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A Special Report on Changing Trends in Preventive Stroke/Cardiovascular Risk Assessment Via B-Mode Ultrasonography

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Abstract

Purpose of Review Cardiovascular disease (CVD) and stroke risk assessment have been largely based on the success of traditional statistically derived risk calculators such as Pooled Cohort Risk Score or Framingham Risk Score. However, over the last decade, automated computational paradigms such as machine learning (ML) and deep learning (DL) techniques have penetrated into a variety of medical domains including CVD/stroke risk assessment. This review is mainly focused on the changing trends in CVD/stroke risk assessment and its stratification from statistical-based models to ML-based paradigms using non-invasive carotid ultrasonography.

Recent Findings In this review, ML-based strategies are categorized into two types: non-image (or conventional ML-based) and image-based (or integrated ML-based). The success of conventional (non-image-based) ML-based algorithms lies in the different data-driven patterns or features which are used to train the ML systems. Typically these features are the patients' demographics, serum biomarkers, and multiple clinical parameters. The integrated (image-based) ML-based algorithms integrate the features derived from the ultrasound scans of the arterial walls (such as morphological measurements) with conventional risk factors in ML frameworks.

Summary Even though the review covers ML-based system designs for carotid and coronary ultrasonography, the main focus of the review is on CVD/stroke risk scores based on carotid ultrasound. There are two key conclusions from this review: (i) fusion of

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image-based features with conventional cardiovascular risk factors can lead to more accurate CVD/stroke risk stratification; (ii) the ability to handle multiple sources of information in big data framework using artificial intelligence-based paradigms (such as ML and DL) is likely to be the future in preventive CVD/stroke risk assessment.

Keywords Atherosclerosis · Carotid artery · Coronary artery · Stroke risk · Cardiovascular risk · Machine learning · Deep learning · Conventional systems · Integrated systems

Introduction

In 2017, cardiovascular diseases (CVD) such as heart attack and stroke killed 17.9 million people (31% of global mortality) around the world [1]. Plaque buildup in carotid and coronary arteries (also called as atherosclerotic disease, see Fig. 1) is one of the major cause of such mortalities. Recent findings indicate that traditional risk factors including ethnicity, age, hyperlipidemia, hypertension, diabetes mellitus, smoking, family history of coronary artery diseases, obesity, and physical inactivity are responsible for a majority of cardiovascular (CV) mortalities [2, 3•, 4]. Optimal management of CVD requires the following: (i) the in-depth understanding of various CV risk factors that are associated with the disease; (ii) early prediction of the CVD/stroke risk; and (iii) the initiation of preventive methods such as usage of statins to treat the disease prior to the occurrence of the vascular events.

In the last decade, various efforts were made for the optimal management of CVD/stroke by developing computational risk prediction models [5–15]. All such clinically well-established risk prediction models provide long-term risk prediction by taking into consideration the traditional and non-traditional CV risk factors to create a tool for primary prevention. However, the majority of these risks prediction models are not generalizable due to specific cohort characteristics from which they were derived. As a result, these models either underestimate or overestimate the CVD risk when applied to a cohort with a different baseline risk profile [16–18]. Another important fact about traditional risk scores is that they do not incorporate the morphological variations of the atherosclerotic plaque detectable during imaging tests. Such image-based data is increasingly being recognized as a key biomarker responsible for the onset of the stroke or CV events [19–21].

Recent advancements in imaging techniques have facilitated a clear visualization of the atherosclerotic plaque morphology and the measurement of several image-based phenotypes. The visualization can be in different shapes and sizes depending upon the nature of imaging (cross-sectional vs. longitudinal). For example, imaging coronary artery using intravascular ultrasound (IVUS) provides the cross-sectional images of plaque morphology, while imaging carotid artery using B-mode ultrasound provides longitudinal images of plaque morphology. In general, some commonly used image-based phenotypes are based on (i) wall area (using B-mode ultrasound)

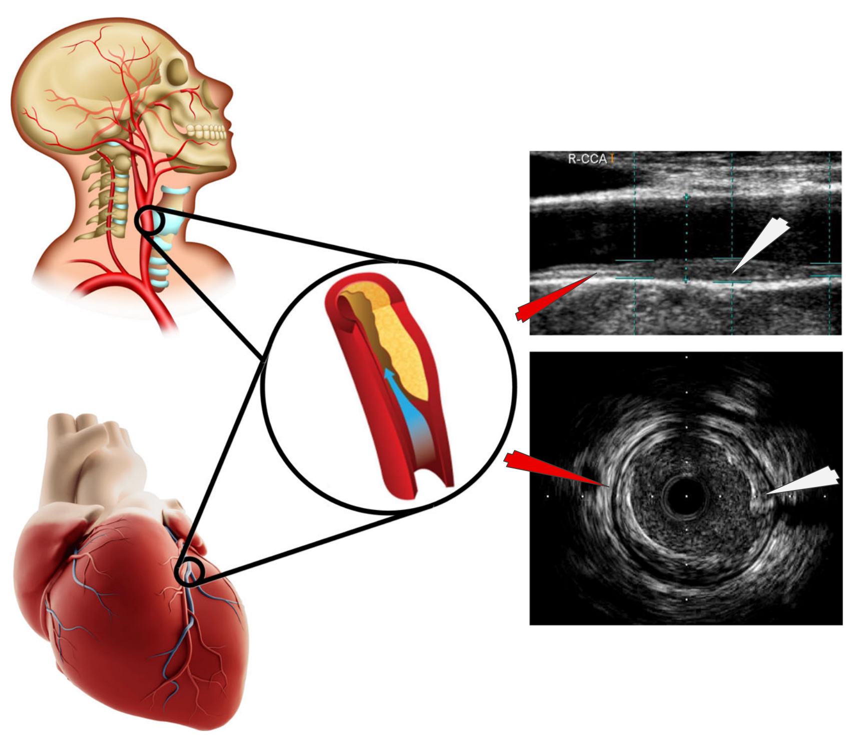


Fig. 1 General schematic diagram depicting the role of non-invasive carotid ultrasound and intravascular ultrasound in the detection of vascular atherosclerosis (Courtesy of AtheroPoint™, Roseville, CA, USA and Reproduced with permission from Elsevier)

and volume of calcium (using IVUS) [22, 23], (ii) thickness of microstructural high-risk atherosclerotic plaque components such as thin-capped fibroatheroma (using intravascular optical coherence tomography) [24, 25], (iii) coronary artery calcium scores (using cardiac computed tomography or CT) [26], (iv) identification of calcified and non-calcified plaques using coronary computed tomography [27], and (v) carotid image features which include carotid intima-media thickness (cIMT), carotid plaque (CP) area [28, 29], wall variability [30], and composite risk scores [31]. In this review, we will focus on the carotid and coronary ultrasound image-based risk factors using advanced machine learning (ML) algorithms.

Carotid arteries are considered to be a surrogate indicator of CVD risk. This is because both carotid and coronary arteries have a similar genetic makeup, and both can be affected by the atherosclerotic plaque buildup in their vascular beds as depicted in Fig. 1. In the last two decades, the use of B-mode carotid ultrasound imaging modality for the assessment of atherosclerotic vascular diseases has gained popularity due to its non-invasive, ergonomic, and economic nature [32–38]. cIMT and CP extracted from B-mode carotid ultrasound images are considered to be the two most vital image-based risk factors of myocardial infarction and stroke events [19, 20, 39–41]. Several longitudinal studies have reported the use of cIMT and CP for the prevention of vascular disease [33–37]. This has resulted in the framing of guidelines that report the use of cIMT and CP for the CVD risk assessment [28, 42–44]. Carotid ultrasound image-based phenotypes are also associated with conventional cardiovascular risk factors (CCVRF) such as age, increased blood pressure, hyperlipidemia, diabetes mellitus, smoking, and body mass index. Nambi et al. [28] reported an improvement in the CVD risk prediction when both the cIMT and CP were taken into consideration along with the traditional risk factors. Thus, scanning the carotid arteries using non-invasive B-mode ultrasound can improve CVD and stroke risk assessment.

At present, more than 100 CVD risk prediction models are available but the selection of the most suitable risk prediction model is still being debated [45]. The majority of the conventional risk prediction models are based on traditional statistical methods such as multivariate linear regression, logistic regression, and Cox regression models [5, 9, 12, 13, 46]. Such methods allow the inclusion of a small number of risk factors (or covariates) in the risk model. Furthermore, all such models are good at indicating an association of risk predictors with CVD [5, 9, 12, 13, 46]. However, in the case of CV or stroke event prediction, they provide little generalizable benefit [47] because the statistically derived risk prediction models are based on the cohort characteristics which may vary from one cohort to another. Furthermore, local patterns in the clinical, demographics-based, and traditional risk factors from different cohorts are prone to noise (such as data fluctuations or missing values or sudden large deviations) and biases which are not accurately captured by such risk predicting models [47]. Lastly, the missing piece of the model is the exclusion of image-based morphological characteristics. This makes the overall risk evaluation systems weak and unreliable. Thus, in order to provide accurate and reliable CVD/stroke risk prediction, it is essential to look beyond the scope of traditional statistically derived risk calculators [47].

Innovations in intelligence-based paradigms such as ML and deep learning (DL) have performed exceptionally well in almost all medical domains [48–52]. The roots of ML systems lie in big data analytics. The term big data indicates the large storage of datasets with multiple clinical demographics (taken at the same time such as coronary, carotid, renal, etc.) collected from multiple sources. In Fig. 2, big data has been represented as a collection of data-driven risk factors from multiple sources that include the patients' demographics, conventional risk factors such as diabetes mellitus, hyperlipidemia, smoking, hypertension, and the image-based phenotypes. Machine learning algorithms can make use of all these stored data and try to analyze different patterns that represent the data. ML systems learn to recognize the different patterns in the dataset and produce CVD and stroke prevention prediction models. ML-based models follow the data-driven approach, meaning that these models automatically learn their coefficients from the different global and local patterns available in the big data which may vary among different population cohorts. In recent years, studies have shown the potential of various ML techniques in CV and stroke risk prediction [53, 54••]. Similarly, ML algorithms have also been adopted for stroke risk assessment by characterizing carotid atherosclerotic plaques tissues from the B-mode ultrasound images [55, 56, 57•, 58•, 59, 60]. In comparison to traditional risk calculators, recent findings indicate better performance of ML techniques for accurate CVD risk estimation [54••]. Kakadiaris et al. [61••] recently published a 13-year follow-up study to show that an ML-based risk calculator outperformed the well-established pooled cohort risk score (PCRS), a risk calculator which is based on the recent guidelines of American Heart Association and American College of Cardiology (also called as ACC/AHA risk score or atherosclerosis CVD risk score).

The breakthrough results presented by Weng et al. [54••] and Kakadiaris et al. [61••] have started a new quest to compare the automated ML (also broadly referred to as artificial intelligence) risk prediction models to well-established conventional risk calculators. Motivated by these results, this review provides a more informative understanding of the different ML techniques and various other approaches utilized for CVD and stroke risk prediction. The main focus of this review is to investigate the various ML-based systems used for CVD/stroke risk assessment in particular to carotid and coronary atherosclerosis diseases and more specifically using ultrasonography. Furthermore, the role of different conventional and image-based features has also been discussed in this review.

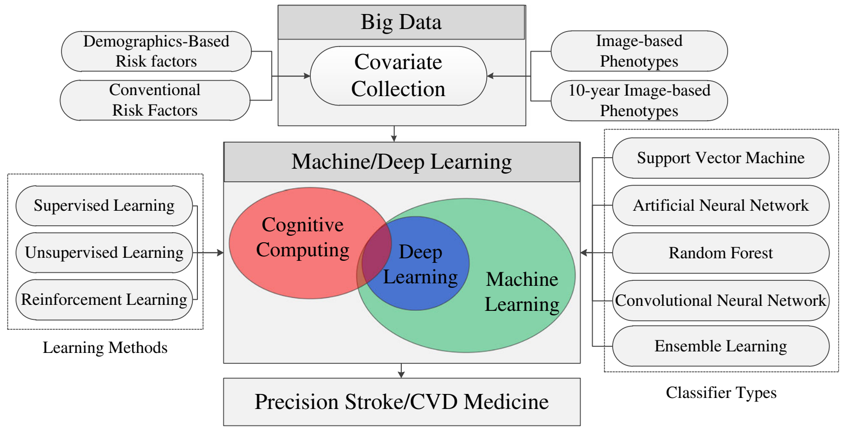


Fig. 2 Machine learning and deep learning system framework using big data

Article Search Strategy

This review is the outcome of rigorous searches on PubMed, Cochrane Library, and Web of Science to obtain the articles which were published in high impact factor peer-reviewed journals. We took a search window spanning the most recent 10 years for selecting the matching publications for this review. The keywords used for searching articles in the most recent 10 years were as follows: "Cardiovascular Risk Assessment," "Stroke Risk Assessment," "10-year CVD risk calculator," "Machine learning-based CVD risk calculator," "carotid ultrasound-based stroke risk," "automated CVD risk estimation," "carotid atherosclerotic plaque and machine learning," "coronary atherosclerotic risk assessment." Furthermore, a list of references from shortlisted research publications was also shortlisted for this review. Topics discussed in this article were initially discussed with experts in the field of cardiology, neurology, biomedical imaging, computer science, and artificial intelligence covering ML- and DL-based risk assessment.

Risk Assessment Using Traditional Methods

Traditional methods of CVD and stroke risk assessment are based upon the statistically derived risk calculators [5–7, 14, 62–66]. Nearly all of these conventional risk prediction models provide the risk estimation based on conventional regression techniques [67]. For example, the well-established Framingham Risk Score (FRS) [5], the United Kingdom Prospective Diabetes Study (UKPDS56) [14], the Reynolds Risk Score (RRS) [9], the NIPPON score [14], and the Pooled Cohort Risk Score [6] were all developed by using a Cox regression model (i.e., a proportional hazard model). Similarly, the Systematic Coronary Risk Evaluation (SCORE) calculator adapted the Weibull regression model [7]. As discussed in the "Introduction" section, such statistical models are well suited when the application is to find the association between risk predictors (so-called risk factors or covariates) and the outcome of interest. Recently, Goldstein et al. [47] pointed out three major challenges associated with these regression-based risk prediction models. (i) These models do not represent the true non-linear relationships between risk predictors and the outcome of interest. This means the regression-based models assume the predictor is linearly associated with the clinical outcome. (ii) The risk predictors are sometimes inter-dependent on each other. Thus, their effect on the outcome may not truly be captured by such regression-based models. (iii) When the number of risk predictors obtained from the dataset is large, then it becomes difficult to decide which risk factors to include in the regression-based models. This may be because of the small but significant associations between some of the risk predictors and the outcome of interest, which may otherwise make the model unstable. More research is required to understand and validate these calculators and further to explain their behaviors with the diverse risk factors. Before we dwell into ML-based CVD/Stroke risk calculators, we will briefly review ML fundamentals and the architectures.

Fundamentals of Machine Learning

Types of Machine Learning Techniques

Primarily, ML-based models are divided into three categories (Fig. 2, labeled as "Learning methods"): (i) *Supervised* learning and (ii) *Unsupervised* learning, and (iii) *Reinforcement* learning. In *Supervised* learning, the predefined binary labels (high-risk or low-risk; *event* or *non-event*) are obtained from the physicians or from the longitudinal trials as inputs that are used to train the ML system on how to correctly predict the risk outcome. For example, an automated cardiovascular event prediction system is usually provided with predefined labels corresponding to an *event* or *no-event* category [53, 68]. In risk assessment systems, the input labels (or response variable) can be obtained from the expert physicians or from results of the longitudinal follow-up studies, or by designing a response variable using a combination of risk factors. The *Unsupervised* learning ML system performs risk stratification without any prior user inputs or labels by identifying and then clustering similar local patterns from the source data [69]. Once trained, each of the clusters corresponds to the one output category; for instance, in the above example, the output clusters can either be an *event* or *no-event* category. *Reinforcement learning* is another ML technique which provides its predictions based on rewards. Reinforcement learning is widely adapted in gaming and robotic applications [70]. This review is focused on the supervised ML-based algorithms used in CVD/stroke risk assessment adapting ultrasonography.

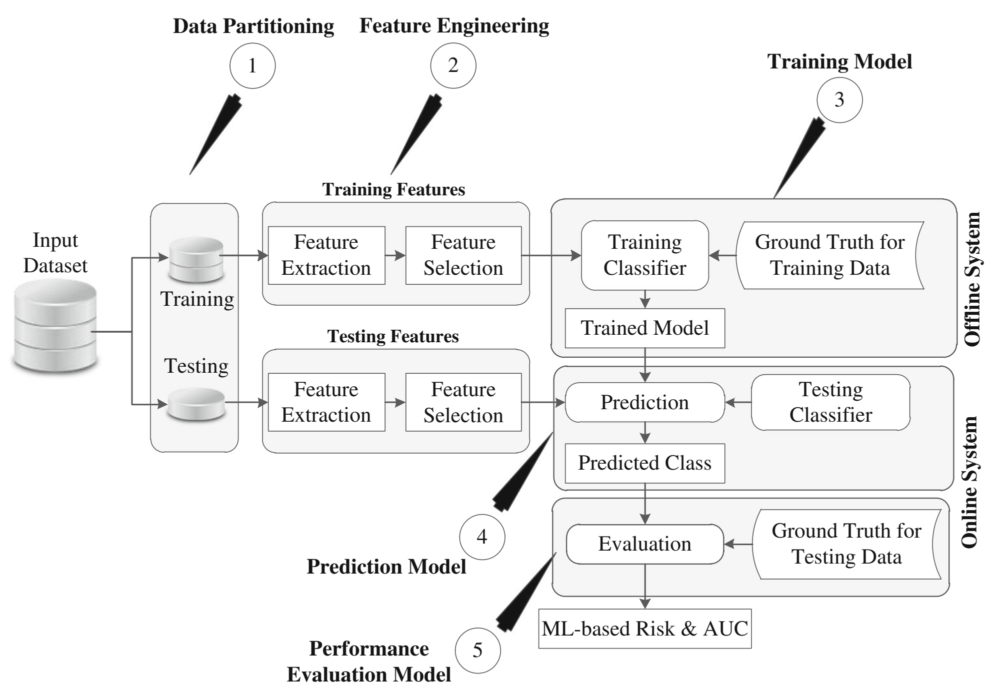
General Framework of Machine Learning

Machine learning combines the knowledge of computer science and mathematical and statistical models to self-train the systems to provide the desired outcome. The outcome can be the prediction of absolute real numbers or it can be a classification of the input data into the set of desired output classes. Figure 3 shows the generalized ML-based framework that is divided into five stages and discussed below in brief in the following order: (i) feature engineering, (ii) data partitioning, (iii) model building (or offline system), (iv) prediction (or online system), and (v) performance evaluation.

Feature Engineering: Extraction and Selection

Feature engineering is the most crucial part of any ML-based system that helps in interpreting the input dataset. In CVD/stroke risk assessment, these features can be either CCVRFs such as patients' demographics, serum biomarkers, and clinical variable or image-based phenotypes such as grayscale features [59, 71, 72], texture-based features [73], discrete wavelet transformed-based features [74], Riesz-based features [75], higher order spectra (HOS)-based features [76, 77], fractal features, and local binary patterns [78]. Quantitative carotid wall-based features extracted from B-mode ultrasound images such as cIMT and CP are also considered to be reliable for CVD/stroke risk assessment. According to the consensus report of the American Society of Echocardiography, cIMT measurements are generally performed in 1 cm region of common carotid artery at a proximal distance of 1 cm from the bulb [42]. However, studies have shown that measuring the distance between lumen-intima (LI) and media-adventitia (MA) throughout the length of the carotid artery including CP thickness provides an additional benefit in the risk assessment [79, 80]. AtheroEdge™ (AtheroPoint™, Roseville, CA, USA) has exclusively published and established a system which can measure fully and automatically cIMT throughout the carotid artery in just a few seconds [81]. The system outputs image-based phenotypes include average cIMT (cIMTave), maximum cIMT (cIMTmax), minimum cIMT (cIMTmin), variability in cIMT (cIMTV), and morphologic total plaque area (mTPA). The system underwent inter- and intra-operator variability analysis recently [82–84]. Under wall-based features, one can also measure lumen diameter (LD) [84], stenosis severity index (SSI) [85, 86], and inter-adventitial diameter (IAD) [87]. Excellent inter- and intra-operator variability for LD and IAD was recently shown in the AtheroEdge™ model (deep learning for LD) [88].

Fig. 3 The architecture of the ML algorithm showing four stages



The CCVRFs and image-based phenotypes provide a detailed understanding of the severity of CVD/stroke disease and can be used to train the ML-based systems. Recently, Khanna et al. [89] presented a study that estimated the 10-year CUS image-based phenotypes by integrating the five types current image-based phenotypes (cIMTave, cIMTmax, cIMTmin, IMTV, mTPA) with conventional risk factors. Such 10-year features can also be used in the ML-based system to provide CVD/stroke risk stratification.

Besides feature extraction, dominant feature selection is another important technique that captures the most relevant features and then trains the ML systems. However, feature selection can only benefit the ML system if a large number of features are captured from the input data. Some commonly used feature selection methods are random forest, logistic regression, mutual information, principal component analysis, analysis of variance, and Fisher discriminant ratio [90, 91].

Data Partitioning

Data partitioning involves dividing the input data set into two parts: (a) training dataset and (b) testing dataset. Multiple protocols exist for performing this data partitioning task. The most common protocol is 10-fold cross-validation, where the input dataset set is divided into ten equal parts, and at any time, nine parts are used for training the ML-based system while the remaining one part is used for validating the predictions of the system. This is also termed as K10 protocol where 10 indicate the number of total partitions designed during ML-based training model (typically using 80% of the dataset for training). The similar well-known data partitioning protocols are K2 protocol, K3 protocol, K4 protocol, and Jack Knife (also called as leave-one-out) cross-validation protocols, depending upon the percentage of data used for training as 50, 66, 75, and 99%, respectively. Since in a leave-one-out cross-validation protocol, N-1 samples are used for training and one sample is used for testing, it is generally adopted when the sample size is relatively small [92].

Training Model Design

Training model design involves teaching the ML-based algorithm to learn from the input training features over several iterations. Since this review is focused on supervised ML systems, predefined ground truth labels are required during the training phase, which in turn generates the offline coefficients. During each of the training iteration, ML-based algorithms provide the output predictions and compute the probable loss (also called an error) by comparing against the supplied labels (response variable). Based on the loss value, the internal coefficients of the model (so-called as hyperparameters) are adjusted. After updating the hyperparameters, ML-based algorithms will be again trained on the input features. The process of updating hyperparameters continues until the loss is minimum (we also call this instance, when the machine is able to split or partition well and the plane of separation is the hyperplane). This is so-called a state in which the ML model is considered to be trained.

Prediction or Testing Model

In the prediction or testing phase, the optimized coefficients from the trained model (training parameters) are used to transform the test features (derived from the test data) into the output or predicted class. This is also called an online process since this model accepts training parameters from the offline system and transforms the test features from the online system. In cross-validation protocols, the test data is a dataset completely different from the training data. Typically a good artificial intelligence model in risk stratification is a one which trains the machine only one time while the predictions can be done on several types of test data sets. More sophisticated machines are required to train and test on different types of datasets.

Performance Evaluation of Machine Learning Systems

Performance evaluation (PE) metrics are generally used to test the ability of ML systems to accurately predict the risk categories of patients [93]. In the PE model, the predicted class labels of the test patient are computed using the prediction model and compared against the corresponding ground truth label, which is then used by the performance evaluation metric. The choice of a PE metric is of utmost importance because it indicates the degree to which the trained and tested model is accomplishing the desired outcomes. Area-under-the-curve (AUC) derived from receiver operating characteristic analysis is a widely adopted PE metric in medical applications. It indicates the overall performance of the system in terms of sensitivity and specificity (see Appendix). Besides the classification accuracy, Brier score [94] and concordance index [95] are commonly used PE metrics in CV risk assessment [12, 53, 96].

ML-Based Algorithms

In general, classification and regression are the two primary tasks in ML-based algorithms. Almost all the ML-based algorithms are capable of performing both of these two tasks. Classification basically categorizes the input data into one of the predefined labels or outcomes. For example, in a CVD/stroke event prediction task, the input features are generally classified into either "*Event*" or "*No-Event*" category. Regression-based ML algorithms are generally used for predictions of some real-valued output. For example, in a CVD/stroke risk estimation task, regression-based ML algorithms provide the real-valued percentage risk between 0 and 100%. This review is mainly focused on the ML-based application consisting of classification task. The most common ML algorithms used in CVD risk assessment are support vector machine (SVM) [97], artificial neural networks (ANN) [98], linear and logistic regression [54••], and tree-based algorithms such as random forest (RF) and decision tree (DT) [54••]. Another category of ML is ensemble learning techniques, in which the outcomes of all ML techniques can be combined to train the ML model to increase the accuracy of risk prediction. In Tables 1, 2, and 3, we have compared multiple studies presented on ML-based CVD/stroke risk assessment. One important observation is that most of the studies have utilized the SVM as a classifier during training and testing of classification tasks.

Risk Assessment in Machine Learning Framework

In last decade, various efforts were made to perform the ML-based CV risk stratification using imaging modalities such as carotid CT [74], coronary CT angiography [107], single photon emission CT (SPECT) [108], echocardiography [71, 109], magnetic resonance imaging [110], and optical coherence tomography [25]. However, since this review is largely focused on the ML-based CV risk stratification using ultrasound imaging, the discussion on other imaging modalities is considered to be out-of-scope for this review. This section covers various efforts made in the direction of ML-based CV risk stratification using ultrasound imaging (of both coronary and carotid arteries).

Image-Based Stroke Risk Assessment Using Machine Learning

Deposition of atherosclerotic plaque leading to restriction of blood flow in the carotid and coronary arteries leads to cerebrovascular (ischemic stroke) and cardiovascular (myocardial infarction) events [111, 112]. In recent years, ML-based algorithms have been widely adopted for stroke risk assessment using non-invasive imaging modalities such as carotid ultrasound [56, 57•, 58•, 59, 60]. Carotid atherosclerotic plaque burden is a crucial biomarker for stroke events and can be readily assessed using imaging tests [20, 113]. The appearance of CP in the B-mode ultrasound image (brighter/hyperechoic/echogenic or darker/hypoechoic/echolucent) adds valuable information about the risk profile of a patient [114]. It has been shown that echolucent (darker) atherosclerotic plaque (darker plaque) is a potential indicator for stroke events [115, 116]. It has also been shown that the effect of this echolucent plaque is more pronounced in patients with diabetes [117]. Similarly, echogenic (brighter) plaque due to the presence of calcium within a plaque [118, 119] may be a marker of less vulnerable/low-risk plaque compared to the echolucent plaque. Identification of both of these plaque phenotypes is a crucial step in stroke risk assessment and can possibly be useful in treatments of stenting or endarterectomy [55, 56, 60, 120]. This decision is clearly a classification task, for which the ML-based systems are well suited. In the last decade, multiple efforts were made to automatically classify CP phenotypes [55, 56, 57•, 60].

In 2010, Acharya et al. [55] presented a study that classified carotid atherosclerotic plaque using the supervised ML-based algorithm such as SVM and AdaBoost classifier. Texture patterns captured using carotid ultrasound images along with the statistical features (mean and standard deviation) were used to train these ML systems. Authors reported 82.4% classification accuracy using SVM-based classifier. In 2013, the same group (Acharya et al. [56]) again classified CP phenotypes by considering the combination of discrete wavelet transform (DWT), HOS, and texture features. With the addition of both the DWT and HOS features, classification accuracy increased to 91.7%. Other similar studies of stroke risk assessment using carotid plaque phenotypes in ML-based algorithms are presented in Tables 1, 2, and 3.

Cardiovascular Diseases Risk Assessment Using Machine Learning

In the last few years, ML-based algorithms have widely penetrated into the domain of primary CVD risk assessment, particularly in (i) coronary artery disease using characterization of coronary atherosclerotic plaque tissues, (ii) CVD risk using coronary calcium score, (iii) coronary artery disease based on conventional risk factors, (iv) overall CVD risk, and (v) prediction of CV events. Risk assessment using ML in each of these different applications requires the data-specific patterns to train the ML model, and then to transform the trained knowledge to predict the risk on the test data. These patterns can be derived from the CCVRFs, serum biomarkers, patients' demographics, imaging modalities or from the combination of these. In the last decade, multiple studies have explored the potential advantages of using different combinations of features for ML-based cardiovascular risk assessment [53, 71, 73, 92].

Using IVUS coronary imaging modality, Araki et al. [92] demonstrated the CAD risk stratification of 15 Japanese patients using 56 grayscale features. The IVUS image-based gray features were captured from the region between inner elastic lamina and external elastic lamina of the coronary wall. The IVUS examinations scanned the coronary arteries including the left and right anterior descending, left circumflex, and left main coronary artery. Overall, when using the SVM-based classifier, the ML classification accuracy for this automated system was 94.95%. This improvement is likely due to inclusion of the following: (i) more dominant features along with

Table 1 Machine learning-based CVD/stroke risk stratification in both carotid and coronary artery

C1 SN	C2 Authors	C3 AT (modality)	C4 Features types	C5 TF	C6 Feature selection	C8 Classifier type	C9 Ground truth	C10 N*	C11 TI	C12 Training protocol	C13 Performance evaluation	C14 Benchmarking
R1	Acharya et al. [56] (2011)	Carotid (CUS)	DWT, HOS, & texture features	7	Statistical test	SVM	Labels from physicians	99	112	K3	Se (97%), Sp (80%), ACC (91.7%)AUC (0.885)	–
R2	Acharya et al. [57•] (2011)	Carotid (CUS)	DWT features	54	Statistical test	SVM	Labels from physicians		346		ACC (83.7%)	–
R3	Acharya et al. [60] (2012)	Carotid (CUS)	Texture	8	Statistical test	SVM	Risk labels from physicians	71	346	–	ACC (83%)	Against kNN, RBPNN
R4	Acharya et al. [59] (2013)	Carotid (CUS)	Grayscale features	17	Statistical test	SVM, GMM, RBPNN, DT, kNN, NBC, FC	Labels from physicians	445	492	K3	DB1:ACC (93.1%)DB1: ACC (85.3%)	–
R5	Acharya et al. [99] (2014)	Carotid(CUS)	Phenotypes & HOS features	7	Statistical test	SVM, RBPNN, kNN, DT	Labels from physicians	59	118	K10	ACC (99.1%)	–
R6	Kariacou et al. [100] (2012)	Carotid (CUS)	Image-based texture	27	Statistical test	SVM, LR	Follow-up data labels	108	–	–	ACC (77%)	–
R7	Gastounioti et al. [101] (2015)	Carotid (CUS)	Kinematics features	1236	FDR, WRS, PCA	SVM	Follow-up data labels	56	4200	–	ACC (88%)	Against kNN, PNN, DT, DA
R8	Araki et al. [92] (2016)	Coronary (IVUS)	Grayscale features	56	PCA	SVM	cIMT	19	4004		ACC (94.95%)AUC (0.98)	

CUS carotid ultrasound, *LR* logistic regression, *SVM* support vector machine, *Se* sensitivity, *Sp* specificity, *ACC* accuracy, *DWT* discrete wavelet transform, *kNN* K-Nearest Neighbor, *RBPNN* Radial Basis Probabilistic Neural Network, *GMM* Gaussian Mixture Model, *DT* decision tree, *NBC* Naïve Bays Classifier, *FC* Fuzzy Classifier, *DB* database, *HOS* higher order spectra, *LBP* local binary pattern, *FDR* Fisher discriminant ratio, *WRS* Wilcoxon Rank-Sum, *PCA* principal component analysis, *DA* discriminant analysis

feature selection methods such as principal component analysis (PCA) or Fisher discriminant analysis; and (ii) plaque motion analysis. Banchhor et al. [73] recently extended Araki's [92] work to include coronary wall parameters. In total, 65 carotid and coronary wall-based features were used to perform the ML-based coronary artery disease risk assessment. Using the PCA-based features selection approach in conjunction with an SVM-based classifier, the authors reported a classification accuracy of 91.28% with AUC of 0.91. Both of these studies (Araki et al. [92] and Banchhor et al. [73]) indicated the link between coronary and carotid atherosclerosis by considering the cIMT and plaque burden as the gold standard to perform the supervised CVD risk stratification.

Risk assessment based on longitudinal trials or follow-up studies is generally considered to be accurate and widely adopted in clinical practice. Proportional hazard models and risk calculators are the conventional tools for CVD risk assessment [5–14]. However, a very recently published study by Ambale-Venkatesh et al. [53] demonstrated that the ML-based algorithms are more accurate and better compared to traditional proportional hazard models for CVD risk assessment. Authors included the participants from the well-known Multi-Ethnic Study for Atherosclerosis (MESA), a 12-year longitudinal cohort study. A total of 735 CV risk predictors or features were extracted from diverse sources such as patients' demographics, traditional risk factors, imaging modalities, questionnaires, and laboratory biomarkers. Authors reported an overall C-index of 0.81 and a Brier score of 0.083 using the random forest-based classifier. The authors also benchmarked their results against the traditional CV risk assessment tools such as FRS and PCRS. Compared to these traditional risk scores, authors indicated in an improvement C-index by ~ 10% and decreased in Brier score by 10–25%.

Weng et al. [54] also presented a prospective study with 378,256 participants and reported better risk stratification using ML-based algorithms over the conventional statistically derived risk calculators. A total of 30 CCVRFs were used for training the ML-based algorithms. Authors compared the performance of four ML-based algorithms such as ANN, random forest, gradient boosting machine, and logistic regression. The study reported ANN to be the best classifier with an AUC of 0.76.

Kakadiaris et al. [61] reported the most recent study based on MESA participants that reported a superior performance of ML-based system compared to the PCRS-based calculator. The PCRS calculator was based on ACC/AHA guidelines that recommended the lipid-lowering statins to the patients whose risk was more than 7.5% to reduce the risk of ASCVD. Kakadiaris et al. [61] used the same PCRS but the statin eligibility threshold was chosen as 9.75%. This was mainly because of the 13-year follow-up nature of the MESA study, while the PCRS was based on 10-year follow-up dataset. The authors used the same nine CCVRFs that was used for

Table 2 Machine learning-based CVD/stroke risk stratification in both carotid and coronary artery

C1 #SN	C2 Authors	C3 AT (modality)	C4 Features types	C5 TF	C6 Feature selection	C8 Classifier type	C9 Ground truth	C10 N*	C11 TI	C12 Training protocol	C13 PE	C14 Benchmarking
R1	Hu et al. [102] (2016)	NA	CCVRFs	41	Fisher	Naïve Bayes, MLP, RF	Follow-up data labels	382	382	K3	AUC (0.797), BS (0.085)	–
R2	Narain et al. [103] (2016)	NA	CCVRFs	7	NA	QNN	Risk labels from physicians	682	NA	*K3	ACC (98.57%)	Against FRS
R3	Unnikrishnan et al. [104] (2016)	NA	CCVRFs	9	NA	SVM	Follow-up data labels	2406	NA	K5	Se (68.2%)Sp (85.9%) AUC (0.71)	Against FRS
R4	Venkatesh et al. [53] (2017)	Coronary MRI Carotid US	CCVRFs, image phenotypes, & serum biomarkers	735	MDMST	RF, Cox, LASSO-cox, AIC-Cox backward regression	Follow-up data labels	6814	NA	K3	C-Index (0.81), BS (0.083)	Against FRS & PCRS
R5	Zarkogianni et al. [105] (2017)	NA	CCVRFs	16	NA	HWNN & SOM	Follow-up data labels	560	NA	–	AUC (0.715),ACC (71.79%), BS (0.07)	Against UKPDS
R6	Banchhor et al. [73] (2017)	Coronary (IVUS)	Texture-based & wall-based features	65	PCA	SVM	Carotid plaque burden	22	4930	K10	ACC (91.28%) AUC (0.91)	–
R7	Araki et al. [68] (2017)	Carotid (CUS)	Image-based texture features	16	Statistical test	SVM	LD-based risk labels	204	407	K5, K10, JK	ACC (NW: 95.08% & FW: 93.47%)	–
R8	Saba et al. [106] (2017)	Carotid (CUS)	Image-based texture	16	PCA	SVM	LD-based risk labels	204	407	K10	ACC (NW: 98.83% & FW: 98.55%)	–

CUS carotid ultrasound, *SVM* support vector machine, *Se* sensitivity, *Sp* specificity, *ACC* accuracy, *PCA* principal component analysis, *MLP* multilayer perceptron, *RF* random forest, *BS* Brier score, *QNN* quantum neural network, *MDMST* Minimal Depth of Maximal Subtree, *SOM* self-organization map

PCRS computation and demonstrated the better performance of ML-based SVM classifier (AUC = 0.92) compared to PCRS (AUC = 0.71). In this review, we have investigated some more studies that adapted ML-based algorithms for CVD risk assessment. A summary of all such studies along with their attributes is presented in Tables 1, 2, and 3.

CVD/Stroke Risk Assessment Indices

Some investigators have recommended the use of the single index that quantifies the CVD/stroke risk [55, 56, 60, 71, 74, 121]. Acharya et al. [71] recommend the use of the single discriminative index called *HeartIndex* for assessing the risk of coronary artery disease (CAD). The *HeartIndex* was derived from the features to classify the echocardiography images into two risk classes: normal and CAD. In order to assess neurological risk, Pedro et al. [121] proposed the *enhanced activity index* (*EID*) that was based on the carotid artery plaque morphology and severity of carotid stenosis to classify the occurrence of ipsilateral ischemic symptoms. Acharya et al. [74] proposed the single values *Atheromatic*™ index (from AtheroPoint™, Roseville, CA, USA) to identify two CP phenotypes: high vs. low risk. The design of the *Atheromatic*™ index was based on the computed tomography image phenotypes which were derived from local binary patterns, wavelet transform, and the textures of the CP image. The same group [55] also proposed a *Symptomatic Asymptomatic Carotid Index* (*SACI*) based on the texture and statistical features derived from the carotid ultrasound image. The *SACI* index has also been tested in a carotid atherosclerotic plaque ultrasound-based tissue characterization study by computing the grayscale features in ML framework [56].

Medical Implications of Machine Learning-Based Risk Assessment

Risk assessment systems are primarily aimed at identifying the risk profiles of patients and to stratify them into one of the several CVD risk classes (e.g., low-risk, moderate-risk, and high-risk classes). Risk stratification tools decide the need and strength of statins (i.e., the well-known lipid-lowering medications) such as atorvastatin, pravastatin, and simvastatin [122] and diabetes-controlling medications such as metformin [123].

Traditional statistically derived risk prediction models have been reported to either underestimate or overestimate the CVD risk [17, 18] and therefore have the unintended consequence of inappropriate medication prescription in some patients and inappropriate under-utilization in other patients, both of which have potential harmful side effects and outcomes. This also could increase the economic burden on the patients and healthcare systems. ML systems provide better risk assessment and supports in avoiding unnecessary over or

Table 3 Machine learning-based CVD/stroke risk stratification in both carotid and coronary artery

C1 #SN	C2 Authors	C3 AT (modality)	C4 Features types	C5 TF	C6 Feature selection	C8 Classifier type	C9 Ground truth	C10 N*	C11 TI	C12 Training protocol	C13 Performance evaluation	C14 Benchmarking
R1	Weng et al. [54••] (2017)	–	CCVRFs	30	–	RF, LR, GBM, ANN	Follow-up data labels	378,256	–	K4	AUC: 0.764	Against PCRS
R2	Kakadiaris et al. [61••] (2018)	–	CCVRFs	9	–	SVM	Follow-up data labels	6459	–	K2	Se (86%), Sp (95%), AUC (0.92)	Against PCRS

LR logistic regression, *SVM* support vector machine, *Se* sensitivity, *Sp* specificity, *RF* random forest

under treatment [54••]. A recent follow-up study presented by Kakadiaris et al. [61••] investigated the statin eligibility for the patients using both (i) PCRS calculator based on ACC/AHA risk prediction guidelines and (ii) ML-based risk calculator. ACC/AHA model recommended statins for 46% of the patients while the ML-based risk calculator identified only 11.7% eligible for statin therapy.

Deep Learning-Based Cardiovascular Risk Stratification

Deep learning is an extension of classical ANNs and efficient ML techniques to analyze medical images. It consists of multiple convolutional layers that allow extraction of more data-dependent patterns and thus, it helps in improving the accuracy of outcome prediction [124]. Convolutional neural network (CNN) is a DL algorithm which has gained large attention while analyzing medical images (Fig. 4). This is because CNN has the ability to extract a large number of image-based features compared to the handcrafted statistical features [125, 126]. In CNN algorithm, an input image gets convolved with a number of kernels which are responsible for the deck of feature extraction (convolution operation is shown by a green rectangle using kernel banks-magenta color). The features are selected using polling operation (shown by an inverted green triangle), where the meaningful features are selected. The coefficients of all these kernels are learned during the training process of CNN. A basic architecture of DL using CNN is as depicted in Fig. 4. There two challenges associated with the basic CNN architecture. (i) The basic architecture may suffer from overfitting due to the input data and thus, results in a reduction in risk stratification accuracy. (ii) The basic architecture may have a limited number of convolution layers. A larger number of convolutional layers extract more features from the input images and thus, provide the power to the DL system to separate the classes accurately. This, however, increases the complexity of the system. The two challenges can be solved (i) by including the dropout strategy in the basics model and (ii) by adding multiple inception layers in the basic model, respectively. The detailed version of DL using CNN has been depicted in Fig. 5. The details of dropout and inception layers are out of the scope of this review. However, their functionality has clearly been discussed in our previous paper [49]. The main advantage in CNN is its ability to extract the context-based features, and as a result does not require any prior information, as in *Supervised* ML, before training the system. Recently, Lekadir et al. [127] used CNN to automatically characterize the plaque tissues from carotid ultrasound images. A very recent set of studies by Biswas et al. [48, 88] used CNN to measure the cIMT and LD, respectively, based on CUS images. Although the focus of this review is on ultrasonography, it must be noted that DL techniques have also

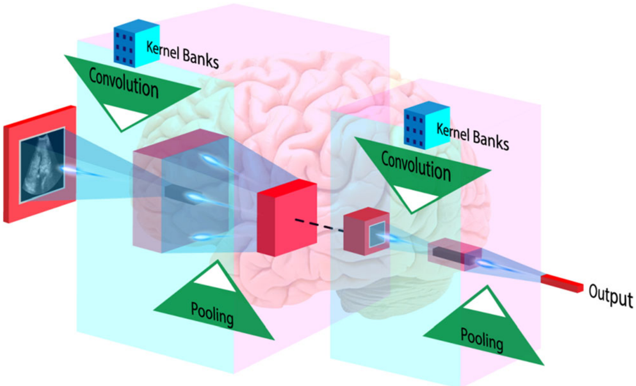


Fig. 4 An architectural diagram for the deep learning-based convolutional neural network algorithm (Courtesy of AtheroPoint™, Roseville, CA, USA and Reproduced with permission from Springer Nature)

been tried to perform risk assessment using different imaging modalities such as coronary CT angiography [128], optical coherence tomography [25], and MRI [110].

Challenges in Machine Learning Design

There are some important key challenges while adapting ML techniques in medical domains especially in CVD/stroke risk assessment, including the following:

- *Black-Box Nature of the ML Techniques*

ML-based algorithms have proven their potential in providing robust and accurate solution almost in every medical domain including CVD/stroke risk assessment. However, it is somewhat challenging for clinical practitioners and physicians to adapt ML techniques in their clinical practice. This may be because of the so-called black box nature of ML algorithms [129] and lack of external validations. Unlike traditional statistical-derived methods which are based on discrete clinical variables (e.g., age, blood pressure, diabetes), the internal working of ML algorithms is not easy to interpret for most physicians. This uncertainty about the logic of ML algorithm may cause some practitioners to be more reluctant to adopt this technology in clinical practice. Further, fewer studies have been published in respectable peer-reviewed journals that show (i) strong scientific validations, (ii) well-established gold standards, (iii) variation analysis of the data sets, and (iv) real-world ML clinical applications that can be adapted on daily basis.

- *Achieving Generalization of ML Models*

It is of paramount importance that the ML model must be generalizable [106]. This means the ML model designs must be tested on almost every relevant dataset including longitudinal follow-up datasets (or during prospective trials or retrospective data sets in which outcomes were recorded) with potentially different features. This makes the model more robust and clinically reliable.

- *Role of Transfer Learning*

Since conducting multiple clinical trials with large sample size to produce highly generalizable and reliable results is not economically viable, a ML technique known as transfer learning may be valuable. Furthermore, if an ML model is trained on a particular dataset with a unique set of features, then it also becomes practically impossible to collect the similar kind of features in multicenter trials due to its lengthy timely collection of data and soaring cost. This puts a limit generalization of ML systems. Transfer learning, therefore, provides the benefit of training on one set and application of transformed parameters on a different set.

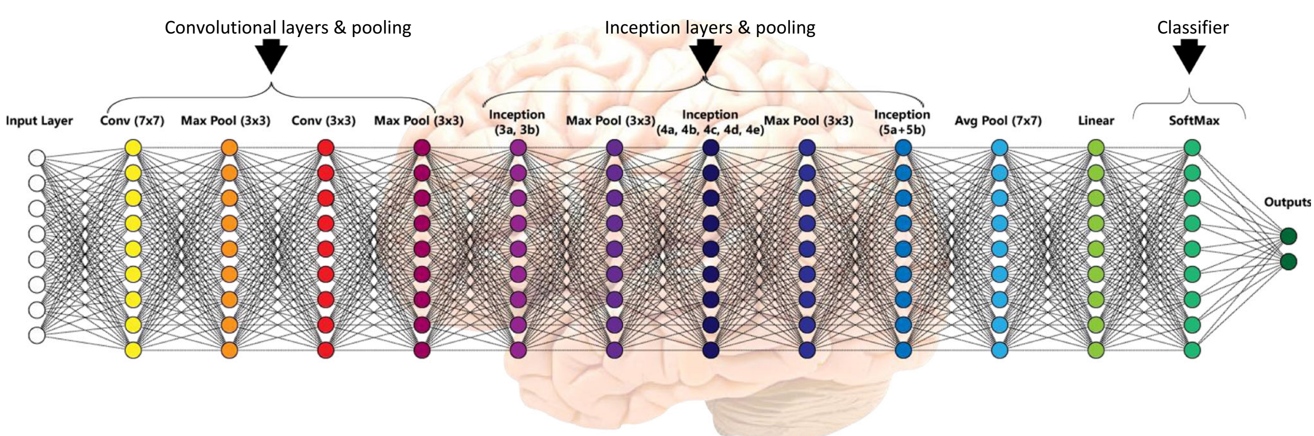


Fig. 5 Advanced CNN model by incorporating convolution, pooling, inception, softmax layers (Courtesy of AtheroPoint™, Roseville, CA, USA USA and Reproduced with permission from Elsevier)

- *Lack of Access to Data*

The biggest and the most important challenge for most ML-based data scientist and developers is the lack of access to the well-established patient and population-based datasets, such as MESA and ARIC. It is true that conducting such multicenter clinical trials is expensive, but further attempts at collaboration and improving access to such datasets are needed to validate these ML-based designs.

Because of these key challenges, medical practitioners are not ready to rely on ML techniques for clinical decision-making [93, 130]. It is of utmost importance for both medical practitioners and data scientists to come together and increase the interpretability of computationally complex ML techniques. In order to make the ML models generalizable, more funding sources should come together and conduct longitudinal multicenter clinical trials or observational studies that can benefit both data scientists and system developers to make more robust models.

Conclusion

In this review, we reported the changing trend for CVD/stroke risk assessment, ranging from traditional statistically derived calculators to advanced ML-based risk assessment systems. ML-based algorithms show better performance compared to traditional methods. In this review, we found that the supervised machine technique such as SVM is the widely adapted ML-based algorithm for CVD risk assessment followed by random forest and ANN. Data-driven features are the most vital part of ML algorithms. Most of the risk assessment techniques (i.e., traditional and ML-based) commonly incorporated traditional CV features in their risk assessment model. For better risk assessment, the feature engineering domain needs to be explored more in the near future. Different image-based risk factors can be incorporated to improve automated risk assessment systems. Deep learning is the rapidly developing field for image analysis which extracts more robust features from images. Image phenotypes extracted using DL combined with CCVRFs can provide a better platform for CVD/stroke assessment. Verification and validation of the ML/DL systems is a crucial component for adopting the system designs in routine clinical practice. Finally, with the advancements in big data and artificial intelligence-based paradigms, we are likely to see more sophisticated CVD/stroke risk assessment tools in the future.

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Compliance with Ethical Standards

Conflict of Interest Ankush Jamthikar, Deep Gupta, Narendra N. Khanna, Tadashi Araki, Luca Saba, Andrew Nicolaides, Aditya Sharma, Tomaz Omerzu, Harman S. Suri, Ajay Gupta, Sophie Mavrogeni, Monika Turk, John R. Laird, Athanasios Protogerou, Petros P. Sfikakis, George D. Kitas, Vijay Viswanathan, Gyan Pareek, and Martin Miner declare no conflict of interest. Dr. Jasjit S Suri is affiliated to AtheroPoint, focused in the area of stroke and cardiovascular imaging.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Appendix: Performance Evaluation Parameters

Sensitivity and specificity are computed using true positive (TP), true negative (TN), false positive (FP), and false negative (FN). TP indicates the count for which predicted class labels matches with ground truth label for high-risk threshold point, FN is defined as the number of times the predicted class labels that are incorrectly classified as low-risk, FP is defined as the number of times the predicted class labels that are incorrectly classified as high-risk, and TN is defined as the number of times predicted class labels that are correctly matched with low-risk ground truth label. Sensitivity and specificity are mathematically represented as, Sensitivity $= \frac{TP}{(TP+FN)}$ and Specificity $= \frac{TN}{(TN+FP)}$. Furthermore, the accuracy of risk stratification is mathematically represented as: Accuracy $= \frac{TP+TN}{(TP+FN+FP+FN)}$.

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- • Of importance
- •• Of major importance

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