATION

Several AI-based models have been proposed to automatically segment carotid plaques, facilitating the evaluation of plaque burden and surface morphology^[52-59]. An automatic plaque segmentation can improve clinical workflow and reduce some limitations of the manual assessment, including long analysis time and inter-observer variability. The current segmentation models proposed can be broadly categorized into two main approaches: those based on traditional image processing and those based on DL. The traditional image processing technique relies on manual or semi-automated algorithms to segment the carotid plaque region. Conversely, the DL models can automatically segment carotid plaque without human input. However, these methods require large annotated datasets for training and may involve complex network architectures^[23].

Automatic carotid plaque segmentation in US

Menchón-Lara *et al.* proposed an AI-based image segmentation method for an automatic intima-media thickness measurement in 60 longitudinal ultrasound images of the common carotid arteries, comparing the automatic segmentation with four manual tracings^[53]. The authors developed a three-stage neural network. Firstly, the US images were preprocessed to automatically detect the region of interest. Then, a network ensemble is utilized to perform pixel classification within the region of interest, distinguishing between two categories: "IMT-boundary" pixels and "non-IMT-boundary" pixels. After obtaining the binary image through the previous classification process, post-processing techniques are applied to extract the final contours representing the interfaces of the lumen-intima and media-adventitia boundaries. The AI models achieved a mean absolute distance, polyline distance, and centerline distance of 0.03763 ± 0.02518 mm, 0.03670 ± 0.02429 mm, and 0.03683 ± 0.02450 mm, respectively^[53].

Jain *et al.* developed a four-layer deep learning U-Net architecture for plaque wall segmentation in the common carotid arteries using two different demographic groups of patients with atherosclerotic carotid disease^[60]. The proposed model achieved a mean accuracy, dice-similarity, and correlation coefficient of 99.01, 86.89, and 0.92, respectively, using a mixed cohort of the different demographic groups^[60].

Automatic carotid plaques segmentation in CT

Dos Santos *et al.* developed a fully automated vascular imaging software tool called VASIM using CT images from 59 randomly selected patients to segment and analyze atherosclerosis in the extracranial carotid arteries^[57]. The image analysis algorithm of VASIM consists of five consecutive stages. The first step involves loading the image stack or dataset of the patient for analysis. The second step is further divided into two steps: airway segmentation and carotid segmentation. In the third step, the algorithm aims to delineate or outline the boundaries of the vascular wall, which includes the inner lumen and outer wall regions of the carotid arteries. Then, the region of carotid atherosclerotic plaque was extracted and identified. Finally, VASIM enables the extraction of several metrics on a side-wise basis, including the minimum lumen area in the region of interest, the maximum area percentage occupied by the arterial wall in a slice, the maximum area percentage occupied by the plaque, and the maximum stenosis of the carotid artery calculated by the algorithm.

The proposed model achieved an overall accuracy of 71% with an average time for the whole segmentation analysis of 1,381 s^[57].

Bortosova *et al.* conducted a secondary analysis of prospectively collected data from the Rotterdam study with the aim of developing a DL-based model for automated segmentation and volume measurement of carotid plaque composition, specifically focusing on intracranial carotid artery calcifications^[56]. The DL model was trained using non-contrast CT scans, and two observers manually delineated ICAC to serve as the ground truth for training and evaluation. The performance of the DL model was then compared to the manual segmentations and volume measurements generated by an independent observer, serving as a reference standard for accuracy assessment. The DL-based model yielded a sensitivity of 83.8% and a positive predictive value of 88.0% in automatic internal carotid calcification with an excellent intraclass coefficient (0.98) between automatic and manual volume measures. Additionally, the automated delineation was judged as more accurate than manual delineations in 131 regions in the blinded visual comparison (131 of 225, 58.2%; $P = 0.01$)^[56].

Automatic carotid plaques segmentation in MRI

The paper by Wu *et al.* introduces an AI-based network, which utilizes convolutional neural networks for the early detection of carotid atherosclerosis using vessel wall-MRI images^[58]. The authors collected 1,057 carotid MRI scans to develop automated software for carotid wall segmentation^[58].

The proposed AI network consists of two main components: the segmentation subnetwork and the diagnosis subnetwork. The network leverages manual annotations of the lumen area, outer wall area, and lesion types following the modified AHA criteria as ground truth for training. The segmentation subnetwork is designed using a deep U-shaped convolutional neural network (CNN) architecture and trained using the triple Dice loss to provide the vessel wall map as morphological information. Conversely, the diagnosis subnetwork consists of two deep CNNs: an image stream and a morphology stream. The image stream processes the black-blood vessel wall-MRI images, while the morphology stream operates on the obtained vessel wall map. These two streams are mixed to derive the diagnosis results for atherosclerosis. The proposed DL models achieved high segmentation performance (0.96 Dice for the lumen and 0.96 Dice for the outer wall) and excellent diagnostic accuracy [0.95 area under the receiver-operating characteristic curve (AUC) and 0.89 Accuracy] in the test dataset. This AI model demonstrates remarkable performance when applied to a different test dataset for both segmentation and diagnosis tasks (0.95 Dice for the lumen and 0.95 Dice for the outer wall, 0.92 AUC and 0.87)^[58].

Ziegler *et al.* developed a segmentation pipeline utilizing a CNN called DeepMedic using contrast-enhanced MR angiography images from 194 subjects of the Swedish CardioPulmonary bioImage Study (SCAPIS) to automatically segment the carotid arteries^[59]. The segmentations produced by the DL model were evaluated through both quantitative and qualitative analyses. In the quantitative assessment, multi-class data from 46 vessels was compared to manually generated ground truth data using various metrics, including the Dice similarity coefficient (DSC), Matthews Correlation Coefficient, F2 score, F0.5 score, and true positive ratio. In the qualitative assessment, the carotid black-blood vessel wall-MRI images were examined qualitatively and the quality by an experienced vascular MRI observer. In the testing cohort, the DL model achieved average scores of DSC = 0.80 ± 0.13 , MCC = 0.80 ± 0.12 , F2 = 0.82 ± 0.14 , F0.5 = 0.78 ± 0.13 , and TPR = 0.84 ± 0.16 ^[59].

CAROTID PLAQUE VULNERABILITY

The integration of AI models in the characterization of carotid plaque can be an additive tool to facilitate the automated distinction of vulnerable plaques, assisting clinicians in risk stratification and guiding personalized treatment decisions for patients with carotid artery disease [Figure 4].

AI-based models to detect vulnerable plaque using US images

Zhang *et al.* tested the performance of US-based texture analysis combined with LASSO regression to detect carotid plaque vulnerability^[61]. The overall cohort comprised 150 consecutive patients with suspected cerebrovascular events, and randomized 7:3 into the training ($n = 105$) and testing ($n = 45$) sets^[61]. The conventional diagnostic model proposed was constructed with four variables of conventional ultrasound (including surface morphology, fibrous cap state, plaque echo, and plaque ulcer formation) and combined with the texture feature model. In the training set, the conventional ultrasound-texture feature combined model achieved an AUC of 0.88 and a C-index of 0.89. In the testing set, the proposed combined model achieved an AUC of 0.87 and a C-index of 0.84^[61]. Akkus *et al.* developed a software package to detect intraplaque neovascularization called carotid intraplaque neovascularization quantification software (CINQS) using 45 contrast-enhanced ultrasound images of carotid plaques from 29 patients^[62]. The derived intraplaque neovascularization parameters (segmentation-based intraplaque neovascularization surface area and intraplaque neovascularization to plaque surface area ratio) were compared to the consensus visual score of two experienced physicians based on a three-point scale achieving excellent agreement with visual intraplaque neovascularization scores with an AUC of 0.92 and 0.93^[62].

A prospective multicenter study evaluated the performance of a DL-based model to identify carotid plaque vulnerability in 205 patients with carotid atherosclerosis using contrast-enhanced ultrasound video and histopathological or high-resolution MRI findings as reference standard^[63]. The authors used a convolutional neural network combined with video information aggregation and compared its performance with two experienced radiologists who manually examined the contrast-enhanced ultrasound video. The proposed DL model demonstrated significant improvements over manual assessment in assessing the vulnerability of carotid plaque, achieving an AUC of 0.85 (*vs.* 0.69 for the manual assessment) with the training cohort and 0.87 (*vs.* 0.66 for the manual assessment) with the validation cohort^[63]. Saba *et al.* developed a series of AI-based models (four machine learning systems, one transfer learning system, and one deep learning) for tissue characterization and classification, namely Atheromatic 2.0 and AtheroPoint, using US-based carotid artery plaque images^[64]. The overall cohort comprises 506 symptomatic and asymptomatic patients collected from multiple centers and randomized 9:1 into the training and testing set. The accuracy of the AI models proposed was 93.55%, 94.55%, and 89%, with an AUC of 0.938, 0.946, and 0.889, respectively^[64].

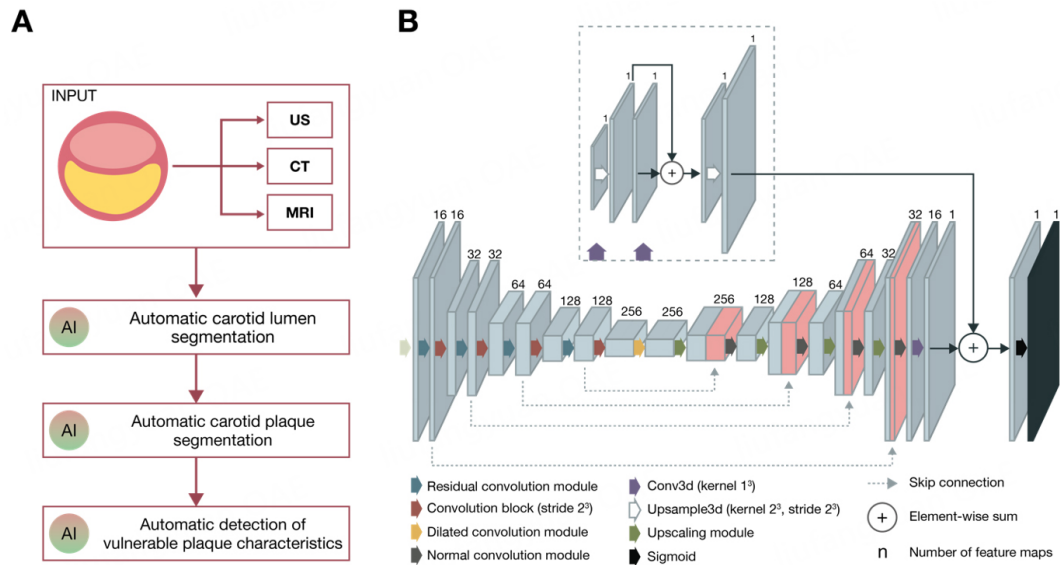


Figure 4. Application of artificial intelligence for vulnerable plaque detection across various imaging modalities. (A) Illustration of a standard processing pipeline encompassing automated segmentation of the carotid lumen, followed by automated plaque detection, segmentation and characterization. (B) The architecture of CarotidNet^[54], a deep learning model built upon the renowned U-Net framework. The CarotidNet integrates a contraction path and an expansion path connected by skip connections, serving the purpose of automating the segmentation of the carotid artery lumen.

AI-based models to detect vulnerable plaque using CT images

A radiomics analysis combined with a ML approach (including logistic regression, support vector machine, and classification and regression tree analysis) was also developed using CT angiography features in the pilot study of Cilla *et al.*^[65]. The authors enrolled 30 consecutive patients with carotid atherosclerosis and divided the carotid plaque into “hard” and “soft” using histological specimens as a ground truth. The predictive radiomic model for identifying “soft” plaques was built in different consecutive steps, including (1) the evaluation of the pairwise feature interdependencies; (2) the choice of the top-ranked features using univariate analysis; (3) the determination of the relative importance of features through a stepwise backward elimination approach. Finally, the identified significant features were employed to construct the models for binary classification of carotid plaques. Among the ML classifiers evaluated, the support vector machine demonstrated the highest performance with accuracy, precision, recall, and F-score equal to 86.7, 92.9, 81.3, and 86.7%, respectively. Additionally, the classification and regression tree analysis model utilizing the entropy and volume features achieved an accuracy of 86.7% with an AUC of 0.987^[65].

Buckler *et al.* evaluated the diagnostic performance of a ML approach for determining plaque vulnerability on CT images in comparison with histologic specimens from carotid endarterectomy classified as minimal disease, stable plaque, or unstable plaque based on the modified AHA histological definition^[66]. The overall cohort includes 53 patients with carotid atherosclerosis randomly assigned to the derivation cohort ($n = 30$) and to the validation cohort ($n = 23$). The ML-based algorithm demonstrated high accuracy for plaque vulnerability determination compared to histological ground truth with weighted kappa of 0.82 and AUC of 0.97, 0.95, and 0.99 for identification of unstable plaque, stable plaque, and minimal disease, respectively^[66].

Another ML-based model was proposed for the identification of vulnerable carotid plaque by Kigka *et al.* combining five distinct types of data as input, including clinical data, risk factors, laboratory data, serum markers, and imaging features such as stenosis ipsilateral and plaque size^[67]. The authors tested several ML algorithms such as Random Forests, Naive Bayes, Support Vector Machine, and Artificial Neural Networks

and integrated into their methodology the implementation of feature selection techniques to delete redundant features. The support vector machine achieved the highest performance with an accuracy of 76% and an AUC of 0.73^[67].

AI-based models to detect vulnerable plaque using MRI images

Zhang *et al.* developed a vulnerable carotid plaque model based on MRI radiomics features and ML algorithm for differentiating vulnerable carotid plaques and compared its performance to a traditional model based on conventional MRI features^[68]. The overall cohort comprised 162 patients with carotid stenosis and were randomized into training and testing sets. The traditional model was constructed using features related to IPH and LRNC identified through multivariable logistic regression analysis. The predictive radiomics model for identifying high-risk plaques was built in different consecutive steps, including (1) normalization to z distribution; (2) selection of the features with $P < 0.05$ in each sequence, and an AUC > 0.65 ; (3) application of the least absolute shrinkage and selection operator (LASSO) for further feature reduction. Through the application of the Lasso algorithm, a subset of 33 radiomics features was selected for the construction of the radiomic model. The results demonstrated the superior performance of the radiomic model compared to the traditional model. In both the training and testing sets, the radiomic model achieved an AUC value of 0.988 and 0.984, respectively. The traditional model yielded AUCs of 0.825 and 0.804 for the training and testing sets, respectively. Furthermore, when combining the radiomic and traditional models, the combined model exhibited even higher AUCs of 0.989 and 0.986 for the training and testing sets, respectively^[68].

Similarly, Li *et al.* developed a high-risk carotid plaque model using three-dimensional (3D) high-resolution magnetic resonance imaging combining radiomics features with ML approach and compared its performance with conventional model^[69]. The authors enrolled 136 patients with symptomatic intracranial artery stenosis. The conventional model comprised plaque length, plaque thickness, remodeling index, plaque burden, degree of luminal stenosis, plaque enhancement, IPH, and plaque surface irregularities. On the other hand, the radiomics model was constructed using a linear support vector classifier after performing feature selection with an analysis of variance F-test statistic. The radiomics model achieved an AUC of 0.923 in the training set, and an AUC of 0.906 with an accuracy of 88.80%, a specificity of 84.78%, and a sensitivity of 81.62% in the test set. The combined radiomics-conventional radiological model showed an AUC of 0.925 in the training set and 0.903 in the test set^[69].

Table 1 summarizes previous studies regarding the application of AI model in carotid plaque evaluation.

LIMITATIONS

Although the current literature shows promising results in utilizing AI model for the identification of vulnerable carotid plaque, there are still limitations in translating this model into real-world clinical practice.

Model transparency and interpretability

First, the “black box” nature of AI models. Indeed, one of the challenges with AI models lies in their lack of transparency and interpretability, which can result in uncertainty regarding the data utilized and the relationships between variables that influence specific outputs. This limitation hinders the integration of AI models in clinical settings, as they require sufficient insight and explanation to be effectively utilized.

Data heterogeneity

Second, data heterogeneity and apprehensions related to the training and testing set. To ensure the

Table 1. Previous studies regarding the application of artificial intelligence model in carotid vessels evaluation

Authors	Years	Number of patients	Imaging modalities	Variables	Model interpretability	Results
Menchón-Lara et al. ^[53]	2014	60	US	Automatic detection of intima-media thickness	Black box	The AI models achieved a mean absolute distance, polyline distance, and centerline distance of 0.03763 ± 0.02518 mm, 0.03670 ± 0.02429 mm, and 0.03683 ± 0.02450 mm, respectively
Jain et al. ^[60]	2021	630	US	Automatic segmentation of low atherosclerotic plaque	Black box	The proposed model achieved a mean accuracy, DSC, and correlation coefficient of 99.01, 86.89, and 0.92, respectively, using a mixed cohort of different demographic groups
Wu et al. ^[58]	2019	1,057	MRI	Automatic vessel and carotid plaque identification	Black box	The proposed DL models achieved high segmentation performance (0.9594 DSC for the lumen and 0.9657 DSC for the outer wall), along with excellent diagnostic accuracy (0.9503 AUC and 0.8916 Accuracy) on the test dataset. Remarkably, these AI models maintained exceptional performance even when applied to a different test dataset, exhibiting DSC of 0.9475 for the lumen and 0.9542 for the outer wall, along with an AUC of 0.9227 and accuracy of 0.8679 for both segmentation and diagnosis tasks
Ziegler et al. ^[59]	2021	194	MRI	Automatic segmentation of the carotid bifurcation into the common, internal, and external carotid arteries	Black box	The proposed DL model attained average scores of DSC = 0.80 ± 0.13 , MCC = 0.80 ± 0.12 , F2 = 0.82 ± 0.14 , F0.5 = 0.78 ± 0.13 , and TPR = 0.84 ± 0.1649
Dos Santos et al. ^[57]	2019	59	CT	Automatic vessel/plaque segmentation	Black box	The proposed model achieved an overall accuracy of 71%, with an average time of 1,381 s for the complete segmentation analysis
Zhou et al. ^[54]	2020	56	CT	Automatic vessel segmentation.	Black box	The U-Net-based DL model achieved an average DSC of 82.3%
Huang et al. ^[55]	2022	24	CT	Automatic vessel segmentation.	Black box	The self-supervised DL model achieved an average DSC of 84.83%
Bortsova et al. ^[56]	2021	2,319	CT	Automatic internal carotid artery calcification segmentation.	Black box	The DL-based model yielded a sensitivity of 83.8% and a positive predictive value of 88.0% for automatic internal carotid calcification segmentation, showing an excellent intraclass coefficient (0.98) between automatic and manual volume measures. Moreover, in the blinded visual comparison, automated delineations were deemed more accurate than manual delineations in 131 regions out of 225 (58.2%; $P = 0.01$)
Zhang et al. ^[61]	2022	150	US	Conventional diagnostic US model (including surface morphology, fibrous cap state, plaque echo, and plaque ulcer formation) combined with texture analysis model	Explainable	On the training set, the model combining conventional ultrasound and texture features achieved an AUC of 0.88 and a C-index of 0.89. On the testing set, the proposed combined model attained an AUC of 0.87 and a C-index of 0.84
Saba et al. ^[64]	2021	506	US	Plaque vulnerability characterization	Black box	The introduced AI models demonstrated accuracies of 93.55%, 94.55%, and 89%, alongside AUC values of 0.938, 0.946, and 0.889, respectively
Akkus et al. ^[62]	2014	29	CEUS	Carotid intraplaque neovascularization quantification	Explainable	The intraplaque neovascularization software exhibited excellent agreement with visual intraplaque neovascularization scores, yielding AUC values of 0.92 and 0.93
Guang et al. ^[63]	2021	205	CEUS	Plaque vulnerability characterization	Black box	The proposed DL model demonstrated significant improvements over manual assessment in evaluating the vulnerability of carotid plaque, achieving AUC values of 0.85 within the training cohort and 0.87 within the validation cohort
Zhang et al. ^[68]	2021	162	MRI	Traditional MRI-based model (including IPH and LRNC) combined with radiomics model	Explainable	The model combining radiomic and traditional features exhibited AUC values of 0.989 and 0.986 for the training and testing sets, respectively

Cilla <i>et al.</i> ^[65]	2022	30	CT	Binary classification in «hard» and «soft» carotid plaque	Interpretable	The support vector machine demonstrated the highest performance, yielding an accuracy, precision, recall, and F-score of 86.7%, 92.9%, 81.3%, and 86.7%, respectively. Additionally, the classification and regression tree analysis model, employing the entropy and volume features, achieved an accuracy of 86.7% along with an AUC of 0.987
Buckler <i>et al.</i> ^[66]	2023	53	CT	LRNC, calcification, matrix, and IPH	Interpretable	The ML-based algorithm demonstrated high accuracy in determining plaque vulnerability compared to histological ground truth. It achieved a weighted kappa of 0.82 and AUC values of 0.97, 0.95, and 0.99 for identifying unstable plaque, stable plaque, and minimal disease, respectively
Kigka <i>et al.</i> ^[67]	2021	208	CT	Clinical data, risk factors, laboratory data, serum markers, imaging features (stenosis ipsilateral and plaque size)	Explainable	The support vector machine achieved the highest performance with an accuracy of 76% and AUC of 0.73
Li <i>et al.</i> ^[69]	2022	136	MRI	Conventional model (plaque length, plaque thickness, remodeling index, plaque burden, degree of luminal stenosis, plaque enhancement, IPH, and plaque surface irregularities) combined with radiomics model	Explainable	The model combining radiomics features and conventional radiological measurements exhibited an AUC of 0.925 in the training set and 0.903 in the test set

reliability and generalizability of AI models, a significant quantity of annotated data from diverse centers, along with specialized software and infrastructure, is essential. Building a large and homogeneous dataset that encompasses images from multiple centers becomes crucial for training AI models effectively. Additionally, once such a dataset is accessible, it is crucial to carefully examine and partition it into training, validation, and testing sets. This partition enables an unbiased assessment of the final models, minimizing potential biases.

Ethical and legal issues

Third, the utilization of AI in healthcare introduces significant ethical and legal implications. Ethical concerns revolve around data privacy and security, the fairness and potential biases of AI systems, and transparency and safety of algorithms. Developing extensive and uniform datasets for AI leads to specific issues regarding data privacy and security.

Future directions

Recent years have seen significant growth in research and projects centered around AI in cardiovascular imaging. Nevertheless, the seamless integration of AI models into specific healthcare domains remains an ongoing challenge. To truly enhance the clinical relevance of AI algorithms, it becomes crucial to not only curate extensive datasets but also to raise clinicians' awareness about the utility of these models. This awareness is pivotal in facilitating their seamless integration into day-to-day clinical practice. Moreover, alongside dataset efforts, incorporating robust privacy protection models and security mechanisms is imperative to ensure the safety of patient data.

Finally, an integrative non-invasive multi-modal approach that amalgamates data from US, CT, and MRI has the potential to significantly enhance the proficiency of AI-based models in discerning and characterizing plaque vulnerability. The performance of these multi-modal AI-based models could further be enhanced by incorporating information derived from patients' electronic health records. Future controlled research on AI-based model for vulnerable carotid plaque across different centers, patient groups, and imaging modalities are essential to instill confidence in the implementation of AI models within clinical decision-making processes. In addition, these multicenter trials should be designed with inherently interpretable models rather than develop black box models and attempt to explain them.

CONCLUSION

The implementation of AI-based models for vulnerable carotid plaque has the potential to greatly improve daily clinical practice in cardiovascular healthcare. AI using US, CT, and MRI has been demonstrated to be an important additional tool in aiding the identification of carotid atherosclerotic plaque and characteristics associated with vulnerability.

The application of AI technologies in real-life clinical practice has the capacity to significantly assist healthcare professionals and contribute to more efficient and effective patient care. Despite the potential benefits of these AI models in clinical practice, their applicability is constrained by several challenges, including data heterogeneity, limited transparency and explainability of numerous AI algorithms, and limited external validation in the current literature.

To expedite the clinical integration of AI-based models into valuable tools for clinical decision-making in multi-modal images, it is essential to tackle the challenges posed by "black box" models and conduct future prospective and multicenter studies with designs that are explainable and interpretable.

DECLARATIONS

Authors' contribution

Conceptualization: Cau R, Pisu F, Saba L

Methodology: Cau R, Muscogiuri G, Mannelli L

Data curation: Cau R, Suri JS, Saba L

Writing - original draft preparation: Cau R; Pisu F, Muscogiuri G, Saba L

Writing - review and editing: Pisu F, Suri JS, Saba L

Supervision: Suri JS, Saba L.

Project administration: Saba L, Cau R

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All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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