Original Article

Cardiovascular/stroke risk prevention: A new machine learning framework integrating carotid ultrasound image-based phenotypes and its harmonics with conventional risk factors

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ABSTRACT

Motivation: Machine learning (ML)-based stroke risk stratification systems have typically focused on conventional risk factors (CRF) (AtheroRisk-conventional). Besides CRF, carotid ultrasound image phenotypes (CUSIP) have shown to be powerful phenotypes risk stratification. This is the first ML study of its kind that integrates CUSIP and CRF for risk stratification (AtheroRisk-integrated) and compares against AtheroRisk-conventional.

Methods: Two types of ML-based setups called (i) AtheroRisk-integrated and (ii) AtheroRisk-conventional were developed using random forest (RF) classifiers. AtheroRisk-conventional uses a feature set of 13 CRF such as age, gender, hemoglobin A1c, fasting blood sugar, low-density lipoprotein, and high-density lipoprotein (HDL) cholesterol, total cholesterol (TC), a ratio of TC and HDL, hypertension, smoking, family history, triglyceride, and ultrasound-based carotid plaque score. AtheroRisk-integrated system uses the feature set of 38 features with a combination of 13 CRF and 25 CUSIP features (6 types of current CUSIP, 6 types of 10-year CUSIP, 12 types of quadratic CUSIP (harmonics), and age-adjusted grayscale median).

Logistic regression approach was used to select the significant features on which the RF classifier was trained. The performance of both ML systems was evaluated by area-under-the-curve (AUC) statistics computed using a leave-one-out cross-validation protocol.

Results: Left and right common carotid arteries of 202 Japanese patients were retrospectively examined to obtain 404 ultrasound scans. RF classifier showed improved performance in AUC (−57%) for leave-one-out cross-validation protocol. Using RF classifier, AUC statistics for AtheroRisk-integrated system was higher (AUC = 0.99, p-value<0.001) compared to AtheroRisk-conventional (AUC = 0.63, p-value<0.001).

Conclusion: The AtheroRisk-integrated ML system outperforms the AtheroRisk-conventional ML system using RF classifier.

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1. Introduction

Cardiovascular disease (CVD) and stroke are the major global challenges for public healthcare.1 The CVD/stroke risk assessment using statistically-derived risk prediction models can support in the prevention and management of these diseases.2–8 But such statistically-derived models either underestimate or overestimate risk CVD risk in certain patients.9–15 The primary reason for this poor performance is the dependence of such models on the cardiovascular risk factors (CRF) that does not provide complete information about cardiovascular health of patients.16–20

Non-invasive ultrasound imaging of carotid arteries can capture the morphological variations in atherosclerotic plaque components.20–25 These variations are indicated using the carotid intima-media thickness (cIMT) and carotid plaque (CP) (Fig. 1).
which are also considered as the surrogate markers of coronary heart disease (CHD). In recent years multiple automated carotid ultrasound image-based phenotypes (CUSIP) were derived, which can provide better CVD/stroke risk stratification, when combined with the conventional risk factors. In order to ease the image analysis and further improve the accuracy of the risk stratification artificial intelligence techniques such as machine learning (ML) algorithms are widely adopted. The ML algorithms are data-driven techniques that classify the patients into risk categories based on various complex interactions between input risk predictors.

The objective of this study is to predict the risk of CVD/stroke using an ML framework on retrospective data while using the event-equivalence gold standards (EEGS). The EEGS are the alternatives to the primary endpoints, we can thus call them as the event-equivalence gold standard (EEGS). The acronyms used in this study are tabulated in Table A and Table B under Section A of the Supplementary Material.

2. Event-equivalence gold standard

Cardiovascular and/or cerebrovascular mortalities are often considered as the primary endpoint to evaluate any clinical studies. However, such primary endpoints are expensive and time-consuming. Furthermore, they require a large number of samples with long follow-up duration. Thus, there is a need to search for secondary endpoints or surrogate biomarkers that can mimic the behavior of the primary endpoints. Such endpoints can be used as a gold standard for assessing the risk of future CV events with fewer sample sizes, at a lower cost, and with shorter study duration. Since these gold standards are the alternatives to the primary endpoints, we can thus call them as the event-equivalence gold standards (EEGS).

Note that atherosclerosis is developed by the accumulation of calcium, lipid, collagen, fibrosis, macrophages, and other similar substances within the walls of the blood vessels. Furthermore, the progression of atherosclerosis is highly associated with the future risk of CVD or stroke events. Thus, the EEGS is the one that explains the progression of atherosclerosis disease. Carotid lumen diameter (LD) reflects the growth in atherosclerosis and also considered as a risk factor of cardiovascular diseases. Furthermore, carotid LD is an indicator of arterial remodeling and thus can provide more information about the vascular health of a person.
Narrowing of the carotid LD (stenosis) has been considered a major risk factor of ischemic stroke events.\textsuperscript{49-51} We thus hypothesize the usage of carotid LD as a powerful EEGS model for CVD/stroke risk assessment.\textsuperscript{52, 54} An LD threshold of 6 mm was selected for risk-stratifying the patients into either high-risk or low-risk category.

\section{Methods}

\subsection{Study cohort and image acquisition}

A cohort of 202 Japanese patients (IRB approved) was recruited for this retrospective study from Toho University, Japan, and written consent was obtained from all participants. Left and right common carotid arteries of all the patients were examined using a B-mode ultrasound scanner (Aplio XG, Xario, Aplio XV, Toshiba Inc., Tokyo, Japan). In total, 395 CUS scans were collected by an expert sonographer (overall mean image resolution of 0.0529 mm per pixel). The protocol for CUS image acquisition was based on the consensus report of the American Society of Echocardiography\textsuperscript{55} and has been discussed in detail in our previous studies.\textsuperscript{17, 39, 57} All the CUS scans were retrospectively analyzed by two operators (an expert and a novice operator). The expert operator had 15 years of experience in ultrasonography and radiology. Compared with all the previously published studies with the same Japanese cohort,\textsuperscript{17, 39, 57} this study is unique in terms of a novel design for ML-based strategy for risk stratification by combining CUSIP\textsubscript{curr} and CRF (a class of AtheroEdge\textsuperscript{™} systems from AtheroPoint\textsuperscript{™}, Roseville, CA, USA).\textsuperscript{61}

\subsection{Carotid ultrasound image phenotype measurements: feature set design}

The feature set is comprised of 38 features: (a) 13 types of CRF and (b) 25 types of CUSIP\textsuperscript{17, 32, 57, 58}. The 13 types of CRF includes age, gender, hemoglobin A1c, fasting blood sugar, low-density lipoprotein, and high-density lipoprotein (HDL) cholesterol, total cholesterol (TC), a ratio of TC and HDL, hypertension, smoking, family history, triglyceride, and ultrasound-based carotid plaque score. The 25 types of CUSIP involved (i) five types of current CUSIP (CUSIP\textsubscript{curr}) such as average cIMT (IMT\textsubscript{ave}), maximal cIMT (cIMT\textsubscript{max}), minimum cIMT (cIMT\textsubscript{min}), variations in cIMT (IMTV), and total plaque area (TPA), (ii) five types of 10-year prediction of CUSIP (CUSIP\textsubscript{10yr}) such as cIMT\textsubscript{ave10yr}, cIMT\textsubscript{max10yr}, cIMT\textsubscript{min10yr}, cIMTV\textsubscript{10yr}, and TPA\textsubscript{10yr}, (iii) two types of AtheroEdge\textsuperscript{™} composite risk scores (AECRS) evaluated using CUSIP\textsubscript{curr} and CUSIP\textsubscript{10yr} such as AECRS\textsubscript{curr} and AECRS\textsubscript{10yr}, (iv) 12 types of quadratic terms (harmonics) of these 12 image-based phenotypes (measured in (i), (ii), and (iii)), and finally, (v) an atherosclerotic plaque morphology-based feature called age-adjusted grayscale median (AAGSM) proposed by Kotsis et al.\textsuperscript{32}

\subsection{Machine learning-based risk stratification: conventional vs. integrated models}

The supervised random forest (RF)-based ML algorithm (see Fig. 2) was used for CVD/stroke risk stratification.\textsuperscript{38, 39, 62} Data partitioning unit separates the input image database into training and testing datasets. The feature engineering block then extracts 38 types of training and testing features. The dotted rectangular box in Fig. 2 provides a choice to perform the CVD/stroke risk stratification either by CRF alone (conventional ML system) or by integrating CRF with CUSIP features (so-called integrated ML system\textsuperscript{63}). The multivariate logistic regression (MLR) was then used for feature selection that resulted in 2 significant features (HT and TC) out of 13 CRF and 10 significant features (gender, age, HbA1c, TC, HT, Smoking, IMT\textsubscript{min}, AECRS\textsubscript{10yr}, AECRS\textsubscript{curr}, and AECRS\textsubscript{10yr}) out of 38 integrated features. These significant features were then used to train the ML-based RF classifier (for RF see Section C of Supplementary Material) under the supervision of training labels obtained from the EEGS. The trained ML coefficients were then

\begin{figure}[h]
    \centering
    \includegraphics[width=\textwidth]{Fig_2.png}
    \caption{The framework of the supervised machine learning system (Reproduced with permission from Authors and Springer publications\textsuperscript{26}).}
\end{figure}
used to transform the features derived from the test data into the output risk classes (high-risk or low-risk). The performance of the ML system was evaluated using area-under-the-curve (AUC) against the gold standard test labels derived from EEGS.

### 3.4. Statistical analysis

SPSS23.0 and R Studio were used to perform statistical analysis. Independent sample t-test and chi-square tests were performed for the continuous and categorical variables, respectively. The baseline characteristics of the study population are presented as mean ± SD for continuous variables and numbers (percentages) for the categorical variables, respectively. Receiver operating characteristics analysis was performed to compare the AUC values of AtheroRisk-integrated against the AtheroRisk-conventional systems. Carotid LD with a threshold of 6 mm has been used as an AUC to perform the performance evaluation using ROC analysis. The selection of LD threshold along with its sensitivity analysis is presented in Section B of the Supplementary Material. In order to test the validity of the recruited sample size, a power analysis was performed using a 95% confidence interval and a 5% error margin. This has resulted in an overall desired sample size of 334. The sample size used in this study (395 scans) was ~18% more than the required sample size of 334 for adequate power.

### 4. Results

The baseline characteristics of the Japanese cohort are presented in Table 1. Out of 395 CUS scans, 317 (78.08%) images had a carotid plaque score greater than 5, and 131 (32.27%) images had cIMTave ≥1.00 mm. The selected patients did not have any information about the atrial fibrillation with or without left atrial appendage clot, and therefore, it was not considered in the design of this study. From Table 1, it is clear that the baseline risk-profile of Japanese patients follow the high-risk category.

Using RF-based classifier, AtheroRisk-integrated showed the highest AUC (AUC = 0.99, P < 0.001) compared to AtheroRisk-conventional (AUC = 0.63, P < 0.001) for leave-one-out cross-validation protocol (see Fig. 3). These results demonstrated an overall improvement in the AUC of AtheroRisk-integrated ML system over AtheroRisk-conventional by 57.14% with RF classifier. Due to the small sample size, we have used a leave-one-out cross-validation protocol. This has clearly indicated the potential role of the integrated set of features in AtheroRisk-integrated which consisted of both 13 CRF and 25 CUSIP (6 CUSIPcurr, 6 CUSIP10yr, AAGSM, and 12 quadratic terms – harmonics), unlike AtheroRisk-conventional that used only 13 CRF.

In order to test the stability of the ML system, five current CUSIP were measured by two operators (an expert and a novice) at different time instants using AtheroEdge™ (AtheroPoint, Roseville, CA, USA)0.56, 64 Using these two different sets of CUSIP, the ML-based system was trained and tested against EEGS. The mean risk stratification accuracy and AUC for two sets of measurements were differed by less than 5% (Accuracy: 93.15% vs. 96.22% and AUC 0.92 vs. 0.96, p < 0.001). The precision-of-merit and figure-of-merit was 96% with an overall mean absolute error of less than ±5%. This indicated CUSIP used for risk stratification was highly stable and reliable.

### 5. Discussion

This study validated our hypothesis that shows a greater risk predictive ability for ML-based systems using integrated risk factors.
5.1. Benchmarking

Pignoli et al23 (2017) presented the use of B-mode ultrasound for Pignoli et al23 (2017) presented the use of B-mode ultrasound for the best choice for EEGS. However, it is also important to note that in our current study using CRF as EEGS may lead to a bias effect. This is because the feature set of 38 risk factors was derived by using 16 types of cIMT values (quadratics terms) of cIMT). Thus, carotid LD was considered to be the best choice for EEGS.

5.2. Effect of using cIMT as EEGS for CVD/stroke risk assessment

Although the study results support our hypothesis, we believe that additional investigations may allow for more progress in ML-based strategies for risk stratification. Even though the pilot study had a small cohort size with acceptable power analysis for sample size test, the ML had an ability to adjust the variations of the image phenotypes when combined with the CRF during training to compute the predicted risk on test patients. Note that the ML system did use the surrogate image-based biomarker (lumen diameter) as EEGS, 17, 19, 32, 39, 58–60, 85 which may add to a slight bias in the overall estimation of predicted risk. Thus, we need a larger multi-ethnic, multi-center cohort for stronger validation and performance evaluation of ML systems using primary endpoints. At last, the current study did not consider the effect of carotid stenosis, which is a well-established atherosclerosis-driven CVD/stroke biomarker,20–23 and hence, needs further validation. The proposed ML-based integrated system can be extended by incorporating inflammatory markers, renal disease markers, grayscale features that

| Table 2 | Machine learning-based CVD/Stroke risk stratification. |
| --- | --- |
| C1 | #SN | Authors | AT (Modality) | Features Types | C2 | Features | C3 | C4 | C5 | C6 | C7 | C8 | C9 | C10 | C11 |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| R1 | Kariacou et al17 (2012) | Carotid (CUS) | Image-based | SVM, LR | 108 | – | – | – | ACC (77%) |
| R2 | Acharya et al19 (2013) | Carotid (CUS) | Grayscale Features | SVM, GMM, RBPNN, DT, kNN, NBC, FC, SVM, RBPNN, kNN, DT | 445 | 492 | K3 | DB1: Accuracy (93.1%), DB2: Accuracy (85.3%) |
| R3 | Acharya et al20 (2014) | Carotid (CUS) | Phenotypes & HoS | 59 | 118 | K10 | Accuracy (99.1%) |
| R4 | Gastounioti et al19 (2015) | Carotid (CUS) | Kinematics | 56 | 4200 | – | Accuracy (88%) |
| R5 | Araki et al20 (2015) | Carotid (CUS) | Image-based | 204 | 407 | K5, K10 | Accuracy (NW: 95.08%), FW: 93.47% |
| R6 | Saha et al21 (2017) | Carotid (CUS) | Image-based | 204 | 407 | K10 | Accuracy (NW: 98.83%), FW: 98.55% |
| R7 | Weng et al22 (2017) | CRF | 30 | RF, LR, GBM, ANN | 378256 | K4 | AUC: 0.764 |
| R8 | Kakadiaris et al23 (2018) | CRF | 9 | SVM | 6459 | – | K2 | Se (86%), Sp (95%), AUC: 0.92 |
| R9 | Proposed (2019) | Carotid (CUS) | Integrated Features | 38 | RF | Labels from physicians | 202 | 395 | K2, K3, K10, JK | AUC: 0.99 |

CUS: Carotid ultrasound, LR: Logistic Regression, SVM: Support Vector Machine; Se: Sensitivity, Sp: Specificity; DWT: Discrete Wavelet Transform, kNN: K-Nearest Neighbor, RBPNN: Radial Basis Probabilistic Neural Network, GMM: Gaussian Mixture Model, 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, MLP: MultiLayer Perceptron, RF: Random Forest, B5: Brier Score, QNN: Quantum Neural Network, IGR: Information Gain Ranking, MDMST: Minimal Depth of Maximal Subtree, SOM: Self Organization Map, FRS: Framingham Risk score, PCRD: Pooled Cohort Risk Score.

(C = 0.99, P < 0.001) compared to the CRF alone (C = 0.63, P < 0.001).

5.1. Benchmarking

Table 2 chronologically compared the proposed AtheroRisk-integrated system against the eight ML-based studies (row R1 to R8) using eleven attributes (column C1 to C11). Nearly all the previous studies used either the conventional blood biomarkers and clinical parameters, or the grayscale image-based features for CVD risk assessment. The conventional risk factors do not capture the morphological variations in the blood vessels, which, however, can be possible using the image-based phenotypes.16–18 It is also important to note that in our current study using CRF as EEGS can provide a stronger effect as EEGS for ML-based CVD/stroke risk stratification. The primary objective of the risk stratification system is to predict the risk profile of the patients and stratify them into one of the several CVD/stroke risk categories such as low-risk, moderate-risk, or high-risk. In general practice, risk assessment systems aid physicians in deciding the need and strength of the medications such as lipid-lowering medications (for example pravastatin, atorvastatin, and simvastatin)83 or diabetes control medication (for example metformin).84 Compared with traditional risk prediction models, ML-based risk assessment systems have the promise to be more accurate37 and avoid the under or overestimation of CVD/stroke risk.

5.4. Strength, limitations, future scope

Although the study results support our hypothesis, we believe that additional investigations may allow for more progress in ML-based strategies for risk stratification. Even though the pilot study had a small cohort size with acceptable power analysis for sample size test, the ML had an ability to adjust the variations of the image phenotypes when combined with the CRF during training to compute the predicted risk on test patients. Note that the ML system did use the surrogate image-based biomarker (lumen diameter) as EEGS, 17, 19, 32, 39, 58–60, 85 which may add to a slight bias in the overall estimation of predicted risk. Thus, we need a larger multi-ethnic, multi-center cohort for stronger validation and performance evaluation of ML systems using primary endpoints. At last, the current study did not consider the effect of carotid stenosis, which is a well-established atherosclerosis-driven CVD/stroke biomarker,20–23 and hence, needs further validation. The proposed ML-based integrated system can be extended by incorporating inflammatory markers, renal disease markers, grayscale features that
are also associated with the risk of CVD and stroke, and further be converted as an online platform for risk stratification. Even though our LD estimation methods were scale-space based, the system can be extended using deep learning-based models for LD estimation. Similarly, image phenotypes can also be computed using deep learning-based solutions.

6. Conclusion

We presented a novel ML system that integrated 25 carotid ultrasound image-based phenotypes (CUSIP) with 13 conventional risk factors (CRF) factors. We proved our hypothesis that AtheroRиск-integrated is far superior to AtheroRisk-conventional for using Random Forest classifier. Our results demonstrated that AtheroRisk-integrated showed an overall improvement of 57.14% in the AUC when using an RF-based classifier. Since our machine learning systems were generalized, it can, therefore, be extended to deep learning-based paradigms.

What is already known?

Generally, statistically derived and machine learning-based risk prediction models use either conventional clinical parameters for CVD risk assessment.

What this study adds:

Integration of conventional clinical risk factors with carotid ultrasound image phenotypes can offer higher risk stratification ability.

Conflicts of interest

All authors have none to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ihj.2020.06.004.

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