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Advances in Machine Learning and Deep Learning Applications for Intracranial/Extracranial Atherosclerotic Plaques and White Matter Hyperintensities

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Abstract

Machine learning (ML) and deep learning (DL), as pivotal components of artificial intelligence (AI), are revolutionizing precision medicine through their robust learning capabilities and image recognition functions. These technologies have significantly impacted disease diagnosis, therapeutic evaluation, prognosis prediction, and survival analysis. This review synthesizes recent advances in ML and DL applications for intracranial/extracranial atherosclerotic plaques and white matter hyperintensities (WMH), while critically analyzing current challenges and future directions.

Keywords: machine learning, deep learning, atherosclerosis, white matter hyperintensities, HR-MR VWI

1. Introduction

Intracranial/extracranial atherosclerotic plaques and white matter hyperintensities (WMH) are critical imaging biomarkers of cerebrovascular diseases. Accurate assessment of these markers is essential for diagnosis, treatment planning, and prognosis prediction. While high-resolution magnetic resonance vessel wall imaging (HR-MR VWI) enables detailed plaque characterization and lumen-wall visualization, traditional manual interpretation suffers from subjectivity and inefficiency. Recent advancements in AI, particularly ML and DL, offer automated solutions for plaque and WMH analysis through superior image recognition and high-dimensional feature extraction. However, existing studies often focus on isolated tasks, lacking systematic integration. This review comprehensively evaluates ML and DL applications in atherosclerotic plaques and WMH research, identifies current limitations, and outlines future directions.

2. Overview of Machine Learning and Deep Learning

The medical field is undergoing a transformative shift in diagnostic and therapeutic paradigms driven by artificial intelligence (AI), with particularly remarkable advancements in automated image analysis and pathological feature identification. Based on differences in modeling principles, machine learning (ML) can be categorized into three paradigms: supervised learning, unsupervised learning, and reinforcement learning (Srinivas & Young, 2023). The foundational theory of ML involves data-driven optimization of model parameters to minimize errors between predicted outputs and ground-truth results (Chen et al., 2017; Yan & Wang, 2022). Supervised learning, the most mature paradigm in clinical diagnostics, has significantly improved the precision of tumor staging assessments and the efficacy of non-invasive detection. Unsupervised learning (Matteucci et al., 2024), which utilizes unlabeled data to construct analytical models, exhibits unique advantages in disease subtype clustering and association rule mining, though it faces limitations in predictive stability. Reinforcement learning (Xuan et al., 2022) employs dynamic decision-making mechanisms, using delayed feedback to optimize agent strategies, with its core principle lying in balancing the exploration of new pathways and the exploitation of existing knowledge.

As a pivotal advancement in ML, deep learning (DL) simulates human cognitive mechanisms through biomimetic neural network architectures. By leveraging backpropagation algorithms, DL achieves hierarchical feature abstraction and demonstrates exceptional performance in medical pattern recognition tasks (Lin, 2023; Thompson et al., 2020; Wagner et al., 2021). Among DL architectures, convolutional neural networks (CNNs) have achieved breakthroughs in medical image classification and lesion segmentation (Li et al., 2022; McBee et al., 2018; Wang et al., 2023). Radiomics technology further enhances diagnostic objectivity by integrating quantitative feature analysis with ML algorithms. This approach automates the extraction of multidimensional parameters from regions of interest and constructs auxiliary diagnostic systems through statistical modeling, thereby significantly improving disease classification and severity assessment (Hatt et al., 2019; Lambin et al., 2012; Mayerhoefer et al., 2020). Recent advances (Y.-F. Chen et al., 2023) highlight that hybrid models combining DL and radiomics enable precise automated identification and quantitative analysis of carotid plaques, offering innovative solutions for vascular pathology evaluation.

Notably, DL is evolving toward large-scale models supported by massive datasets and computational power. The Transformer architecture overcomes limitations in sequence modeling through attention mechanisms, diffusion generative models are emerging in medical image synthesis, and pretrained models such as GPT and BERT have pioneered new pathways for cross-modal medical data analysis. These technological breakthroughs continue to drive the profound integration of AI into healthcare applications.

3. Applications of Machine Learning and Deep Learning in Intracranial/Extracranial Atherosclerosis

3.1 Plaque Segmentation and Feature Assessment

Current imaging modalities for detecting intracranial and extracranial atherosclerotic plaques include ultrasonography, computed tomography angiography (CTA), and high-resolution magnetic resonance vessel wall imaging (HR-MR VWI). Although ultrasonography demonstrates high sensitivity in identifying carotid plaques and detecting hemodynamic alterations, its utility in intracranial artery evaluation remains limited due to acoustic shadowing from the skull, insufficient penetration depth for assessing deep vessels, and challenges in collateral circulation evaluation. CTA effectively evaluates lumen stenosis and calcified components but lacks precision in characterizing small calcified or non-calcified plaques, with further limitations in assessing plaque composition and vulnerability. In contrast, HR-MR VWI, with its superior spatial resolution, provides unique advantages for morphological measurements of intracranial/extracranial arterial walls and quantitative analysis of plaque composition (Saba et al., 2018). However, traditional manual interpretation exhibits significant limitations: Operators require specialized expertise in atherosclerotic pathology and extensive clinical experience, results are susceptible to inter-operator variability in expertise and subjective interpretation, manual delineation suffers from high inter-observer variability and time inefficiency. Recent advancements in artificial intelligence (AI), particularly machine learning (ML) and deep learning (DL), offer novel solutions for plaque analysis. These technologies leverage existing data to extract high-dimensional features, construct diagnostic and predictive models, and significantly enhance the accuracy and efficiency of plaque evaluation and cerebrovascular event prediction.

DL-based automated analysis systems standardize image segmentation workflows through feature learning from large-scale annotated datasets, markedly improving processing efficiency and result consistency. Current research on HR-MR VWI image analysis focuses on algorithmic architecture innovation and multi-model synergy. For instance: Wan et al. (Wan et al., 2022) developed a 3D convolutional network system that achieves automatic vascular centerline tracking, geometric correction, and wall morphology parameter measurement, with segmentation accuracy exceeding 0.9 for intracranial/extracranial arteries. Shi et al. (F. Shi et al., 2019) pioneered the application of U-Net architecture for whole-brain HR-MR VWI segmentation, achieving Dice similarity coefficients of 0.89 (wall) and 0.77 (lumen). Their model successfully identified statistically significant differences in normalized plaque indices between symptomatic and asymptomatic groups across 24 severe stenosis cases. Wu et al. (Wu et al., 2019, 2024) proposed the DeepMAD multi-task framework, which excels in carotid plaque segmentation and pathological assessment, with performance further enhanced through joint optimization strategies.

3.2 Radiomics-Driven Quantitative Plaque Assessment

Radiomics-based quantitative plaque evaluation introduces a new dimension for risk stratification in ischemic cerebrovascular diseases. Pathological studies of acute ischemic stroke (AIS) reveal that atherosclerotic plaque morphology and composition are more effective predictors of cerebrovascular events than lumen stenosis severity (Prabhakaran et al., 2021; Tian et al., 2023). Current research paradigms employ ML algorithms to construct high-dimensional feature analysis models, enabling intelligent assessment of plaque heterogeneity. Quantitative analysis of anterior circulation plaques demonstrates that symptomatic cases exhibit significantly higher signal intensity distributions in histogram parameters compared to asymptomatic controls (Yu et al., 2019), a pattern also validated in posterior circulation plaque evaluation (Z. Shi et al., 2018). Shi et al. (Z. Shi et al., 2020) further demonstrated that histogram feature dispersion serves as a robust biomarker for discriminating culprit plaques, underscoring the superiority of quantitative imaging features in characterizing plaque heterogeneity. Notably, integrated models combining HR-MR VWI multimodal data with random forest algorithms have demonstrated diagnostic efficacy surpassing traditional methods in vulnerable plaque identification (Z. Shi et al., 2018). For culprit plaque discrimination, Zhang et al. (Zhang Guiling et al., 2023) optimized classification performance using extreme gradient boosting in a multi-sequence fusion model, providing technical support for precision diagnostics.

3.3 Cerebrovascular Events

Current research on the association between atherosclerosis and acute ischemic stroke (AIS) focuses on three dimensions: elucidation of pathogenic mechanisms, event risk prediction, and recurrence warning. The prevailing research paradigm involves integrating quantitative features from high-resolution vessel wall imaging (HR-VWI) with conventional imaging parameters to construct machine learning (ML)-based predictive frameworks. For instance: Li et al. (Li et al., 2023) developed an ensemble learning model that demonstrated superior performance in discriminating stroke mechanisms, achieving a 32% improvement in predictive accuracy compared to traditional models. Wang et al. (Wang et al., 2023) employed survival analysis to build a recurrence risk assessment system, identifying high-order texture features (e.g., gray-level co-occurrence matrix parameters) as optimal predictors of prognosis. Recent evidence (Tang et al., 2022) indicates that combining radiomic features with nomogram tools enhances stroke recurrence warning sensitivity to 92%, providing quantitative guidance for personalized treatment. The integration of deep learning (DL) and radiomics has established novel pathways for cerebrovascular event risk assessment. For example: Chen et al. (Y.-F. Chen et al., 2023) developed an intelligent diagnostic system using an object detection network to automate plaque component analysis, achieving 94.81% accuracy in AIS risk stratification. In image preprocessing, a transfer learning-based DL model achieved precise vascular wall segmentation (Song et al., 2023). This method, when combined with a support vector machine (SVM)-based multimodal diagnostic system, demonstrated exceptional performance in tumor grading, suggesting its potential applicability in cerebrovascular diseases.

Notably, AIS pathogenesis involves multidimensional factors, including plaque stability, hemodynamic alterations, and molecular biological regulation (Ajoolabady et al., 2021; AlRuwaili et al., 2024; Arul et al., 2023; Biose et al., 2023). Models relying solely on imaging features risk systemic bias due to incomplete representation of these complex interactions. Emerging proteomics studies (Theofilatos et al., 2023) have confirmed that multi-omics data integration models improve predictive performance by 19.7% compared to single-modality approaches.

4. Applications of Machine Learning and Deep Learning in WMH Research

4.1 WMH Segmentation

Accurate segmentation of white matter hyperintensities (WMH) is fundamental for investigating their pathological mechanisms and clinical correlations. Traditional manual segmentation, reliant on radiologists' expertise, is time-consuming, subjective, and suffers from poor reproducibility. Deep learning (DL) techniques have significantly enhanced segmentation efficiency and precision through automation. For instance: Dadar et al. (Dadar et al., 2017) compared 10 classification techniques for WMH segmentation and demonstrated that the random forest classifier achieved optimal performance on a dataset comprising T1-weighted imaging (T1WI), T2-weighted imaging (T2WI), proton density (PD), and fluid-attenuated inversion recovery (FLAIR) scans, with a Dice Kappa coefficient of 0.66 ± 0.17. One study (L et al., 2019) have proposed a context restoration-based self-supervised learning strategy for medical image analysis, which exhibited superior performance in classification, localization, and segmentation tasks across fetal ultrasound, abdominal CT, and brain MR images. Park et al. (Park et al., 2021) developed a multi-scale highlighted foreground U-Net for WMH segmentation, achieving the highest overall evaluation score, Dice similarity index, and F1-score in the MICCAI 2017 WMH Segmentation Challenge. Shan et al. (Shan et al., 2021) clinically validated a DL-based automated system for segmenting cerebral small vessel disease-related WMH (CSVD-WMH), which outperformed existing methods on both internal and external test sets. A study (S et al., 2024) combined deep neural networks with Transformer architectures for automated cervical cancer segmentation and survival prediction, demonstrating superior segmentation performance and significantly outperforming traditional methods in survival analysis.

4.2 WMH Quantification and Clinical Decision-Making

Cerebral small vessel disease (CSVD) is a common neurological disorder predominantly affecting elderly populations. Its pathophysiological mechanism primarily involves microvascular structures, including small arteries, arterioles, capillaries, venules, and small veins, leading to clinical manifestations such as cognitive impairment and vascular dementia. Due to the nonspecific clinical presentation, diagnosis currently relies heavily on neuroimaging. White matter hyperintensities (WMH) represent one of the hallmark imaging features of CSVD, alongside other radiological markers such as lacunar infarcts, cerebral microbleeds (CMBs), enlarged perivascular spaces (EPVS), recent small subcortical infarcts, brain atrophy, and cortical superficial siderosis (cSS) (Hu Wenli et al., 2021). Previous studies on WMH (Erten-Lyons et al., 2013; Pan et al., 2024; Williams et al., 2017; Zhai et al., 2020) have focused on associations between imaging features and clinical phenotypes, exploration of pathophysiological mechanisms, and prediction of cognitive outcomes and prognosis. However, these investigations often relied on cross-sectional designs, manual or semi-automated segmentation methods, and single-modality imaging analyses, resulting in limitations such as challenges in causal inference, high sample heterogeneity, inconsistent quantification standards, and insufficient biological mechanistic explanations.

The integration of radiomics and deep learning (DL) has provided robust tools for WMH quantification. For example: Shi et al. (Y. Shi et al., 2022) conducted a bibliometric analysis to elucidate the intellectual structure and emerging trends in WMH research, emphasizing its associations with cognitive impairment, stroke, and neuroimaging characteristics in CSVD. Rudie et al. (Rudie et al., 2019) employed a 3D

U-Net model to differentiate glioma-related abnormalities from WMH in brain MRI data, achieving a Dice coefficient of 0.42, thereby demonstrating DL's efficacy in processing multi-disease neuroimaging datasets. Rachmadi et al. (Rachmadi et al., 2018) proposed a convolutional neural network (CNN) framework incorporating global spatial information, which significantly improved segmentation accuracy by integrating spatial coordinates, yielding a mean Dice similarity coefficient of 0.5389. Huff et al. (Huff et al., 2021) focused on enhancing the interpretability of DL models, exploring visualization techniques such as Gradient-weighted Class Activation Mapping (Grad-CAM) and attention maps to decipher model decision-making processes. This advancement is critical for improving the transparency and clinical acceptability of WMH analysis. Collectively, these studies demonstrate that DL not only enhances WMH segmentation accuracy but also supports clinical decision-making through interpretability techniques, laying a solid foundation for future research and clinical applications of WMH.

4.3 Cognitive Impairment Disorders and Mechanistic Insights into WMH Pathology

Artificial intelligence (AI) has demonstrated significant value in predicting the association between white matter hyperintensities (WMH) and cognitive impairment. Feng et al. (Feng et al., 2025) employed VB-Nets, a deep learning convolutional neural network, to automatically identify and segment whole-brain subregions and WMH. By extracting radiomic features from WMH and bilateral hippocampal regions, they constructed a combined feature model to detect cognitive impairment in WMH patients. The 3D VB-Net algorithm exhibited strong performance in WMH segmentation (Dice = 0.789, lesion F1-score = 0.764). Additionally, studies indicate that combined analysis of WMH and Aβ-amyloid significantly enhances the predictive capability for cognitive impairment, particularly in early stages. For example, Lorenzini et al. (Lorenzini et al., 2022) evaluated regional associations between WMH and Aβ-amyloid across brain regions using PET imaging, revealing two distinct pathological patterns that significantly predict cognitive decline.

Another study (da Silva et al., 2023) elucidated the mechanistic link between WMH and information processing speed (IPS) deficits in cerebral small vessel disease (CSVD) by investigating cortical thinning and network disruption. By assessing the mediating roles of cortical thickness and structural/functional brain connectivity in the relationship between WMH and IPS, the study identified significant associations ($p < 0.05$) among WMH volume/location, cortical thickness, brain connectivity, and IPS performance in CSVD patients. Specifically, frontal cortical thickness, functional sensorimotor networks, and the posterior thalamic radiation were identified as critical mediators of the WMH-IPS relationship. These findings underscore the importance of multimodal imaging data in early cognitive impairment diagnosis. Future research should prioritize the development of multimodal causal inference models to clarify the temporal relationships and interactions between WMH, neurodegeneration, and vascular pathologies.

5. Conclusions and Future Perspectives

The integration of deep learning (DL), machine learning (ML), and radiomics has introduced transformative methodologies for rapid plaque characterization and cerebrovascular event risk stratification. Despite these advancements, significant challenges persist, such as limited model interpretability, ambiguous correlations between high-dimensional features and clinical characteristics, insufficient reproducibility, and constraints in data quality and algorithmic robustness. Furthermore, most studies rely on single algorithms trained on small, single-center datasets lacking external validation, which compromises model generalizability. To address these limitations, future efforts should prioritize the following strategies: Clinical translation, enhancing AI transparency and clinical adoption through visualization techniques (e.g., gradient heatmaps) and medical knowledge graphs. Standardization, establishing unified imaging protocols and data acquisition workflows via multi-center collaborations. Data infrastructure, developing large-scale databases for head and neck atherosclerosis to improve model generalizability. Multi-Omics integration, combining radiomics with genomics, pathomics, and clinical biomarkers to elucidate molecular mechanisms and advance personalized therapeutics.

Critical research directions include constructing multidimensional data fusion frameworks, leveraging HR-MR VWI radiomics to characterize plaque morphology, integrating proteogenomic data to decode molecular pathways, and establishing precision prediction models that bridge imaging, molecular, and clinical domains. In parallel, ML/DL applications in white matter hyperintensity (WMH) research have expanded from basic segmentation tasks to mechanistic exploration and clinical prediction. Nevertheless, challenges remain: Data heterogeneity-inconsistent standardization across multi-center WMH datasets necessitates international shared databases (e.g., ADNI, UK Biobank) to enhance algorithmic robustness. Interpretability, the "black-box" nature of DL models hinders clinical trust, this limitation can be mitigated by integrating attention mechanisms (e.g., Grad-CAM) to visualize critical lesion regions. Multimodal limitations, overreliance on MRI underscores the urgency to incorporate PET (e.g., amyloid imaging) and liquid biopsy data, enabling holistic pathological mapping of WMH.

By fostering technological innovation and interdisciplinary collaboration, AI-driven frameworks hold immense potential to revolutionize the precision diagnosis and treatment of cerebrovascular diseases and WMH, ultimately improving patient outcomes.

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