The International Journal of Cardiovascular Imaging
https://doi.org/10.1007/s10554-021-02294-0

ORIGINAL PAPER

Role of artificial intelligence in cardiovascular risk prediction and outcomes: comparison of machine-learning and conventional statistical approaches for the analysis of carotid ultrasound features and intra-plaque neovascularization

Amer M. Johri[1] · Laura E. Mantella[2] · Ankush D. Jamthikar[3] · Luca Saba[4] · John R. Laird[5] · Jasjit S. Suri[6]

Received: 27 March 2021 / Accepted: 19 May 2021
© The Author(s), under exclusive licence to Springer Nature B.V. 2021

Abstract
The aim of this study was to compare machine learning (ML) methods with conventional statistical methods to investigate the predictive ability of carotid plaque characteristics for assessing the risk of coronary artery disease (CAD) and cardiovascular (CV) events. Focused carotid B-mode ultrasound, contrast-enhanced ultrasound, and coronary angiography were performed on 459 participants. These participants were followed for 30 days. Plaque characteristics such as carotid intima-media thickness (cIMT), maximum plaque height (MPH), total plaque area (TPA), and intraplaque neovascularization (IPN) were measured at baseline. Two ML-based algorithms—random forest (RF) and random survival forest (RSF) were used for CAD and CV event prediction. The performance of these algorithms was compared against (i) univariate and multivariate analysis for CAD prediction using the area-under-the-curve (AUC) and (ii) Cox proportional hazard model for CV event prediction using the concordance index (c-index). There was a significant association between CAD and carotid plaque characteristics [cIMT (odds ratio (OR) = 1.49, p = 0.03), MPH (OR = 2.44, p < 0.0001), TPA (OR = 1.61, p < 0.0001), and IPN (OR = 2.78, p < 0.0001)]. IPN alone reported significant CV event prediction (hazard ratio = 1.24, p < 0.0001). CAD prediction using the RF algorithm reported an improvement in AUC by ~ **3%** over the univariate analysis with IPN alone (0.97 *vs.* 0.94, p < 0.0001). Cardiovascular event prediction using RSF demonstrated an improvement in the c-index by ~ **17.8%** over the Cox-based model (0.86 *vs*. 0.73). Carotid imaging phenotypes and IPN were associated with CAD and CV events. The ML-based system is superior to the conventional statistically-derived approaches for CAD prediction and survival analysis.

Keywords Coronary artery disease · Focused carotid ultrasound · Intraplaque neovascularization · Machine learning · Risk prediction · And cardiovascular event prediction

Introduction

Cardiovascular (CV) disease is a major cause of global mortality and morbidity [1]. Vascular ultrasound may serve as a useful screening tool to detect atherosclerotic plaque, a cause of the cardiovascular disease (CVD) [2, 3]. Specifically, carotid intima-media thickness (cIMT), maximum plaque height (MPH), and total plaque area (TPA) are considered surrogate markers of coronary artery disease (CAD) and are associated with CV outcomes [3–6]. Recently, a plaque progression and instability metric called intraplaque neovascularization (IPN) were reported as a significant and independent predictor of CAD and CV events [7].

At present, the association between carotid ultrasound-based image phenotypes and CAD is established using

✉ Jasjit S. Suri
jasjit.suri@atheropoint.com

1 Department of Medicine, Division of Cardiology, Queen's University, Kingston, ON, Canada

2 Department of Biomedical and Molecular Sciences, Queen's University, Kingston, ON, Canada

3 Department of ECE, Visvesvaraya National Institute of Technology, Nagpur, MH, India

4 Department of Radiology, Azienda Ospedaliero Universitaria (A.O.U.), Cagliari, Italy

5 Heart and Vascular Institute, Adventist Health St. Helena, St Helena, CA, USA

6 Stroke Diagnosis and Monitoring Division, AtheroPoint™, Roseville, CA 95661, USA

Published online: 29 May 2021

conventional statistical regression-based approaches that assume a linear association between baseline risk predictors and the cardiovascular outcomes [8, 9]. This assumption oversimplifies the complex nonlinear patterns available in the input risk predictors [8, 9]. Furthermore, regression-based approaches handle a limited set of risk predictors, therefore, when a large number of risk predictors are included in their model, such approaches fail to provide accurate risk assessment and event prediction [8, 10, 11]. The field of artificial intelligence (AI) now provides a potential solution to overcome the problem of conventional statistical analysis. The utility of AI has been established in various medical imaging applications [12] and, in particular, is emerging for a carotid ultrasound for CVD risk assessment [13]. An AI entity can learn from the inter-relationships of risk predictors and their association with the endpoints to create an offline model, which can then be used in an online paradigm for predicting future CV events using the test risk predictors.

Machine-learning (ML) is the component of AI, which helps in overcoming the limitations of conventional statistical approaches. Previous studies have demonstrated the superiority of ML-based algorithms in predicting CVD risk over conventional statistically derived risk calculators [11, 13–16]. Furthermore, while handling censored datasets for survival analysis, ML-based algorithms have shown promising results with high discrimination between desired CV outcomes [17, 18]. Therefore, in this study, we investigated whether the ML-based algorithms can provide a better prediction of CAD and future CV events compared with a conventional statistical model. Figure 1 depicts the global view of the proposed ML-based CAD prediction system.

Methods

Study population

We previously published details of the derivation study and conventional statistical analysis prior to the application of ML methods [7, 19, 20]. This prospective study recruited 459 consecutive participants between December 2016 and June 2018 from the Kingston General Hospital's Cardiac Catheterization Laboratory, Ontario, Canada [7]. The inclusion criteria were: (i) age ≥ 18 years; (ii) referred for clinically indicated angiography for CAD assessment; and (iii) the absence of clinical contraindication to angiography. Exclusion criteria were: (i) previous carotid endarterectomy; (ii) allergy to perflutren; (iii) known or suspected cardiac shunt; (iv) previous percutaneous coronary intervention (≥ 1 week) or coronary artery bypass graft surgery; and (v) prior myocardial infarction, stroke, or transient ischemic attack (≥ 1 week). Baseline information was collected from all participants, including medical and surgical history, and vitals. Cholesterol values could not be obtained prior to angiography due to timing and personnel constraints. Written

Figures

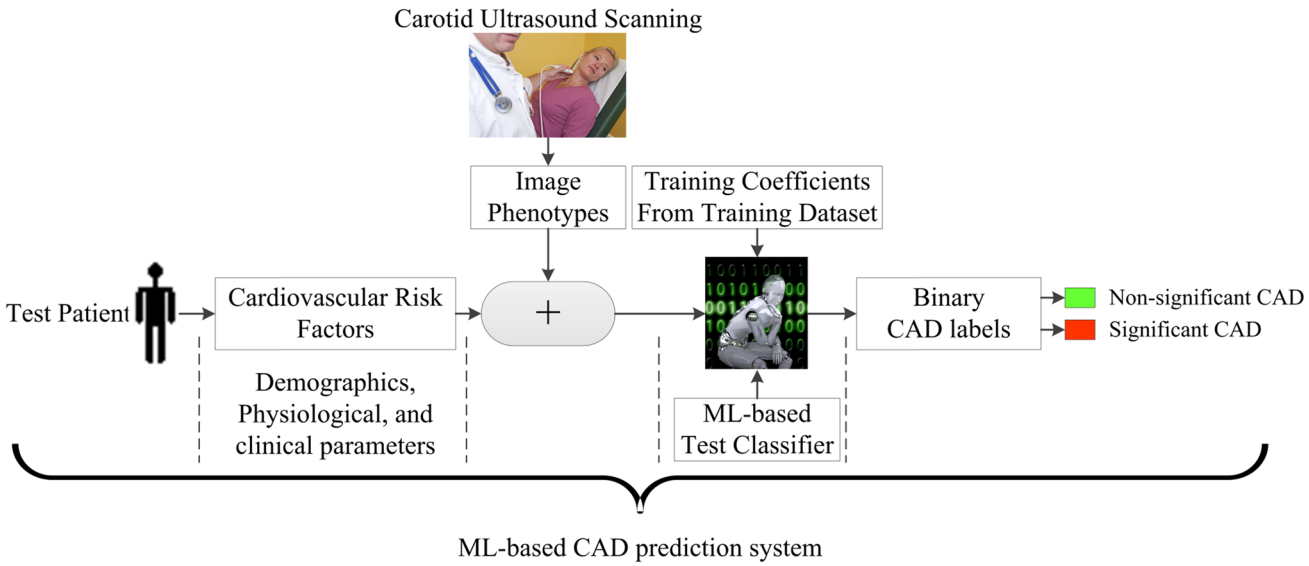

Fig. 1 The global architecture of the ML-based CAD prediction system. CAD, coronary artery disease; ML, machine learning. System courtesy of AtheroPoint™, Roseville, CA, USA

informed consent was obtained from all participants. This study conforms to the ethical guidelines of the 1975 Declaration of Helsinki, as reflected in a priori approval by the Queen's University Health Sciences and affiliated Teaching Hospitals Research Ethics Board, Queens, Ontario, Canada.

Coronary artery evaluation using angiography as a gold standard

In the derivation study, coronary angiograms were recorded using the GE system 2000 (GE Healthcare) [19, 21] and scored by expert researchers blinded to the clinical features of participants. Stenosis in the left main left anterior descending, circumflex, and right coronary arteries were recorded as 0: no or minimal disease (0–19% narrowing), 1: mild disease (20–49% narrowing), 2: moderate disease (50–69% narrowing), and severe disease (≥ 70% narrowing within any segment of the main branches of the coronary artery or ≥ 50% in the left main coronary artery) [19]. Coronary angiography is generally used as a gold standard to determine the CAD [22] This study used coronary angiography scores to determine the significant CAD (≥ 50% stenosis), making a binary endpoint. In another similar approach, coronary angiography was used as the gold standard in an AI framework for the detection of myocardial ischemia. [23].

Focused carotid B mode ultrasound imaging

A focused carotid B-mode ultrasound (cBUS) was performed on all participants using a vascular ultrasound scanner (Vivid E9 Ultrasound System, GE Healthcare) equipped with a 9L-D linear array transducer (2.4–10 MHz) [21]. Ultrasound scanning was performed by an experienced imaging technician within 24 h of coronary angiography. All images were stored in the digital image and communications in medicine (DICOM) format and analyzed offline. Image phenotypes namely, cIMT, MPH, and TPA were measured using EchoPAC software (GE Healthcare). MPH is the maximum distance between the lumen-intima media interfaces when comparing both sides of the neck [19, 21]. MPH was manually quantified in the bulb or internal carotid artery region using caliper function shown by two stars (Fig. 2). Plaque areas were traced manually in the carotid bifurcation and the proximal 1 cm (or 10 mm) of the internal and external carotid arteries of both sides. All the plaque areas on both sides were accumulated to give the TPA. The presence of carotid plaque was defined as the focal structure encroaching into the lumen with plaque height > 1.5 mm or 50% of the surrounding intima-media thickness [3, 24].

Contrast enhance carotid ultrasound imaging

IPN is another indicator of plaque progression and plaque instability that can be measured using contrast-enhanced carotid ultrasound (CEUS) [25]. In this derivation study, IPN was determined as a rapid movement of contrast microbubbles from the adventitial side to the carotid plaque core and graded as 0: no visible microbubbles in carotid plaque, 1: the presence of minimal microbubbles confined towards the adventitial side of the plaque, and 3: the presence of microbubbles throughout the plaque [25]. The average IPN grade of both sides of the neck was computed and a single overall score was provided per patient. Our recent study demonstrated a high predictive value of IPN while detecting significant CAD and future CV events [7].

Follow-up for CV events

Follow-up from all study participants was taken for a period of 30 days or until they experienced one of the following CV events: coronary revascularization (i.e. percutaneous coronary intervention, coronary artery bypass surgery), heart failure, nonfatal myocardial infarction, stroke, or cardiac death. Participants with the acute coronary syndrome

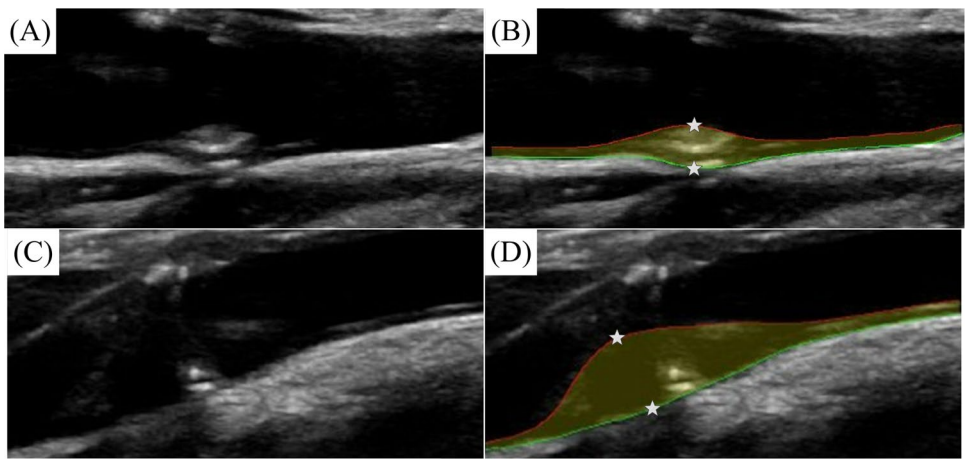

Fig. 2 Sample focused B-mode carotid ultrasound scans showing maximum plaque height (MPH). Example 1-top row (**A** and **B**) with MPH of 2.85 mm and example 2-bottom row (**C** and **D**) with MPH of 5.51 mm

at the time of coronary angiography were excluded from the follow-up analysis to reduce bias. In addition, participants with coronary revascularization within 7 days of the original angiogram were excluded from the analysis to prevent planned revascularization therapy from being assessed.

Machine learning for CAD prediction

The challenge of CAD prediction is translated into the characterization of the CAD. This characterization has been directly linked to AI or data mining in recent years and our group has attempted this in the non-CAD area [26–29]. These AI systems are an extension arm of computer-aided designs [30]. Such a design for a generalized ML-based CAD prediction system is divided into two parts (Fig. 3): (i) an offline model generation [31] and (ii) an online model application [32]. The data-partitioning block follows a leave-one-out cross-validation protocol [33–35] (supplementary material, section S1) separating the input dataset into two sets—(a) training dataset and (b) testing dataset. This study also investigated the performance CAD and CV event prediction system using fivefold and tenfold cross-validation protocols (supplementary material, section S2). The offline model uses 24 risk predictors from the training dataset (i.e. n = 458 samples) along with the binary endpoint (see Section Coronary Artery Evaluation using Angiography as a Gold Standard) to train the ML-based classifier. In this study, we used a random forest (RF) classifier to perform significant CAD prediction [36]. RF is an ensemble of several decision trees and follows a voting-based strategy to make the final prediction. A detailed description of the RF classifier is provided in section S3 of the supplementary material.

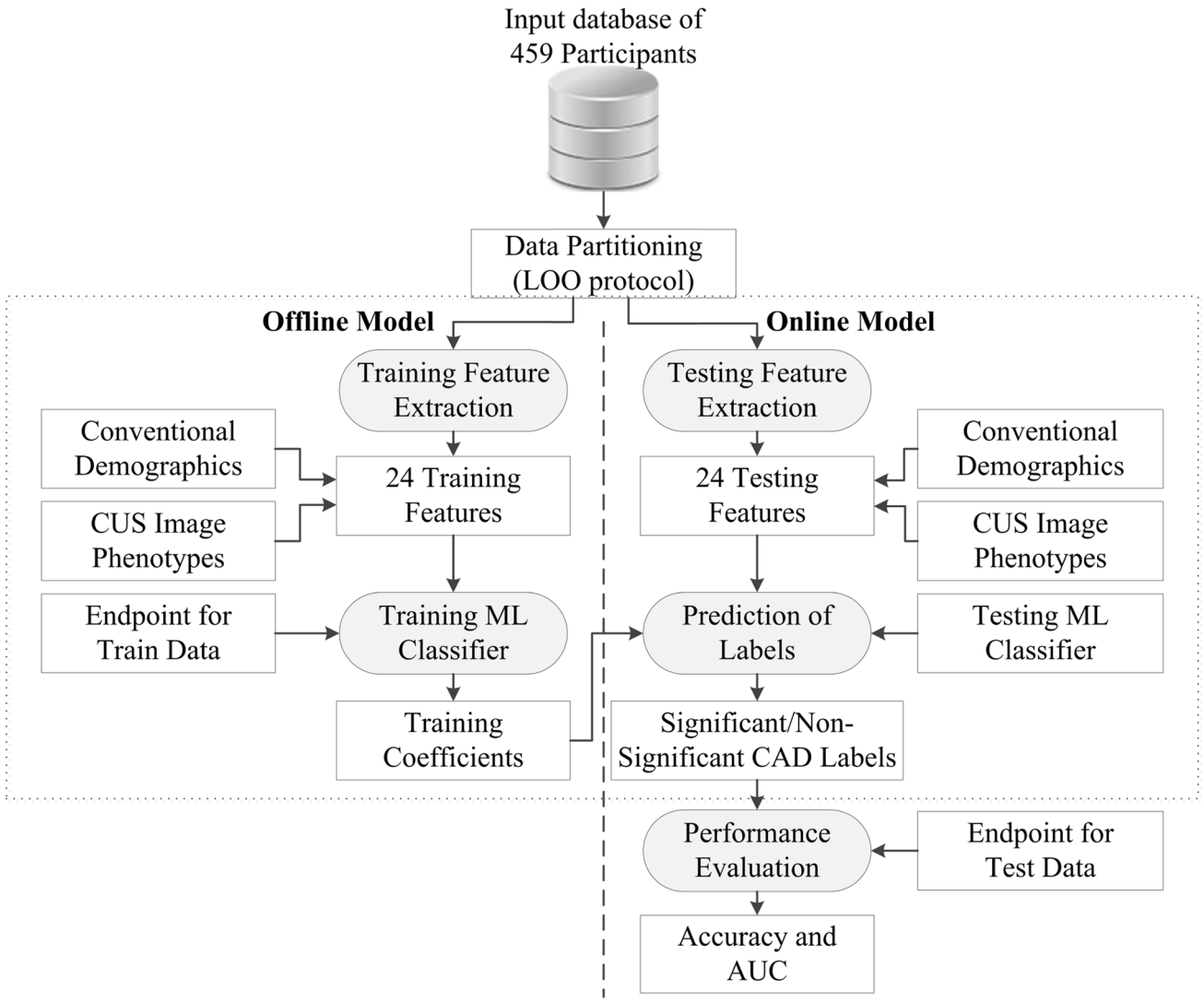

Fig. 3 The architecture of an ML-based (AtheroEdge™ 3.0_{ML}, AtheroPoint™, CA, USA) coronary artery disease prediction system. CUS, carotid ultrasound; LOO, leave-one-out cross-validation protocol

The offline system trains the ML-based model by generating offline training coefficients. These offline training coefficients were then used in the online model to transform 24 "test predictors" derived from the "test dataset" into the predicted labels (significant or non-significant CAD). Note that the testing sample was unknown to the offline ML model and also was not part of the training dataset. The performance of the ML-based system was evaluated using area-under-the-curve (AUC), sensitivity, specificity, and accuracy metrics against the endpoint. The endpoint was only used for the performance evaluation and not part of the "online test system". This is a unique feature of online ML-based systems that automatically predicts CAD labels from the risk predictors, without any requirement of endpoint labels. Finally, we benchmarked the ML-based CAD prediction system against the derivation study taken from Mantella et al. [7] that provided the CAD prediction using univariate analysis with IPN as an independent risk predictor. Furthermore, we also compared the ML-based CAD prediction system with the standard-of-care pooled cohort risk (PCR) equation developed by the American College of Cardiology and American Heart Association that provide atherosclerotic CVD (ASCVD) risk assessment [37]. ASCVD is typically adopted for 10-year risk computation, while LR and AtheroEdge™ 3.0_{ML} were used to compute the 30-day survival analysis. Note that ASCVD lacks performance due to a lack of carotid plaque or coronary information. Unlike ASCVD, the ML system learns from the cohort using gold standard and carotid covariates, providing the trained models, which can then be used for predicting the risk label on the test data sets. A detailed description of the ASCVD risk calculator is provided in section S4 and section S5 of the supplementary material.

Statistical analysis

Statistical Analysis was performed using IBM's SPSS (version 23) software. Independent sample t-test and Chi-square (χ^2) were used to investigate the association between continuous and categorical risk predictors with the endpoint. All the statistical tests were two-tailed with a level of significance of < 0.05. Continuous variables were expressed as mean ± standard deviation and categorical variables as percentages (see Table 1 baseline characteristics). Coronary angiography score-based binary endpoint indicating a status of significant CAD ($\geq 50\%$ stenosis) or non-significant CAD was used to train the ML-based algorithms.

Univariate and multivariate logistic regression was performed and the odds ratios (ORs) with 95% confidence interval (CI) were computed to determine the risk predictors significantly associated with the endpoint. ML-based CAD prediction system was evaluated against endpoint using AUC, sensitivity, specificity, and accuracy. The mathematical expressions for these metrics are provided in section S6 of the supplementary material. An extended version of the RF algorithm called—random survival forest (RSF), was used for survival analysis [38]. CV event prediction for the 30 days follow-up was performed using ML-based survival analysis with the RSF algorithm further compared against the Cox proportional hazard model (CPHM). The performance of the survival analysis was evaluated using the concordance index (c-index). The importance of risk predictors in CV event prediction was determined using RSF. Survival and hazard curves for 30-day follow-up for all patients were plotted using the RSF. Inter- and intra-observer reliability analysis was performed using the intra-class correlation coefficient (ICC) in a subset of 30 participants. The ML-based system for CAD prediction and ML-based survival analysis (called AtheroEdge™ 3.0_{ML}) was developed by AtheroPoint™, Roseville, CA, the USA using Scikit-learn software, [39] which has python-based open-source libraries [40].

Results

Baseline characteristics

The derivation study screened 1211 participants referred for coronary angiography. Participants were excluded in three phases (Fig. 4): (i) in the first phase, 610 participants met the inclusion and exclusion criteria. Thus, the remaining 601 participants were excluded from the study. In the second phase, 110 participants were excluded mainly because of the withdrawn of consent, cancellation of the coronary angiogram, and no IV access. Thus, the scanning was performed only on 500 participants. After image analysis, 41 participants were excluded due to the absence of carotid artery plaque. Overall, 459 participants were selected for this study. There was a significant difference in age (63.71 ± 10.5 *vs.* 65.97 ± 10.0 years, $p = 0.022$), sex (32.5% *vs.* 67.5%, $p < 0.0001$), hyperlipidemia (32.3% *vs.* 67.7%, $p = 0.003$), diabetes mellitus (29.7% *vs.* 70.3%, $p = 0.048$), and smoking history (34.3% *vs.* 65.7%, $p = 0.02$) for participants with non-significant and significant CAD as well as number of participants taking medications such as statins (33.2% *vs.* 66.8%, $p = 0.023$), beta-blockers (30.8% *vs.* 69.2%, $p = 0.002$), and anti-platelet/anti-coagulants (33.6% *vs.* 66.4%, $p = 0.001$). Reasons for referral such as myocardial infarction and positive stress test were also significantly associated with CAD ($p < 0.05$). There was also a significant difference between carotid ultrasound plaque-based characteristics such as cIMT (0.72 ± 0.1 *vs.* 0.78 ± 0.2 mm, $p < 0.0001$), MPH (2.43 ± 1.0 *vs.* 3.11 ± 1.3 mm, $p < 0.0001$), TPA (38.87 ± 37.3 *vs.* 59.74 ± 45.9 mm^2, $p < 0.0001$), and IPN (0.45 ± 0.6 *vs.*

Table 1 Baseline characteristics for the study participants based on significant and non-significant CAD

SN	Parameters	Overall (n = 459)	Non-significant CAD (n = 175)	Significant CAD[#] (n = 284)	p-value
R1	Age, (years)[ǂ]	65.11 ± 10.3	63.71 ± 10.5	65.97 ± 10.0	0.022
R2	Male Sex, n (%)[ǂ]	326 (71.0%)	106 (60.6%)	220 (77.5%)	< 0.0001
R3	BMI (kg/m^2)	30.10 ± 5.9	30.44 ± 6.2	29.89 ± 5.8	0.334
R4	eGFR (ml/min/1.73 m2)	78.34 ± 18.2	80.01 ± 17.6	77.31 ± 18.4	0.122
R5	Hypertension, n (%)	317 (69.1%)	113 (64.6%)	204 (71.8%)	0.126
R6	Hyperlipidemia, n (%)[ǂ]	269 (58.6%)	87 (49.7%)	182 (64.1%)	0.003
R7	Diabetes Mellitus, n (%)[ǂ]	111 (24.2%)	33 (18.9%)	78 (27.5%)	0.048
R8	Smoking Hx, n (%)[ǂ]	309 (67.3%)	106 (60.6%)	203 (71.5%)	0.02
R9	Family Hx of CVD, n (%)	297 (64.7%)	108 (61.7%)	189 (66.5%)	0.341
Medication use					
R10	Statins, n (%)[ǂ]	250 (54.5%)	83 (47.4%)	167 (58.8%)	0.023
R11	ACE Inhibitors, n (%)	179 (39.0%)	66 (37.7%)	113 (39.8%)	0.731
R12	ARBs Angiotensis, n (%)	44 (9.6%)	12 (6.9%)	32 (11.3%)	0.163
R13	Beta-Blockers, n (%)[ǂ]	221 (48.1%)	68 (38.9%)	153 (53.9%)	0.002
R14	Calcium Channel Blockers, n (%)	87 (19.0%)	34 (19.4%)	53 (18.7%)	0.935
R15	Anti-Platelet/Anti-Coagulants, n (%)[ǂ]	339 (73.9%)	114 (65.1%)	225 (79.2%)	0.001
R16	Diuretics, n (%)	92 (20.0%)	38 (21.7%)	54 (19%)	0.561
Referral parameters					
R17	Referral: MI, n (%)[ǂ]	154 (33.6%)	12 (6.9%)	142 (50%)	< 0.0001
R18	Referral: Chest Pain, n (%)	214 (46.6%)	84 (48%)	130 (45.8%)	0.713
R19	Referral: + Stress Test, n (%)[ǂ]	145 (31.6%)	71 (40.6%)	74 (26.1%)	0.002
R20	Referral: Shortness of Breath, n (%)	121 (26.4%)	54 (30.9%)	67 (23.6%)	0.108
Carotid ultrasound plaque characteristics					
R21	cIMT (mm) [ǂ]	0.76 ± 0.2	0.72 ± 0.1	0.78 ± 0.2	< 0.0001
R22	MPH (mm) [ǂ]	2.85 ± 1.2	2.43 ± 1.0	3.11 ± 1.3	< 0.0001
R23	TPA (mm^2) [ǂ]	51.78 ± 44.0	38.87 ± 37.3	59.74 ± 45.9	< 0.0001
R24	IPN Score[ǂ]	1.26 ± 0.8	0.45 ± 0.6	1.76 ± 0.4	< 0.0001

[ǂ]Risk predictor is significant with $p < 0.05$

[#]Significant CAD: stenosis ≥ 50%

CVD cardiovascular disease; *CAD* coronary artery disease; *BMI* body mass index; *eGFR* estimated glomerular filtration rate; *ACE* Angiotensin-converting enzyme; *ARB* Angiotensin Receptor Blockers; *MI* myocardial infarction; *cIMT* carotid intima-media thickness; *MPH* maximum plaque height; and *IPN* intra-plaque neovascularization

1.76 ± 0.4, $p < 0.0001$) for non-significant and significant CAD groups.

Univariate and multivariate analysis

Univariate logistic regression (Table 2) indicated a significant association between CAD and age (OR = 1.02, $p < 0.023$), male sex (OR = 2.24, $p < 0.0001$), hyperlipidemia (OR = 1.81, $p = 0.003$), diabetes mellitus (OR = 1.63, $p = 0.037$), smoking history (OR = 1.63, $p = 0.016$), use of statins (OR = 1.58, $p = 0.018$), beta-blockers (OR = 1.84, $p = 0.002$), and anti-platelet/anti-coagulants (OR = 2.04, $p = 0.001$), and plaque characteristics such as cIMT (OR = 1.90, $p < 0.0001$), MPH (OR = 2.32, $p < 0.0001$), TPA (1.92, $p < 0.0001$), and IPN (OR = 2.41, $p < 0.0001$). Multivariate analysis was performed in two phases by considering significant risk predictors from univariate analysis (i) by excluding the plaque characteristics and (ii) including plaque characteristics one at a time. All carotid ultrasound plaque characteristics reported a significant association with CAD after adjusting with the conventional parameters ($p < 0.05$). However, in univariate and multivariate analysis using the Cox-proportional hazard model (Table S4 in supplementary material), CV events were significantly associated with IPN (hazard ratio = 1.27, $p < 0.0001$) and cIMT (hazard ratio = 1.40, $p < 0.0001$).

ML-based CAD prediction and survival analysis

In the ML-based CAD prediction (Fig. 5), the RF classifier reported improvement in AUC by ~ 3% over the previously published study [7] with univariate logistic regression

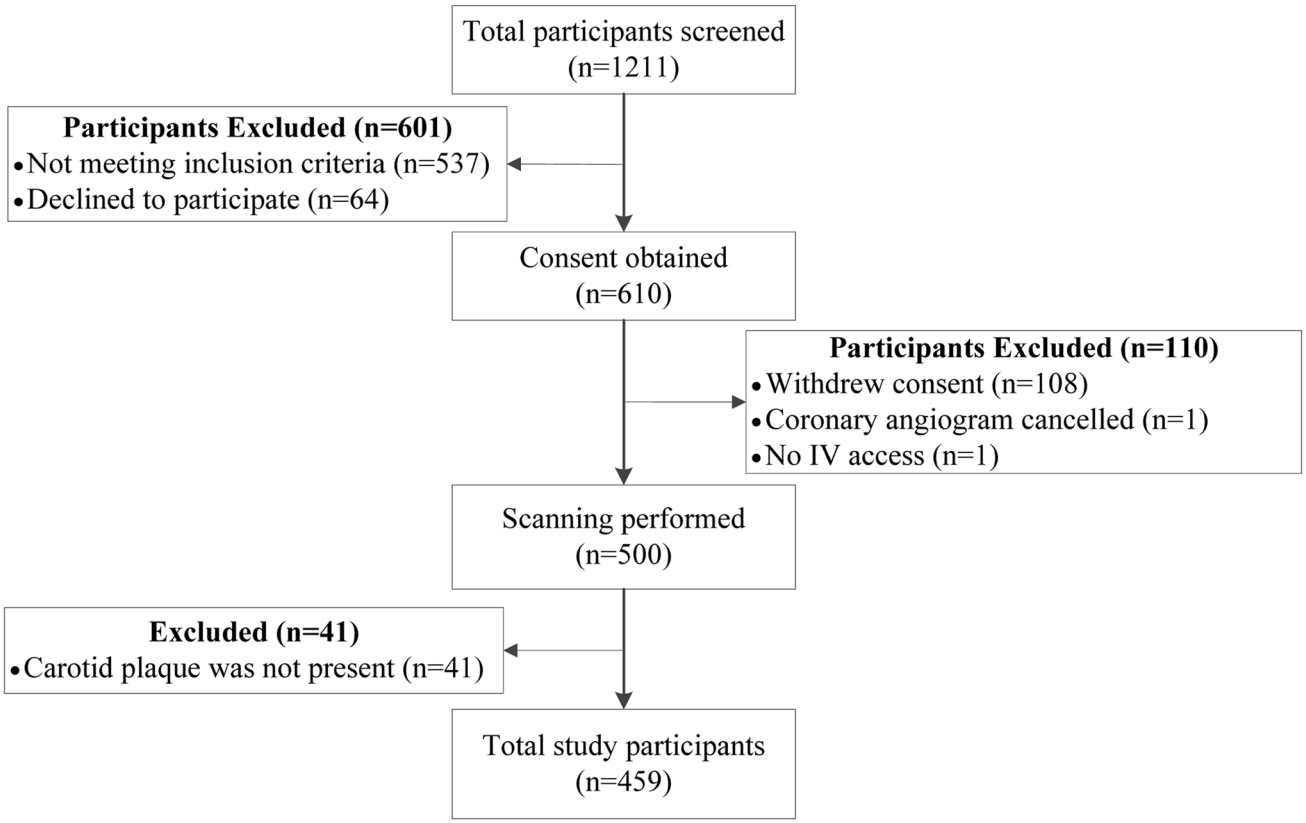

Fig. 4 Flow chart showing participants meeting inclusion and exclusion criteria. IV, intravenous

with IPN as a single independent risk predictor (0.97 *vs.* 0.94, $p = 0.003$). Considering IPN alone, the RF classifier demonstrated highly similar results to the univariate logistic regression with IPN (0.92 *vs.* 0.94, $p < 0.0001$). However, when compared against the current ASCVD calculator, the ML-based algorithm reported significantly superior performance indicated by an improvement in the AUC by ~ 54% (0.97 *vs.* 0.63, $p < 0.0001$). These results suggest that the ML-based algorithm provides a better prediction of CAD and, therefore, the CVD over the conventional statistically-derived algorithms. This trend resembles the previous studies where ML-based strategies showed better performance compared to conventional risk calculators with different gold standard paradigms [15, 16, 41]. Furthermore, the ML-based RSF algorithm used for survival analysis and time-to-event prediction demonstrated an improvement in the C-index by **17.8%** over the conventional Cox proportional hazard model (0.86 *vs.* 0.73). Figure 6 shows the survival and cumulative hazard curves for the study participants. Figure 7 shows the top 20 risk predictors that had the greatest ability to predict CV events. IPN was the highest-ranked metric for CV risk prediction, indicating its importance.

Discussion

This is a unique study that combined the information from conventional clinical risk predictors and carotid ultrasound plaque characteristics to predict significant angiographic CAD and CV events using ML methods compared head-to-head with conventional statistical methods. An improvement of ~ 3% in AUC over the univariate analysis and of ~ 17.8% in C-index over the cox proportional hazard model showed the superiority of ML-based algorithms for predicting CAD and CV events. This study retains the findings of previous studies that carotid ultrasound image-based plaque characteristics are independent and significant predictors of CAD [7, 21, 42] while suggesting analysis by ML methods should be considered. The ML-based survival analysis using RSF indicated IPN as the most important risk predictor in CV events (Fig. 7). IPN measured from CEUS showed good intra-observer reliability with an ICC of 0.88 and good inter-observer reliability with an ICC of 0.87 (section S8 of the supplementary material).

From the baseline characteristics (discussed in Section Baseline characteristics), it is clear that in this selected cohort, elderly patients are having more risk of developing significant CAD. The risk of developing CAD at baseline

Table 2 Univariate and multivariate binomial logistic regression to investigate risk predictors associated with CAD

SN	Variable	Univariate Analysis			Multivariate Analysis		
		OR	95% CI	p-value	OR	95% CI	p-value
1	Age[‡]	1.02	1.00–1.04	0.023	1.03	1.01–1.05	0.005
2	Sex[‡]	2.24	1.48–3.38	< 0.0001	2.11	1.36–3.27	0.001
3	BMI	0.99	0.95–1.02	0.334	–	–	–
4	eGFR	0.99	0.98–1.00	0.123	–	–	–
5	Hypertension	1.40	0.94–2.10	0.103	–	–	–
6	Hyperlipidemia	1.81	1.23–2.65	0.003	1.42	0.90–2.25	0.14
7	Diabetes Mellitus	1.63	1.03–2.58	0.037	1.43	0.86–2.36	0.17
8	Smoking History[‡]	1.63	1.10–2.43	0.016	1.54	1.00–2.35	0.049
9	Family History of CVD	1.23	0.83–1.83	0.293	–	–	–
10	Statins	1.58	1.08–2.31	0.018	0.98	0.62–1.56	0.94
11	ACE Inhibitors	1.09	0.74–1.61	0.658	–	–	–
12	ARBs Angiotensis	1.73	0.86–3.45	0.123	–	–	–
13	Beta-Blockers[‡]	1.84	1.25–2.70	0.002	1.57	1.03–2.38	0.036
14	Calcium Channel Blockers	0.95	0.59–1.54	0.839	–	–	–
15	Anti-Platelet/Anti-Coagulants[‡]	2.04	1.34–3.12	0.001	1.61	1.02–2.54	0.042
16	Diuretics	0.85	0.53–1.35	0.483	–	–	–
17	cIMT (per IQR)[‡]	1.90	1.42–2.55	< 0.0001	1.59	1.16–2.17	0.004
18	MPH (per IQR)[‡]	2.32	1.72–3.14	< 0.0001	1.85	1.34–2.57	< 0.0001
19	TPA (per IQR)[‡]	1.92	1.47–2.51	< 0.0001	1.5	1.12–2.00	0.007
20	IPN Score (per score 0.25)[‡]	2.41	2.08–2.79	< 0.0001	2.43	2.09–2.83	< 0.0001

[‡]Significant predictor in univariate and multivariate analysis

CVD, cardiovascular disease, CAD, coronary artery disease; OR, odds ratio; BMI, body mass index; eGFR, estimated glomerular filtration rate; ACE, Angiotensin-converting enzyme; ARB, Angiotensin Receptor Blockers; cIMT, carotid intima-media thickness; MPH, maximum plaque height; IPN, intraplaque neovascularization; IQR, interquartile range

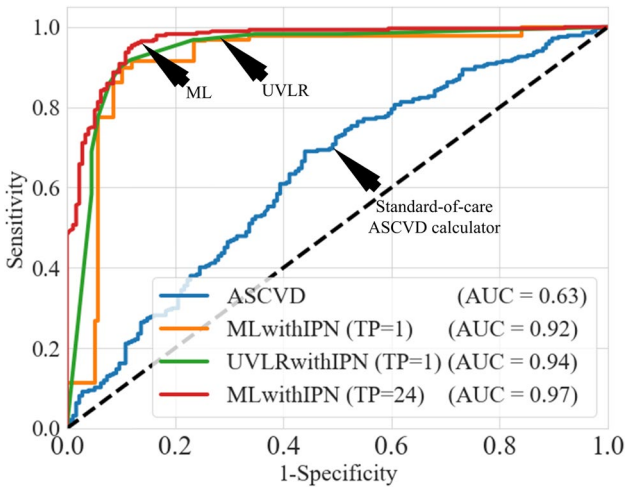

Fig. 5 Comparison between machine learning-based CAD prediction system against the conventional algorithms. TP, total predictors

was also high in participants with having risk predictors such as hyperlipidemia, diabetes mellitus, or smoking history. At baseline (Table 1), patients with significant CAD also reportedly had high image-based phenotypes such as cIMT, MPH, TPA, and IPN. These observations were verified using the univariate and multivariate analysis in Section Univariate and Multivariate Analysis. Higher odds ratios (with p-value < 0.000) for IPN followed by MPH and other carotid ultrasound image-phenotypes showed a significant association between the increase in these image-based phenotypes with the CAD. Thus, high-risk patients with elevated values of risk predictors are more likely to experience cardiovascular events in the near future. This study did not track the participants for the longer follow-up duration, but the 30-days of follow-up had indicated the high chances of cardiovascular events in participants with the increase in IPN and cIMT (Section Univariate and Multivariate Analysis).

Study limitations

In this study, all participants were collected from the cardiac catheterization lab, and, therefore, they were mostly symptomatic, having an inherently higher baseline risk profile. Even though ML was able to automatically classify and predict the CVD risk in the current pool of higher baseline risk profiles using the current set of CVD predictors, this application could more evolve, demonstrating its

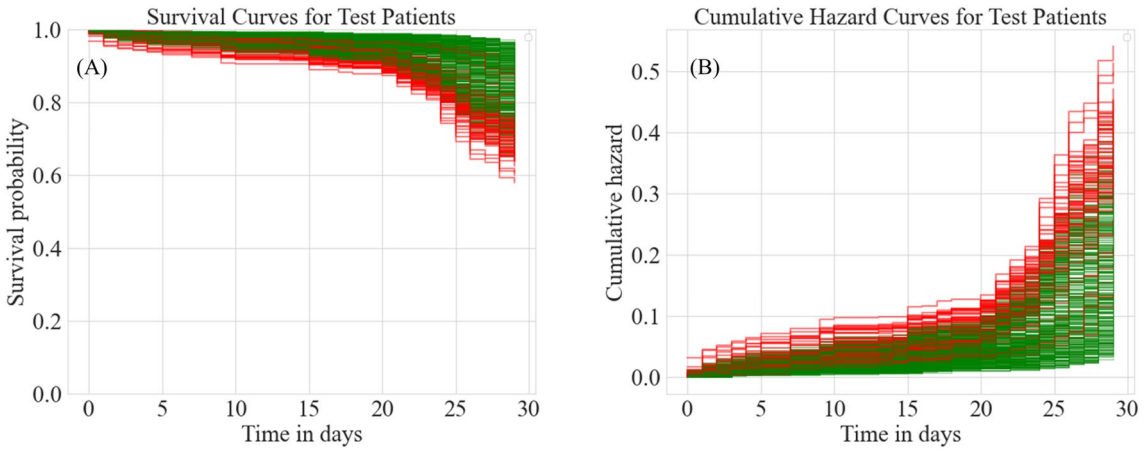

Fig. 6 ML-based Survival analysis plots for study participants. (**A**) Survival curves and (**B**) Cumulative hazard curves for 459 participants. Red colored curves indicate the participants, who experienced events in the 30 days of follow-up period

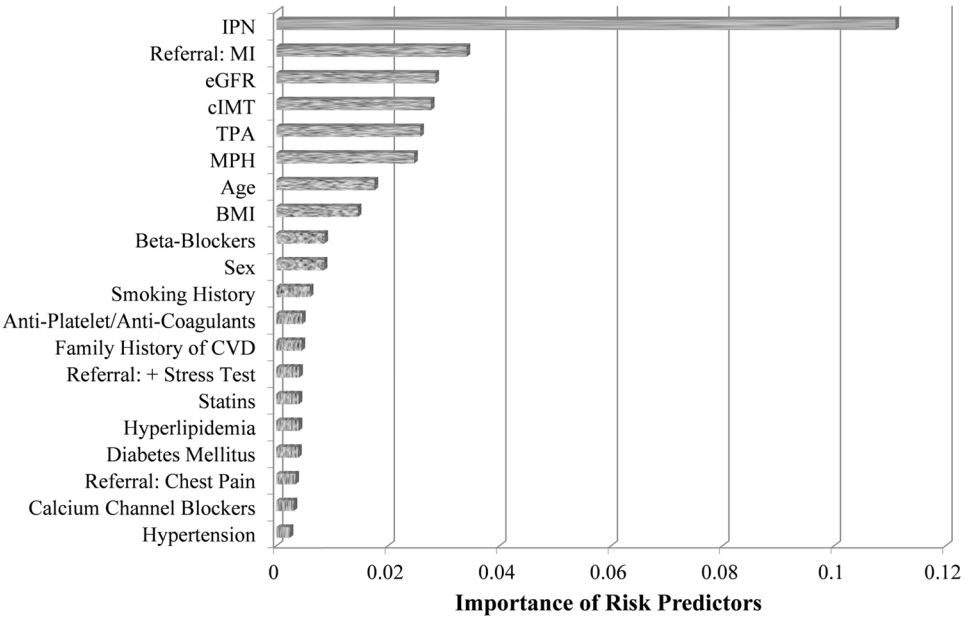

Fig. 7 Machine learning-based importance of risk predictors in the 30-day cardiovascular event prediction. *IPN* intra-plaque neovascularization, *MI* myocardial infarction, *eGFR* estimated glomerular filtration rate, *cIMT* carotid intima-media thickness, *TPA* total plaque area, *MPH* maximum plaque height, *BMI* body mass index, *CVD* cardiovascular disease

power to effectively predict CVD, if the data pool were low to moderately symptomatic participants. In our previous studies, which used the surrogate biomarkers of CAD as the endpoint for designing the ML system, we had reported the superiority of ML-based systems over the other conventional algorithms [13, 15, 16]. Although, the previous studies have successfully attempted the role of ML, [43, 44] we intend to collect participants who were not referred for coronary angiography and fall under low-to-moderate risk category to validate the superiority of the proposed ML-based system. In order to generalize this study results, it is important to collect a large database with cohorts of diverse ethnicities. In this study, since the blood cholesterol values were absent, the CVD risk prediction using the ASCVD calculator was performed using conservative values for total cholesterol and high-density lipoprotein cholesterol (see supplementary material). However, our previous studies with blood cholesterol readings have also demonstrated the superiority of the ML-based system over the conventional cardiovascular risk calculators [13, 15, 16]. Due to lack of access to the image database, variability studies on measurements could not be conducted and readings provided by the cardiologists were taken as a face value. Note that authors have conducted variability analysis, reproducibility analysis in their previous studies successfully [45–49] and intend to use that strategy again on this image data in the future. Another limitation of our study is the short follow-up time of 30 days. We intend to conduct future studies with longitudinal follow-up to predict CAD and CV events using ML algorithms. An additional extension for this study could be the inclusion of

grayscale image-based features into the ML algorithm. Previous studies have demonstrated an improvement in CV risk assessment using the grayscale features [29, 50, 51]. Therefore, the inclusion of grayscale features alongside related plaque characteristics such as pixel distribution analysis or 3D ultrasound features can further provide improvement in CAD and CV event prediction. However, all of these additional features would mean a heavy burden of data handling required, therefore the ML-based framework we have developed herein is the first requirement for developing an intelligent feature analysis system attuned to CV risk prediction using Deep Learning [26, 52, 53].

Conclusion

Machine learning-based algorithms (AtheroEdge™ 3.0_{ML}, AtheroPoint™, Roseville, CA, USA) applied to carotid ultrasound features, such as a combination of image phenotypes and intra-plaque neovascularization, can provide better CAD prediction compared to conventional statistically-derived approaches. ML-based survival analysis is superior to the conventional Cox proportional hazard models for CV event prediction.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10554-021-02294-0.

Declarations

Conflict of interest All authors declare that they have no conflict of interest to disclose.

References

1. Organization WH. *Cardiovascular diseases (CVDs): Key facts by WHO May 2016*. http://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds).
2. Suri JS, Kathuria C, Molinari F (2010) Atherosclerosis disease management. Springer Science & Business Media, New York
3. Saba L, Jamthikar A, Gupta D, Khanna NN, Viskovic K, Suri HS, Gupta A, Mavrogeni S, Turk M, Laird JR, Pareek G, Miner M, Sfikakis P, Protogerou A, Kitas GD, Viswanathan V, Nicolaides A, Bhatt D, Suri JS (2019) Global perspective on carotid intima-media thickness and plaque: should the current measurement guidelines be revisited? Int Angiol 38(6):451–465
4. Amato M, Montorsi P, Ravani A, Oldani E, Galli S, Ravagnani PM, Tremoli E, Baldassarre D (2007) Carotid intima-media thickness by B-mode ultrasound as surrogate of coronary atherosclerosis: correlation with quantitative coronary angiography and coronary intravascular ultrasound findings. Eur Heart J 28(17):2094–2101
5. Bots ML (2006) Carotid intima-media thickness as a surrogate marker for cardiovascular disease in intervention studies. Curr Med Res Opin 22(11):2181–2190
6. Spence JD (2002) Ultrasound measurement of carotid plaque as a surrogate outcome for coronary artery disease. Am J Cardiol 89(4):10–15
7. Mantella LE, Colledanchise KN, Hétu M-F, Feinstein SB, Abunassar J, Johri AM (2019) Carotid intraplaque neovascularization predicts coronary artery disease and cardiovascular events. Eur Heart J Cardiovasc Imaging 20(11):1239–1247
8. Goldstein BA, Navar AM, Carter RE (2016) Moving beyond regression techniques in cardiovascular risk prediction: applying machine learning to address analytic challenges. Eur Heart J 38(23):1805–1814
9. Jamthikar AD, Gupta D, Saba L, Khanna NN, Viskovic K, Mavrogeni S, Laird JR, Sattar N, Johri AM, Pareek G, Miner M, Sfikakis PP, Protogerou A, Viswanathan V, Sharma A, Kitas GD, Nicolaides A, Kolluri R, Suri JS (2020) Artificial intelligence framework for predictive cardiovascular and stroke risk assessment models: A narrative review of integrated approaches using carotid ultrasound. Comput Biol Med. https://doi.org/10.1016/j.compbiomed.2020.104043
10. Alaa AM, Bolton T, Di Angelantonio E, Rudd JH, van Der Schaar M (2019) Cardiovascular disease risk prediction using automated machine learning: A prospective study of 423,604 UK Biobank participants. PloS one. https://doi.org/10.1371/journal.pone.0213653
11. Weng SF, Reps J, Kai J, Garibaldi JM, Qureshi N (2017) Can machine-learning improve cardiovascular risk prediction using routine clinical data? PloS one. https://doi.org/10.1371/journal.pone.0174944
12. Biswas M, Kuppili V, Saba L, Edla DR, Suri HS, Cuadrado-Godia E, Laird JR, Marinhoe RT, Sanches JM, Nicolaides A (2019) State-of-the-art review on deep learning in medical imaging. Front Biosci (Landmark edition) 24:392–426
13. Jamthikar A, Gupta D, Khanna NN, Saba L, Araki T, Viskovic K, Suri HS, Gupta A, Mavrogeni S, Turk M, Laird JR, Pareek G, Miner M, Sfikakis PP, Protogerou A, Kitas GD, Viswanathan V, Nicolaides A, Bhatt DL, Suri JS (2019) A low-cost machine learning-based cardiovascular/stroke risk assessment system: integration of conventional factors with image phenotypes. Cardiovasc Diagn Ther 9(5):420–430
14. Kakadiaris IA, Vrigkas M, Yen AA, Kuznetsova T, Budoff M, Naghavi M (2018) Machine Learning Outperforms ACC/AHA CVD Risk Calculator in MESA. J Am Heart Assoc. https://doi.org/10.1161/JAHA.118.009476
15. Jamthikar A, Gupta D, Saba L, Khanna NN, Araki T, Viskovic K, Mavrogeni S, Laird JR, Pareek G, Miner M, Sfikakis PP, Protogerou A, Viswanathan V, Sharma A, Nicolaides A, Kitas GD, Suri JS (2020) Cardiovascular/stroke risk predictive calculators: a comparison between statistical and machine learning models. Cardiovasc Diagn Ther 10(4):919–938
16. Jamthikar A, Gupta D, Khanna NN, Saba L, Laird JR, Suri JS (2020) Cardiovascular/stroke risk prevention: A new machine learning framework integrating carotid ultrasound image-based phenotypes and its harmonics with conventional risk factors. Indian Heart J. https://doi.org/10.1016/j.ihj.2020.06.004
17. Wallert J, Tomasoni M, Madison G, Held C (2017) Predicting two-year survival versus non-survival after first myocardial infarction using machine learning and Swedish national register data. BMC Med Inform Decis Mak 17(1):99
18. Miao F, Cai Y-P, Zhang Y-X, Fan X-M, Li Y (2018) Predictive modeling of hospital mortality for patients with heart failure by using an improved random survival forest. IEEE Access 6:7244–7253
19. Johri AM, Chitty DW, Matangi M, Malik P, Mousavi P, Day A, Gravett M, Simpson C (2013) Can carotid bulb plaque assessment rule out significant coronary artery disease? A comparison

of plaque quantification by two-and three-dimensional ultrasound. J Am Soc Echocardiogr 26(1):86–95
20. Jamthikar A, Gupta D, Mantella LE, Saba L, Laird JR, Johri AM, Suri JS (2020) Multiclass machine learning vs. conventional calculators for Stroke/CVD Risk assessment using carotid plaque predictors with coronary angiography scores as gold standard: A 500 participants study. Int J Cardiovasc Imaging. https://doi.org/10.1007/s10554-020-02099-7
21. Johri AM, Calnan CM, Matangi MF, MacHaalany J, Hétu M-F (2016) Focused vascular ultrasound for the assessment of atherosclerosis: a proof-of-concept study. J Am Soc Echocardiogr 29(9):842–849
22. Members TF, Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, Bugiardini R, Crea F, Cuisset T (2013) 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J 34(38):2949–3003
23. Braun T, Spiliopoulos S, Veltman C, Hergesell V, Passow A, Tenderich G, Borggrefe M, Koerner MM (2020) Detection of myocardial ischemia due to clinically asymptomatic coronary artery stenosis at rest using supervised artificial intelligence-enabled vectorcardiography–A five-fold cross validation of accuracy. J Electrocardiol 59:100–105
24. Touboul P-J, Hennerici M, Meairs S, Adams H, Amarenco P, Bornstein N, Csiba L, Desvarieux M, Ebrahim S, Hernandez RH (2012) Mannheim carotid intima-media thickness and plaque consensus (2004–2006–2011). Cerebrovasc Dis 34(4):290–296
25. Deyama J, Nakamura T, Takishima I, Fujioka D, Kawabata K-I, Obata J-E, Watanabe K, Watanabe Y, Saito Y, Mishina H (2013) Contrast-enhanced ultrasound imaging of carotid plaque neovascularization is useful for identifying high-risk patients with coronary artery disease. Circ J 77(6):1499–1507
26. Acharya UR, Mookiah MRK, Sree SV, Afonso D, Sanches J, Shafique S, Nicolaides A, Pedro LM, Fernandes JF, Suri JS (2013) Atherosclerotic plaque tissue characterization in 2D ultrasound longitudinal carotid scans for automated classification: a paradigm for stroke risk assessment. Med Biol Eng Comput 51(5):513–523
27. Acharya UR, Sree SV, Ribeiro R, Krishnamurthi G, Marinho RT, Sanches J, Suri JS (2012) Data mining framework for fatty liver disease classification in ultrasound: a hybrid feature extraction paradigm. Med Phys 39(7Part1):4255–4264
28. Martis RJ, Acharya UR, Prasad H, Chua CK, Lim CM, Suri JS (2013) Application of higher order statistics for atrial arrhythmia classification. Biomed Signal Process Control 8(6):888–900
29. Acharya UR, Sree SV, Krishnan MMR, Krishnananda N, Ranjan S, Umesh P, Suri JS (2013) Automated classification of patients with coronary artery disease using grayscale features from left ventricle echocardiographic images. Comput Methods Programs Biomed 112(3):624–632
30. El-Baz A, Suri JS (2011) Lung imaging and computer aided diagnosis. CRC Press, Boca Raton
31. Acharya UR, Faust O, Sree SV, Molinari F, Saba L, Nicolaides A, Suri JS (2012) An accurate and generalized approach to plaque characterization in 346 carotid ultrasound scans. IEEE Trans Instrum Meas 61(4):1045–1053
32. Saba L, Dey N, Ashour AS, Samanta S, Nath SS, Chakraborty S, Sanches J, Kumar D, Marinho R, Suri JS (2016) Automated stratification of liver disease in ultrasound: An online accurate feature classification paradigm. Comput Methods Programs Biomed 130:118–134
33. Wong T-T (2015) Performance evaluation of classification algorithms by k-fold and leave-one-out cross validation. Pattern Recogn 48(9):2839–2846
34. Duval S, Van't Hof JR, Steffen LM, Luepker RV (2020) Estimation of cardiovascular risk from self-reported knowledge of risk factors: insights from the Minnesota heart survey. Clin Epidemiol 12:41–49
35. Sammut C, Webb GI (2010) Leave-One-Out Cross-Validation. In: Sammut C, Webb GI (eds) Encyclopedia of Machine Learning. Springer US, Boston, MA, pp 600–601
36. Ho TK. Random decision forests. In: Document analysis and recognition, 1995., proceedings of the third international conference on. 1995: Abstract 1, p. 278–282. IEEE.
37. Goff DC, Lloyd-Jones DM, Bennett G, Coady S, Dagostino RB, Gibbons R, Greenland P, Lackland DT, Levy D, Odonnell CJ (2014) 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Ame Coll Cardiol 63(25):2935–2959
38. Ishwaran H, Kogalur UB, Blackstone EH, Lauer MS (2008) Random survival forests. Ann Appl Stat 2(3):841–860
39. Pedregosa F, Varoquaux G, Gramfort A, Michel V, Thirion B, Grisel O, Blondel M, Prettenhofer P, Weiss R, Dubourg V (2011) Scikit-learn: Machine learning in Python. J Mach Learn Res 12:2825–2830
40. Sebastian P (2020) Scikit-survival: A library for time-to-event analysis built on top of scikit-learn. J Mach Learn Res 21(212):1–6
41. Jamthikar AD, Gupta D, Johri AM, Mantella LE, Saba L, Kolluri R, Sharma AM, Viswanathan V, Nicolaides A, Suri JS (2020) Low-cost office-based cardiovascular risk stratification using machine learning and focused carotid ultrasound in an Asian-Indian cohort. J Med Syst 44(12):208
42. Johri AM, Behl P, Hétu MF, Haqqi M, Ewart P, Day AG, Parfrey B, Matangi MF (2016) Carotid ultrasound maximum plaque height–a sensitive imaging biomarker for the assessment of significant coronary artery disease. Echocardiography 33(2):281–289
43. Krittanawong C, Virk HUH, Bangalore S, Wang Z, Johnson KW, Pinotti R, Zhang H, Kaplin S, Narasimhan B, Kitai T (2020) Machine learning prediction in cardiovascular diseases: a meta-analysis. Sci Rep 10(1):1–11
44. Velusamy D, Ramasamy K (2021) Ensemble of heterogeneous classifiers for diagnosis and prediction of coronary artery disease with reduced feature subset. Comput Methods Programs Biomed. https://doi.org/10.1016/j.cmpb.2020.105770
45. Ikeda N, Araki T, Sugi K, Nakamura M, Deidda M, Molinari F, Meiburger KM, Acharya UR, Saba L, Bassareo PP, Di Martino M, Nagashima Y, Mercuro G, Nakano M, Nicolaides A, Suri JS (2014) Ankle-brachial index and its link to automated carotid ultrasound measurement of intima-media thickness variability in 500 Japanese coronary artery disease patients. Curr Atheroscler Rep 16(3):393
46. Ikeda N, Dey N, Sharma A, Gupta A, Bose S, Acharjee S, Shafique S, Cuadrado-Godia E, Araki T, Saba L, Laird JR, Nicolaides A, Suri JS (2017) Automated segmental-IMT measurement in thin/thick plaque with bulb presence in carotid ultrasound from multiple scanners: Stroke risk assessment. Comput Methods Programs Biomed 141:73–81
47. Saba L, Than JCM, Noor NM, Rijal OM, Kassim RM, Yunus A, Ng CR, Suri JS (2016) Inter-observer variability analysis of automatic lung delineation in normal and disease patients. Journal of Medical Systems. https://doi.org/10.1007/s10916-016-0504-7
48. Molinari F, Meiburger KM, Zeng G, Saba L, Rajendra Acharya U, Famiglietti L, Georgiou N, Nicolaides A, Sriswan Mamidi R, Kuper H, Suri JS (2012) Automated carotid IMT measurement and its validation in low contrast ultrasound database of 885 patient Indian population epidemiological study: results of AtheroEdge™ Software. Int Angiol 31(1):42–53
49. Saba L, Banchhor SK, Araki T, Suri HS, Londhe ND, Laird JR, Viskovic K, Suri JS (2018) Intra-and inter-operator reproducibility

analysis of automated cloud-based carotid intima media thickness ultrasound measurement. J Clin Diagn Res 12(2):KC01-KC11
50. Acharya UR, Sree SV, Molinari F, Saba L, Nicolaides A, Suri JS (2015) An automated technique for carotid far wall classification using grayscale features and wall thickness variability. J Clin Ultrasound 43(5):302–311
51. Banchhor SK, Londhe ND, Araki T, Saba L, Radeva P, Khanna NN, Suri JS (2018) Calcium detection, its quantification, and grayscale morphology-based risk stratification using machine learning in multimodality big data coronary and carotid scans: A review. Comput Biol Med 101:184–198
52. Saba L, Biswas M, Kuppili V, Godia EC, Suri HS, Edla DR, Omerzu T, Laird JR, Khanna NN, Mavrogeni S (2019) The present and future of deep learning in radiology. Eur J Radiol. https://doi.org/10.1016/j.ejrad.2019.02.038
53. Molinari F, Mantovani A, Deandrea M, Limone P, Garberoglio R, Suri JS (2010) Characterization of single thyroid nodules by contrast-enhanced 3-D ultrasound. Ultrasound Med Biol 36(10):1616–1625

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.