**Predicting Stroke in Asian Patients with Atrial Fibrillation Using Machine Learning: A report from the KERALA-AF Registry, with external validation in the APHRS-AF Registry**

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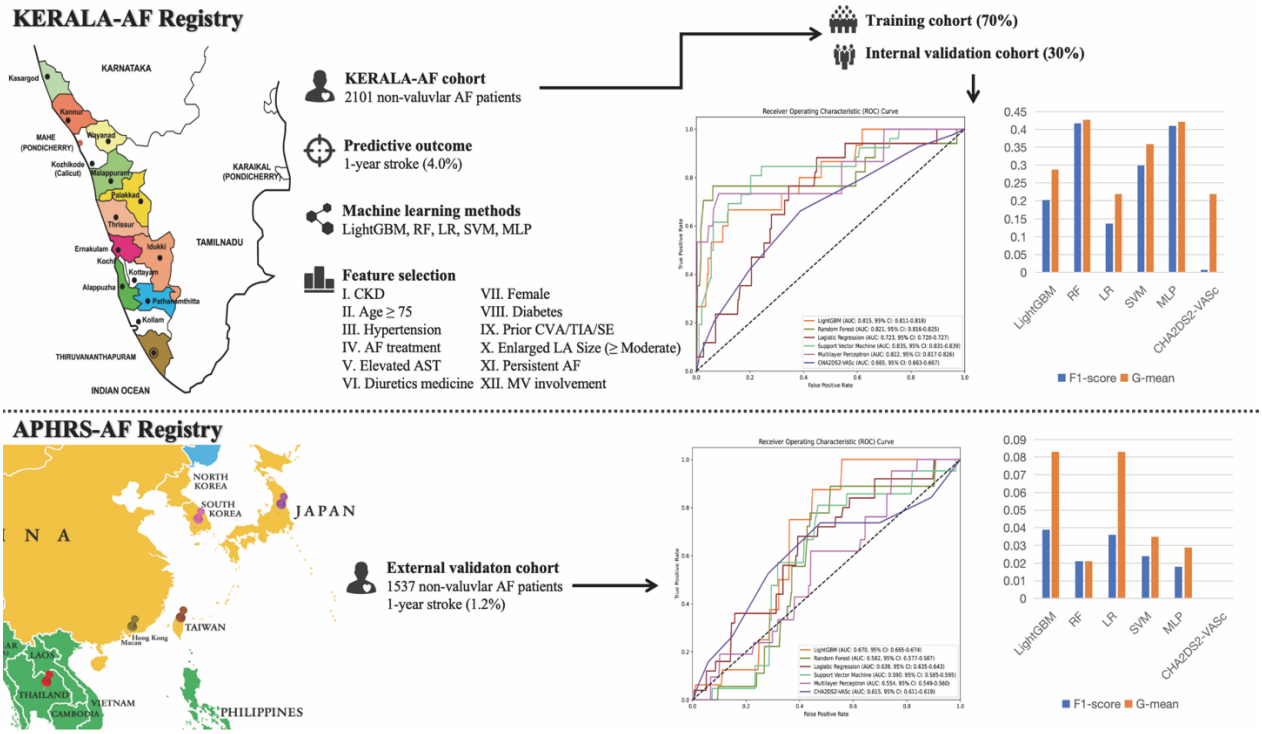
**Ariticle Word Count:** 3599

## Graphical Abstract



## Short Abstract

Atrial fibrillation (AF) is a significant risk factor for stroke. Based on the higher stroke associated with AF in the South Asian population, we constructed a one-year stroke prediction model using machine learning (ML) methods in KERALA-AF South Asian cohort. External validation was performed in the prospective APHRS-AF registry. We studied 2101 patients and 83 were to patients with stroke in KERALA-AF registry. The random forest showed the best predictive performance in the internal validation with receiver operator characteristic curve (AUC) and G-mean of 0.821 and 0.427, respectively. In the external validation, the light gradient boosting machine showed the best predictive performance with AUC and G-mean of 0.670 and 0.083, respectively. We report the first demonstration of ML's applicability in an Indian prospective cohort, although the more modest prediction on external validation in a separate multinational Asian registry suggests the need for ethnic-specific ML models.

**Keywords:** atrial fibrillation, stroke, machine learning, Kerala, South Asia

## Introduction

Atrial fibrillation (AF) is the commonest cardiac arrhythmia and is associated with an increased risk of stroke and mortality. [1] A recent cross-national comparative study has shown that the age- and sex-standardised AF prevalence varies considerably by region, with South Asia having the lowest rate of approximately 30-60 cases per 100,000 people. [2] Despite South Asia's relatively low prevalence of AF, as a region with rapid population growth, the burden of AF will increase. [3]

Recent studies have demonstrated ethnic and regional disparities in the occurrence of stroke associated with AF. In a multinational cohort study, the one-year stroke incidence was approximately 4.3% in Asian AF (including India, China, and South-East Asian countries), which was higher than that (2.5%) in White AF (North America, Western Europe, and Australia). [4] In a multi-ethnic study, the risk of stroke as estimated using the $CHA_2DS_2$-VASc score was 1.67 times higher in South Asians than in Whites. [5] However, in a non-anticoagulated Asian AF cohort of over 180,000 people, the $CHA_2DS_2$-VASc score was not highly discriminatory for ischaemic stroke, with the area under curve (AUC) of 0.698. [6] Additionally, the $CHA_2DS_2$-VASc score does not include many other risk factors for stroke, such as chronic kidney disease (CKD) [7], type of AF [8], and electrocardiographic features [9], nor does it distinguish between the relative importance of individual risk factors (for example, both hypertension and diabetes score +1, but may represent different levels of risk in reality). Also, stroke risk varies in different ethnicities, and many prior studies have focused on white Caucasian and east Asian cohorts, with limited data on stroke risk prediction in south Asian cohorts.

Thus, there is a need for better risk prediction models beyond the $CHA_2DS_2$-VASc score, particularly in South Asian AF. Generally, predictive models are developed using traditional logistic regression, which is based on the assumption of the linear relationship between variable and outcome, but the model may be unstable with increasing quantities of variables. However, machine learning (ML) enables the construction of predictive models by controlling variables' covariance through regularisation and thus inputting more factors, which is increasingly used in clinical studies for outcome prediction. [10] Current studies applying ML to predict stroke in the Asian AF cohort are limited, with only Korea and Japan, whose ML models with more input factors have been shown to perform better than the $CHA_2DS_2$-VASc score. [11, 12] As far as we are aware, no ML study predicting stroke associated with AF in South Asia has been previously reported.

In this ancillary analysis from a prospective Indian cohort of patients with AF, we aimed to build a novel model for predicting stroke associated with AF in a South Asian cohort and validate it in an external Asian cohort based on ML, effectively incorporating various risk factors for more accurate stroke risk stratification.

## Methods

### Study participants

The KERALA-AF registry is an ongoing prospective, multicentre cohort study of AF patients in the Kerala region of India, and is the largest prospective AF study in South Asia. The proposal and results of this study with one-year follow-up have been previously reported. [13, 14] During 2016-2017, 3401 AF patients were recruited from 53 independent centres. As an external validation cohort, we used the APHRS-AF registry which was also a prospective multinational multicentre cohort study of AF patients, with a total of 4,664 AF patients recruited from 52 independent centres in five Asian countries (but not India) from the end of 2015 to the beginning of 2017, and with one-year follow-up. [15]

### Inclusion and exclusion criteria

In our KERALA-AF analysis, we included non-valvular AF patients and excluded those who were lost to follow-up prior to one-year. The APHRS-AF registry for external validation included 1531 NVAF patients according to the same inclusion and exclusion criteria. (Figure 1).

### Data collection and outcome

Demographic characteristics, lifestyle, disease history, comorbidities, pharmacological and surgical treatment, imaging features and laboratory parameters were collected at baseline. The primary outcome of interest was stroke at one-year follow-up.

**Definitions**

Using categorical variables makes the interpretation of the model clearer and more intuitive, making it easier to share and explain how the model works to the applicants. We converted the continuous variables into categorical variables to include them as alternative variables in the model construction (their names and definitions are given in Supplementary Table S1).

**Feature selection and model construction**

The overall dataset was randomly split into a training and validation cohort on a 7:3 ratio. Based on the limited positive events in our analysis, incorporating too many variables in the predictive model may increase the risk of overfitting and cause the machine learning to over-memorise noise in the training cohort, making generalisation difficult. When explaining the model to non-technical applicants, fewer variables can make interpretation clearer and simpler. Also, reducing variables can decrease the computational and storage costs of the model, making it more practical and efficient. However, too few variables may lead to loss of information. Therefore, we selected 12 variables in order to strike a balance between information sufficiency and model simplicity, leading to the construction of more accurate, robust and explanatory predictive models. We filtered the 12 most critical features in the training cohort using the Chi-square test, which is most

applicable to categorical variables. To avoid variable collinearity and multicollinearity, we performed Pearson correlation analysis and calculated the variance inflation factor.

We applied these features to five ML classifiers commonly used in medical binary problems to predict one-year stroke associated with AF, including light gradient boosting machine (LightGBM), random forest (RF), ML logistic regression, support vector machine, and multilayer perceptron. The ratio of positive to negative events in our dataset was approximately 1:26, so this is an unbalanced dataset, and we allocated sample weights to each category when constructing our model. Then, we used grid search and five-fold cross-validation on the training cohort to optimise and obtain the best hyperparameters for each ML classifier.

**Evaluation of parameters**

We plotted the receiver operating characteristic curve (ROC), obtained the mean area under the receiver operator characteristic curve (AUC) and 95% confidence interval (CI) of each classifier using 1000 bootstrapping iterations to assess their performances in the internal and external validation cohorts. When performing external validation, given the heterogeneity of the external cohort, we would attempt to retrain the model in 20% of the external cohort using the Fine-tuning technique to better adapt it to the external validation. Given that our data were unbalanced, we calculated the accuracy, specificity, sensitivity, precision, recall, F1-score and G-mean for each classifier, respectively, to assess the differences in their performance, and compared these with the $CHA_2DS_2$-VASc score.

**Online tool for the prediction model**

We developed a web-based tool utilising the predictive model with a simple user-friendly interface that allows clinicians to quickly and intuitively determine one-year risk of stroke in NVAF patients by collecting and inputting the appropriate features into the model to assist in making treatment decisions.

**Statistical analysis**

We used STATA (version 17) to clean the original dataset. Variables with more than 50% missing values (Supplementary Table S2) were discarded because the values populated for these variables may not be sufficiently accurate or reliable, even when techniques such as multiple imputation are used. For other variables with missing values, we applied multiple imputation using the package 'miceforest' in Python (version 3.11.4). The variables were described using SPSS (version 27). For continuous variables, mean with standard deviations or median with interquartile range (IQR) were used based on the distribution, and t-tests or Mann-Whitney U tests were used to compare differences between stroke and non-stroke groups. For categorical variables, counts with percentages were used, and Fisher's exact test and Chi-square test were used to compare differences between groups. All statistical significance levels were set at two-tailed $P < 0.05$. Feature selection and model construction were implemented in Python (version 3.11.4), with the packages Scikit-learn (version 1.2.2) and lightgbm (version 3.3.5). Furthermore, in the best model, each sample produced a corresponding prediction value, and each feature in that sample was assigned a specific value, SHapley Additive exPlanation value, [16] to explain the importance of the

feature to the model, and we used the Python's package for SHapley Additive exPlanation (version 3.11.4).

## Results

### Patient Characteristics

From the KERALA-AF registry, 2,101 NVAF patients with completed follow-up were included in the analysis. The median age was 68.0 years (IQR: 60.0 to 76.0), and 979 (46.2%) were female, AF treatment was predominantly rate control (83.3%), and common comorbidities were hypertension (61.3%), diabetes (37.2%), dyslipidaemia (46.8%) and chronic kidney disease (CKD) (50.3%). 83 (4.0%) were in the stroke group (Table 1). Compared to the non-stroke group, the stroke group were older (median: 75.0 vs 68.0), more frequently female (61.4% vs 45.8%), and had higher rates of hypertension (79.5% vs. 60.5%) and CKD (69.9% vs. 49.7%), as well as higher $CHA_2DS_2$-VASc scores (median: 4.0 vs 3.0).

### Feature Selection

The overall dataset was randomly split into a training and validation cohort on a 7:3 ratio. Based on the limited positive events in our analysis, incorporating too many variables in the predictive model may increase the risk of overfitting and cause the machine learning to over-memorise noise in the training cohort, making generalisation difficult. When explaining the model to non-technical applicants, fewer variables can make interpretation clearer and simpler. Also, reducing variables can decrease the computational and storage costs of the model, making it more practical and efficient. However, too few variables may lead to loss of information. Therefore, we selected 12

variables in order to strike a balance between information sufficiency and model simplicity, leading to the construction of more accurate, robust and explanatory predictive models.

**Collinearity Test**

To avoid serious collinearity among the variables within the model, we conducted a Pearson correlation analysis and plotted the heatmap. As shown in Figure 2A, the coefficients between all variables were less than 0.4, which implied no strong correlation.

The variance inflation factor was calculated to perform the multicollinearity test. As displayed in Figure 2B, the values of all variables were less than 2.5, suggesting weak multicollinearity. Therefore, these variables could avoid the negative impact of variable collinearity to be effectively used for the predictive model.

**Model Construction**

Based on the 12 selected features, we built a predictive model for one-year stroke. Using commonly applied classifiers for medical binary problems, including LightGBM, RF, ML logistic regression, support vector machine, and multilayer perceptron, the best hyperparameters of each classifier were obtained after five-fold cross-validation in the training cohort (Supplementary Table S3).

**Model Evaluation**

In the internal validation cohort (Figure 3A), support vector machine obtained the highest AUC (0.835, 95% CI 0.831-0.839) and ML logistic regression obtained the lowest AUC (0.723, 95% CI 0.720-0.727) among the five classifiers, but all classifiers had AUCs higher than the $CHA_2DS_2$-VASc (0.665, 95% CI 0.663-0.667). Further calculating the other metrics for the classifiers (Table 2), RF had the highest F1-score (0.417) and G-mean (0.427), thus RF had the best classification ability in that unbalanced data. So, RF was considered as the best classifier in internal validation.

According to the previous result of feature selection, the characteristics of the external validation cohort are presented in Supplementary Table S4. Since aspartate transaminase (AST) values were not collected from participants in the APHRS-AF registry, we used liver disease as a replacement. After using Fine-tuning, only LightGBM's performance was improved. Thus, we presented the ROCs and AUCs of LightGBM post Fine-tuning and the other classifiers without Fine-tuning (Figure 3B), with LightGBM obtaining the highest AUC (0.670, 95% CI 0.665-0.674) and multilayer perceptron obtaining the lowest AUC (0.554, 95% CI 0.549-0.560) among the five classifiers. Only LightGBM and ML logistic regression had AUCs higher than the $CHA_2DS_2$-VASc (0.615, 95% CI 0.611-0.619). For the other metrics for the classifiers (Table 2), LightGBM had the highest F1-score (0.039) and G-mean (0.083). Therefore, LightGBM was considered as the best classifier in external validation.

**Feature Importance**

To further identify the most influential features in the RF and LightGBM, we calculated and visualised the SHapley Additive exPlanation for each feature. According to Figure 4, the top-to-bottom position on the Y-axis indicates the order of importance of all variables. The top five risk features of RF were CKD, age ≥ 75, hypertension, diuretic use, and abnormal AST. The top five risk features of LightGBM were CKD, age ≥ 75, prior cerebrovascular accident/transient ischaemic attack/systemic embolism, enlarged LA size (≥ moderate), and AF treatment.

**Online Prediction Tools**

Based on the RF and LightGBM model, web-based tools were constructed with a simple and user-friendly interface containing options corresponding to the 12 features in the model. Using RF's as an example, specific features can be input to obtain an intuitive score. the probability of output was used to assess outcome risk, so we set the optimal threshold of 0.438, with higher than 0.438 preferring one-year stroke and lower than 0.438 preferring no stroke. Figure 5 demonstrates the utility of the online tool; in this case: female sex, age ≥ 75 years, hypertension, diabetes, CKD, abnormal AST, atrial fibrillation rate control, and diuretic use gave the patient a predictive function score of 0.74, so the predicted outcome was stroke.

## Discussion

In our study, we developed a reasonably accurate ML model for personalised estimation of one-year stroke associated with non-valvular AF, using readily obtained variables from a South Asian cohort. Our model is the first stroke prediction model constructed in a South Asian (Indian) AF cohort that incorporates potential risk factors not included in the $CHA_2DS_2$-VASc score with better predictive performance. The more modest prediction on external validation in a separate multinational Asian registry suggests the need for ethnic-specific ML models.

The incidence of one-year stroke associated with AF in our study was approximately 4.0%. One multinational cohort study of 47 countries showed that the occurrence of stroke associated with AF in Southeast Asia was around 7% at 1 year, which was higher than our result. [4] This may be related to the AF cohort in Southeast Asia being older (median age 72), with more hypertension (64%), more previous stroke/transient ischaemic attack (22%), and less oral anticoagulation therapy use (50%); however, the proportions of anticoagulant use and baseline characteristics of the North American, Western European, and Australian regional cohorts were similar to our cohort, and our one-year stroke rate in KERALA-AF was still approximately twice as high as theirs (2%). Additionally, a large systematic analysis of AF epidemiology in Asia reported that the annual stroke risk was approximately 3.0% in AF patients, which was broadly similar to our results. [17] Thus, the stroke rates in our study are consistent with existing evidence, and support the notion that South Asian people might have a higher stroke incidence than that seen in other regions.

How do our models compare with other prediction tools for stroke in single-centre Asian AF cohorts? Jung *et al.* constructed a prediction model using variables of demographic information, history of disease, and health screening to predict five-year stroke in a Korean AF cohort of more than 750,000 participants. [11] Their best model was the deep neural network (AUC: 0.722, 95% CI: 0.718-0.726, F1-score: 0.223), which was lower than our RF and LightGBM, probably because they did not incorporate some of the known potential risk factors for stroke. Alternatively, as their model included larger numbers for significantly longer follow-up than in our study, it is possible that model accuracy over this timeframe deteriorates. For example, patient characteristics vary over time, and some may develop new co-morbidities such as hypertension or diabetes during follow-up, which may not be detected if only baseline characteristics are applied. Similarly, the longer follow-up continues for, the more competing mortality risks apply. The KERALA-AF registry is continuing follow-up and we hope to assess how our model performs in longer-term follow-up in the future.

The performance of our models in the external validation APHRS cohort was less satisfactory. Nishi *et al.* constructed a model for predicting stroke during the follow-up using the CatBoost algorithm in the Japanese non-anticoagulant AF cohort. [12] The model obtained an AUC of 0.82 but F1-score of only 0.26 for the internal cohort (where our models performed better), and AUC and F1-score of 0.72 and 0.18 for the external cohort (where our models performed worse). The better performance of our models in the internal validation cohort might result from methodological differences. For example, whilst Nishi *et al.* recognised that their cohorts were imbalanced with respect to outcome measures (7.9% stroke vs 92.1% non-stroke in the training cohort), they did not apply any methodology to manage this; however, it should be noted that the

AUC and F1 scores for our best model in the external validation were only 0.67 and 0.08, probably because the one-year stroke to non-stroke ratio in the APHRS-AF cohort was approximately 1:100, the more extremely imbalanced data may lead to worse performance. Also, although the APHRS-AF contained Asian AF patients (but not including India), there remains non-negligible heterogeneity with the South Asian AF cohort in KERALA-AF, ie. Asians are not homogeneous. Nonetheless, although the performance of our models in external validation is currently less satisfactory, we remain confident that ML can potentially be used as a precision prediction tool for stroke in South Asian AF population, with the caveat that_ethnic-specific ML models may be needed for different ethnic groups.

There was no serious overfitting occurs in our model during the training process and the performance of models may improve a little as the amount of data are further increased. Although the accuracy of the models appears to be very high, the scarcity of positive samples may result in the difficulty predicting positive events. Our model overcomes this limitation by applying "class weights", allowing higher weighting of the smaller number of positive events, thereby improving performance. This is one of the most valuable techniques for coping with modelling in unbalanced data.

SHapley Additive exPlanation explains the relative importance of each variable in the ML model. The variables in our best model were partially similar to the $CHA_2DS_2$-VASc score (age, female, prior transient ischaemic attack / systemic embolism, hypertension, diabetes). We also added widely accepted stroke risk factors, e.g., CKD, enlarged left atrium (≥ moderate), persistent AF, and mitral valve involvement. [8, 18, 19, 20] We also included several potential additional stroke risk

factors, AF treatment strategy, abnormal AST and diuretic use. These may be relevant, as Weng *et al*. reported a lower incidence of IS (adjusted HR: 0.65, $P = 0.002$) in AF patients with rhythm control than with rate control. [21] Also, Choi *et al.* demonstrated that higher AST was significantly associated with the IS occurrence (adjusted HR: 1.04, 95% CI: 1.03-1.05, $P < 0.001$). [22] Green's group showed that lower serum potassium triggered by diuretic use was significantly associated with increased stroke risk (relative risk: 2.5, 95% CI: 1.7-3.5, $P < 0.0001$). [23] Alternatively, the use of diuretics may be reflective of heart failure, which is a well-described stroke risk factor. Despite these data supporting our results, whether they increase the stroke risk per se remains controversial. Overall, the predictions computed by our ML model are based on stroke-related variables, with significantly better overall performance than the $CHA_2DS_2$-VASc score.

*Limitations*

Several important limitations of this study must be emphasised. First, despite the performance of our models in the external validation was less satisfactory, most still outperformed the clinical factor based $CHA_2DS_2$-VASc score. Second, due to the imbalance of the dataset, although the several ML algorithms show good discrimination in this respect, it still needs to be treated with caution and further validation in larger cohorts is required. Third, the number of variables in the initial collection exceeded 100, and two stroke experts preselected the variables for inclusion in the feature screening before incorporation, which could not wholly exclude personal bias. Fourth, because of the small positive sample in our study, we included only the 12 best variables to prevent model overfitting, but we may have missed some potentially essential variables. Fifth, about 16% of patients were lost follow-up and excluding these patients may cause bias; however, this is a common exclusion criterion in real world observational cohorts. Sixth, the KERALA-AF cohort

had a large proportion of missing data, however, to minimise the potential bias that this could cause, we used the multiple interpolation technique to strive to ensure that our analysis results were more robust and reliable. Seventh, AST was missing in the APHRS-AF, although the use of liver disease as a surrogate was an attempt to work within the constraints of the data available; however, we must acknowledge that this substitution may have affected the accurate assessment of model performance. Inclusion of accurate AST in future studies would help to improve the performance of our model. Eighth, a common and inherent limitation is the inability to incorporate all variables that may be relevant to incidence of stroke, such as proteinuria or albuminuria, tumour status, and time in therapeutic range for anticoagulation therapy. Finally, patients were enrolled due to previously diagnosed AF, however the duration of AF was not known and hence our model performance may underestimate stroke risk in those with longer-standing disease, or overestimate risk in those with new onset AF.

## Conclusion

In this first demonstration of ML's applicability in a South Asian cohort, we propose novel models based on the largest AF cohort in India using ML to predict one-year stroke associated with AF, thereby enhancing monitoring and preventing stroke at an early stage. The poorer prediction on external validation in a separate multinational Asian (but non-Indian) registry suggests the need for ethnic-specific ML models. The results of internal and external validation showed that our ML models had better performance than the $CHA_2DS_2$-VASc score.

## Author Contributions

All Kerala-AF Registry and APHRS-AF Registry investigators contributed to resources. Y.C., Y.G. and G.Y.H.L. contributed to conceptualization, and methodology. Y.C. and P.C. contributed to data curation. Y.C. contributed to software, formal analysis, visualization, and original draft writing. Y.G. and G.Y.H.L. contributed to project administration and supervision. Y.G., P.C., D.G., G.M., J.L.A., N.N., T.B., J.A., H.F.T., T.F.C., G.Y.H.L., and B.C.G contributed to review & editing. All authors contributed to critical revision of the manuscript and final approval.

## Ethical Compliance

The data in this analysis were anonymised and did not require ethical approval.


## Acknowledgments

The authors thank all the participants and researchers in the KERALA-AF Registry and APHRS-AF Registry.

## FUNDING

No funding was received towards this work.


## Data Availability Statement

In accordance with KERALA-AF and APHRS-AF policy, the data underlying this article cannot be shared publicly.

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Figure 1. Flow chart for study. AF, atrial fibrillation; APHRS-AF, Asia-Pacific Heart Rhythm Society Atrial Fibrillation.

Figure 2. Variables covariance (A) and multicollinearity (B) tests in our model. AF, atrial fibrillation; AST, aspartate Transaminase; CKD, chronic kidney disease; CVA, cerebrovascular accident; LA, left atrium; MV, mitral valve; SE, systemic embolism; TIA, transient ischaemic attack.

Figure 3. The AUC of 5 machine learning classifiers and $CHA_2DS_2$-VASc in the interal validation cohort (A) and external validation cohort (B). AUC, area under curve; CI, confidence interval; LightGBM, light gradient boosting machine.

Figure 4. SHAP value and importance of each feature in our RF (A) and LightGBM (B) models. AF, atrial fibrillation; AST, aspartate Transaminase; CKD, chronic kidney disease; CVA, cerebrovascular accident; LA, left atrium; LightGBM, light gradient boosting machine; MV, mitral valve; RF, random forest; SE, systemic embolism; SHAP, SHapley Additive exPlanation; TIA, transient ischaemic attack.

Figure 5. The user interface of the online tool for our RF model. AF, atrial fibrillation; AST, aspartate Transaminase; CKD, chronic kidney disease; CVA, cerebrovascular accident; LA, left atrium; MV, mitral valve; RF, random forest; SE, systemic embolism; TIA, transient ischaemic attack.

Table 1. Characteristics between stroke and non-stroke patients in the NVAF cohort.

| Characteristic | All | Non-stroke | Stroke | *P*-value |
|---|---|---|---|---|
| N | 2101 | 2018 | 83 | |
| Age, years | 68.0 (60.0, 76.0) | 68.0 (60.0, 76.0) | 75.0 (65.0, 80.0) | < 0.001 |
| Female, n (%) | 976 (46.5%) | 925 (45.8%) | 51 (61.4%) | 0.005 |
| BMI, kg/m2 | 24.5 (22.0, 26.8) | 24.5 (22.0, 26.8) | 24.4 (22.0, 26.9) | 0.931 |
| Heart Rate, beats/min | 90.0 (72.0, 115.0) | 90.0 (72.0, 115.0) | 100.0 (74.0, 120.0) | 0.278 |
| Systolic Blood Pressure, mmHg | 130.0 (120.0, 150.0) | 130.0 (120.0, 150.0) | 140.0 (120.0, 160.0) | 0.010 |
| Diastolic Blood Pressure, mmHg | 80.0 (70.0, 90.0) | 80.0 (70.0, 90.0) | 80.0 (70.0, 90.0) | 0.019 |
| CHA2DS2-VASc Score, n (%) | | | | < 0.001 |
| 0 | 98 (4.7%) | 96 (4.6%) | 2 (2.4%) | |
| 1 | 253 (12.0%) | 249 (12.3%) | 4 (4.8%) | |
| 2 | 441 (21.0%) | 430 (21.3%) | 11 (13.3%) | |
| 3 | 470 (22.4%) | 459 (22.7%) | 11 (13.3%) | |
| 4 | 400 (19.0%) | 380 (18.8%) | 20 (24.1%) | |
| 5 | 288 (13.7%) | 270 (13.4%) | 18 (21.7%) | |
| 6 | 122 (5.8%) | 110 (5.5%) | 12 (14.5%) | |
| 7 | 26 (1.2%) | 21 (1.0%) | 5 (6.0%) | |
| 8 | 3 (0.1%) | 3 (0.1%) | 0 (0%) | |
| Lifestyle, n (%) | | | | |
| Smoking Status | | | | 0.050 |
| Never | 1570 (74.7%) | 1504 (74.5%) | 66 (79.5%) | |
| Past | 461 (21.9%) | 444.0 (22.0%) | 17 (20.5%) | |
| Current | 70 (3.3%) | 70 (3.5%) | 0 (0%) | |
| Alcohol Consumption | | | | 0.030 |
| Never | 1646 (78.3%) | 1572 (77.9%) | 73 (89.0%) | |
| Past | 120 (5.7%) | 118 (5.8%) | 2 (2.4%) | |
| Current | 335 (15.9%) | 328 (16.3%) | 7 (8.4%) | |
| Disease History, n (%) | | | | |
| History of Rheumatic Fever | 136 (6.5%) | 132 (6.5%) | 4 (4.8%) | 0.532 |
| History of Valvular Disease | 345 (16.4%) | 326 (16.2%) | 19 (22.9%) | 0.104 |
| History of Congenital Heart Disease | | | | 0.829 |
| None | 2054 (97.8%) | 1973 (97.8%) | 81 (97.6%) | |
| Acyanotic | 43 (2.0%) | 41 (2.0%) | 2 (2.4%) | |
| Cyanotic | 4 (0.2%) | 4 (0.2%) | 0 (0%) | |
| Prior CVA/TIA/SE Event | 300 (14.3%) | 282 (14.0%) | 18 (21.7%) | 0.049 |

| Characteristic | All | Non-stroke | Stroke | *P*-value |
|---|---|---|---|---|
| Prior Bleeding Event | 131 (6.2%) | 125 (6.2%) | 6 (7.2%) | 0.702 |
| Coronary Disease | 214 (10.2%) | 205 (10.2%) | 9 (10.8%) | 0.840 |
| Aortic Involvement | 51 (2.4%) | 49 (2.4%) | 2 (2.4%) | 1.000 |
| Mitral Involvement | 212 (10.1%) | 198 (9.8%) | 14 (16.9%) | 0.036 |
| Comobidities, n (%) | | | | |
| Hypertension | 1287 (61.3%) | 1221 (60.5%) | 66 (79.5%) | < 0.001 |
| Diabetes | 782 (37.2%) | 745 (36.9%) | 37 (44.6%) | 0.157 |
| Dyslipidaemia | 983 (46.8%) | 943 (46.7%) | 40 (48.2%) | 0.793 |
| Thyroid Disease | 239 (11.4%) | 227 (11.2%) | 12 (14.5%) | 0.367 |
| Chronic Kidney Disease | 1060 (50.5%) | 1002 (49.7%) | 58 (69.9%) | < 0.001 |
| Respiratory Disease | 450 (21.4%) | 431 (21.4%) | 19 (22.9%) | 0.739 |
| Chronic Liver Disease | 40 (1.9%) | 37 (1.8%) | 3 (3.6%) | 0.208 |
| HF | | | | 0.241 |
| None | 1560 (74.3%) | 1504 (74.5%) | 56 (67.5%) | |
| HFrEF (< 50%) | 339 (16.1%) | 324 (16.1%) | 15 (18.1%) | |
| HFpEF (≥ 50%) | 202 (9.6%) | 190 (9.4%) | 12 (14.5%) | |
| NYHA Class | | | | 0.423 |
| Class I & II | 1739 (82.8%) | 1673 (82.9%) | 66 (79.5%) | |
| Class III & IV | 362 (17.2%) | 345 (17.1%) | 17 (20.5%) | |
| Cardiomyopathy | 240 (11.4%) | 228 (11.3%) | 12 (14.5%) | 0.375 |
| History of therapeutic operation, n (%) | | | | |
| CABG | 108 (5.1%) | 107 (5.3%) | 1 (1.2%) | 0.125 |
| Valve Replacement | | | | 0.564 |
| None | 2028 (96.5%) | 1946 (96.4%) | 82 (98.8%) | |
| Aortic | 4 (0.2%) | 4 (0.2%) | 0 (0%) | |
| Mitral | 63 (3.0%) | 62 (3.1%) | 1 (1.2%) | |
| Combined | 6 (0.3%) | 6 (0.3%) | 0 (0%) | |
| CHD Repair | 7 (0.3%) | 6 (0.3%) | 1 (1.2%) | 0.246 |
| Catheter Ablation | 10 (0.5%) | 10 (0.5%) | 0 (0%) | 1.000 |
| Pacemaker Implant | 120 (5.7%) | 115 (5.7%) | 5 (6.0%) | 0.810 |
| Surgery for AF | 3 (0.1%) | 3 (0.1%) | 0 (0%) | 1.000 |
| ICD Implant | 10 (0.5%) | 10 (0.5%) | 0 (0%) | 1.000 |
| LAAO | 6 (0.3%) | 5 (0.2%) | 1 (1.2%) | 0.215 |
| Bridged UFH | 257 (12.2%) | 250 (12.4%) | 7 (8.4%) | 0.281 |
| Bridged LMWH | 242 (11.5%) | 229 (11.3%) | 13 (15.7%) | 0.228 |
| Bridged Fondaparinux | 29 (1.4%) | 28 (1.4%) | 1 (1.2%) | 1.000 |
| Medicine, n (%) | | | | |

| Characteristic | All | Non-stroke | Stroke | *P*-value |
|---|---|---|---|---|
| ACEI Medicine | 194 (9.2%) | 189 (9.4%) | 5 (6.0%) | 0.303 |
| ARB Medicine | 352 (16.8%) | 339 (16.8%) | 13 (15.7%) | 0.786 |
| DHP CCB Medicine | 270 (12.9%) | 256 (12.7%) | 14 (16.9%) | 0.265 |
| Diuretics Medicine | 840 (40.0%) | 797 (39.5%) | 43 (51.8%) | 0.025 |
| Statin Medicine | 1189 (56.6%) | 1141 (56.5%) | 48 (57.8%) | 0.816 |
| Class I AAD | 36 (1.7%) | 33 (1.6%) | 3 (3.6%) | 0.168 |
| Class III AAD | 452 (21.5%) | 432 (21.4%) | 20 (24.1%) | 0.559 |
| VKA Medicine | 1228 (58.4%) | 1181 (58.5%) | 47 (56.6%) | 0.731 |
| NOAC Medicine | 174 (8.3%) | 168 (8.3%) | 6 (7.2%) | 0.723 |
| Non Anticoagulant Medicine | 703 (33.5%) | 673 (33.3%) | 30 (36.1%) | 0.597 |
| Antiplatelet Medicine | 1009 (48.0%) | 968 (48.0%) | 41 (49.4%) | 0.798 |
| AF-related variables, n (%) | | | | |
| AF Treatment Strategy | | | | 0.080 |
| Rhythm | 350 (16.7%) | 342 (16.9%) | 8 (9.6%) | |
| Rate | 1751 (83.3%) | 1676 (83.1%) | 75 (90.4%) | |
| Persistent AF | 379 (18%) | 356 (17.6%) | 23 (27.7%) | 0.019 |
| AF Symptom | | | | |
| Palpitations | 990 (47.1%) | 953 (47.2%) | 37 (44.6%) | 0.636 |
| Breathlessness | 980 (46.6%) | 935 (46.3%) | 45 (54.2%) | 0.158 |
| Chest Pain | 453 (21.6%) | 431 (21.4%) | 22 (26.5%) | 0.264 |
| Syncope Presyncope | 178 (8.5%) | 171 (8.5%) | 7 (8.4%) | 0.990 |
| Fatigue | 331 (15.8%) | 313 (15.5%) | 18 (21.7%) | 0.130 |
| Imaging Feature, n (%) | | | | |
| ECG | | | | |
| Rhythm Enrollment | | | | 0.748 |
| Normal Sinus Rhythm | 304 (14.5%) | 294 (14.6%) | 10 (12.0%) | |
| AF | 1738 (82.7%) | 1668 (82.7%) | 70 (84.3%) | |
| Paced Rhythm | 59 (2.8%) | 56 (2.8%) | 3 (3.6%) | |
| Ischaemic Change | 290 (13.8%) | 275 (13.6%) | 15 (18.1%) | 0.250 |
| LBBB | 116 (5.5%) | 113 (5.6%) | 3 (3.6%) | 0.623 |
| RBBB | 101 (4.8%) | 100 (5.0%) | 1 (1.2%) | 0.183 |
| LVH | 352 (16.8%) | 332 (16.5%) | 20 (24.1%) | 0.068 |
| ST Change | 574 (27.3%) | 547 (27.1%) | 27 (32.5%) | 0.277 |
| Echocardiography | | | | |
| LVEF, % | 58.0 (50.0, 64.0) | 58.0 (50.0, 64.0) | 59.0 (50.0, 63.0) | 0.610 |
| LA Size, mm | 40.0 (36.0, 45.0) | 40.0 (36.0, 45.0) | 42.0 (38.0, 46.0) | 0.016 |
| LVH | 608 (28.9%) | 584 (28.9%) | 24 (28.9%) | 0.996 |

| Characteristic | All | Non-stroke | Stroke | *P*-value |
|---|---|---|---|---|
| RWMA | 374 (17.8%) | 362 (17.9%) | 12 (14.5%) | 0.417 |
| MS | 204 (9.7%) | 194 (9.6%) | 10 (12.0%) | 0.463 |
| AS | 97 (4.6%) | 91 (4.5%) | 6 (7.2%) | 0.276 |
| MR (≥ Moderate) | 632 (30.1%) | 606 (30.0%) | 26 (31.3%) | 0.801 |
| AR (≥ Moderate) | 171 (8.1%) | 163 (8.1%) | 8 (9.6%) | 0.610 |
| PAH (≥ Moderate) | 471 (22.4%) | 453 (22.4%) | 18 (21.7%) | 0.871 |
| Rheumatic Involvement | 225 (10.7%) | 215 (10.7%) | 10 (12.0%) | 0.687 |
| Labotary | | | | |
| Hemoglobin, g/dL | 12.5 (11.2, 13.6) | 12.5 (11.2, 13.6) | 12.3 (10.8, 13.1) | 0.098 |
| Total Cholesterol, mg/dL | 163.0 (134.0, 193.0) | 163.0 (134.0, 193.3) | 164.0 (136.0, 192.0) | 0.976 |
| LDL-C, mg/dL | 97.0 (72.0, 124.0) | 97.0 (71.0, 124.0) | 105.0 (75.0, 124.0) | 0.405 |
| HDL-C, mg/dL | 43.0 (37.0, 51.5) | 43.0 (37.0, 51.0) | 45.0 (36.0, 53.0) | 0.813 |
| AST, U/L | 31.0 (24.0, 42.0) | 31.0 (24.0, 42.0) | 32.0 (24.0, 61.0) | 0.107 |
| ALT, U/L | 121.0 (68.0, 121.0) | 121.0 (68.0, 121.0) | 121.0 (59.0, 121.0) | 0.837 |
| FBS, mg/dL | 110.0 (96.0, 138.0) | 110.0 (96.0, 136.0) | 113.0 (99.0, 165.0) | 0.108 |
| INR, sec | 1.4 (1.1, 2.0) | 1.4 (1.1, 2.0) | 1.4 (1.1, 2.0) | 0.793 |
| Serum Creatinie, mg/dL | 1.0 (0.9, 1.3) | 1.0 (0.9, 1.3) | 1.1 (0.9, 1.3) | 0.255 |
| Total Bilirubin, mg/dL | 0.9 (0.7, 1.2) | 0.9 (0.7, 1.2) | 0.9 (0.7, 1.0) | 0.700 |
| eGFR, ml/min | 56.8 (41.7, 73.4) | 57.3 (41.9, 73.8) | 48.3 (34.3, 59.3) | < 0.001 |

Legend: AAD, antiarrhythmic drug; ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ALT, alanine transaminase; AR, aortic regurgitation; ARB, angiotensin receptor blocker; AS, aortic stenosis; AST, aspartate transaminase; BMI, body mass index; CABG, coronary artery bypass graft; CHD, congenital heart disease; CVA, cerebrovascular accident; DHP CCB, dihydropyridine calcium channel blocker; ECG, electrocardiography; ECHO, echocardiogram; FBS, fasting blood sugar; eGFR, estimated glomerular filtration rate; HDL-C, high density lipoprotein cholesterol; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; ICD, implantable cardioverter defibrillator; INR, international normalized ratio; LA, left atrium; LAAO, left atrial appendage occlusion; LBBB, left bundle branch block; LDL-C, low density lipoprotein cholesterol; LMWH, low molecular weight heparin; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; MR, mitral regurgitation; MS, mitral stenosis; NOAC, non-vitamin K antagonist oral anticoagulant; NVAF, non-valvular atrial fibrillation; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; RBBB, right bundle branch block; RWMA, regional wall motion abnormality; UFH, unfractionated heparin; SE, systemic embolism; TIA, transient ischaemic attack; VKA, vitamin K antagonist.

Table 2. The Performance of classifiers and $CHA_2D_2$-VASc in the internal and external validation cohort.

| Classifiers | AUC (95% CI) | Accuracy | Specificity | Sensitivity | Precision | Recall | F1-score | G-mean |
|---|---|---|---|---|---|---|---|---|
| Internal Validation Cohort | | | | | | | | |
| LightGBM | 0.815 (0.811, 0.818) | 0.824 | 0.824 | 0.833 | 0.118 | 0.708 | 0.202 | 0.288 |
| Random Forest | 0.821 (0.816, 0.825) | 0.945 | 0.950 | 0.824 | 0.340 | 0.560 | 0.417 | 0.427 |
| Logistic Regression | 0.723 (0.720, 0.727) | 0.741 | 0.744 | 0.684 | 0.077 | 0.682 | 0.137 | 0.219 |
| Support Vector Machine | 0.835 (0.831, 0.839) | 0.912 | 0.919 | 0.692 | 0.196 | 0.672 | 0.299 | 0.359 |
| Multilayer Perceptron | 0.822 (0.817, 0.826) | 0.943 | 0.992 | 0.276 | 0.494 | 0.370 | 0.410 | 0.421 |
| $CHA_2DS_2$-VASc | 0.665 (0.663, 0.667) | 0.957 | 1.000 | 0.000 | 0.008 | 0.048 | 0.007 | 0.219 |
| External Validation Cohort | | | | | | | | |
| LightGBM | 0.670 (0.665, 0.674) | 0.812 | 0.816 | 0.417 | 0.021 | 0.339 | 0.039 | 0.083 |
| Random Forest | 0.582 (0.577, 0.587) | 0.974 | 0.987 | 0.000 | 0.020 | 0.024 | 0.021 | 0.021 |
| Logistic Regression | 0.639 (0.635, 0.643) | 0.679 | 0.681 | 0.529 | 0.019 | 0.381 | 0.036 | 0.083 |
| Support Vector Machine | 0.590 (0.585, 0.595) | 0.918 | 0.928 | 0.190 | 0.014 | 0.091 | 0.024 | 0.035 |
| Multilayer | 0.554 (0.549 | 0.952 | 0.964 | 0.048 | 0.012 | 0.041 | 0.018 | 0.029 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Perceptron | , 0.560) | | | | | | | |
| $CHA_2DS_2$-VASc | 0.615 (0.611, 0.619) | 0.986 | 1.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |

Legend: AUC, area under curve; CI, confidence interval; LightGBM, light gradient boosting machine.

## Highlights

### What is already known:

1. Atrial fibrillation is a known risk factor for stroke, especially ischaemic stroke. Atrial fibrillation causes irregular and rapid contractions of the atria, which can cause blood to stagnate in the atria, increasing the risk of blood clots forming. These clots can dislodge and travel with the blood to the brain, causing stroke. The risk of stroke is about five times higher in atrial fibrillation patients than in those without atrial fibrillation.
2. Strokes associated with atrial fibrillation are generally more severe than those not associated with atrial fibrillation and are more likely to result in more extensive brain tissue damage, higher risk of recurrent stroke post-stroke, poorer functional outcomes, and higher mortality.
3. Higher incidence of stroke has been reported in the South Asian atrial fibrillation population than in other races.
4. Currently, physicians generally use the CHA2DS2-VASc scoring system to assess the risk of stroke in atrial fibrillation populations. However, the predictive performance of CHA2DS2-VASc has been reported to be unsatisfactory in Asian atrial fibrillation populations.

### What this study adds:

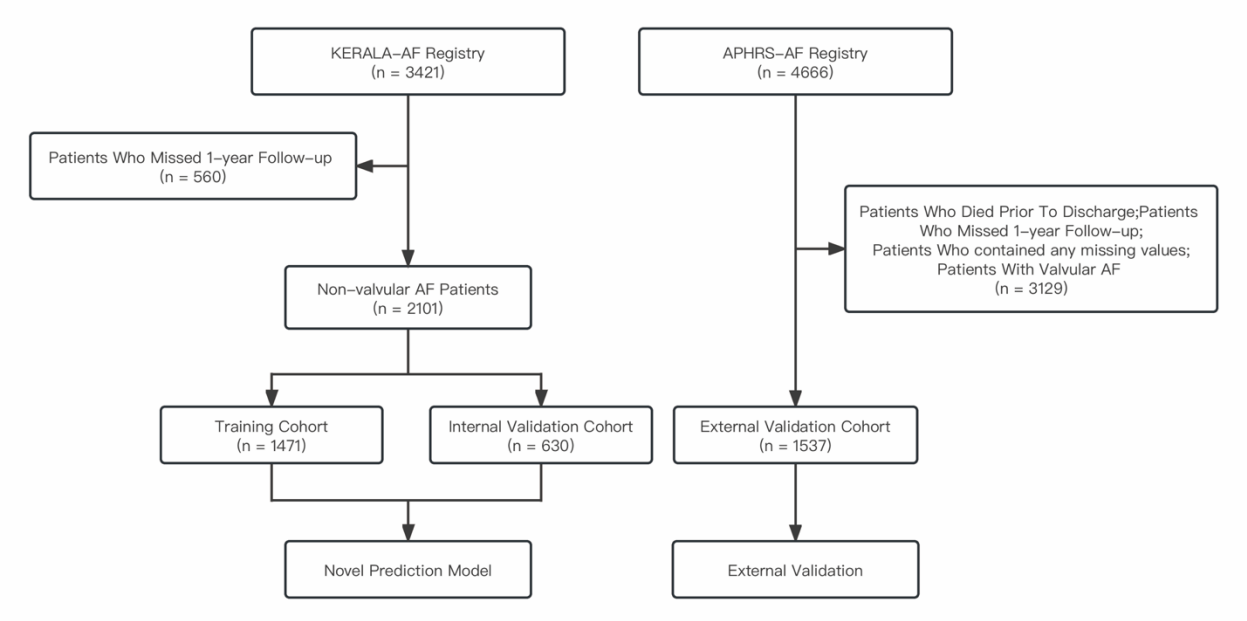
1. The prospective South Asian atrial fibrillation cohort we used (KERALA-AF) is currently the largest in the world within our knowledge.
2. In our included cohort, the 1-year stroke incidence was approximately 4% in the South Asian atrial fibrillation population compared with approximately 1% in other Asian atrial fibrillation

population, and the stroke incidence in South Asian atrial fibrillation was much higher than in other Asian atrial fibrillation population.

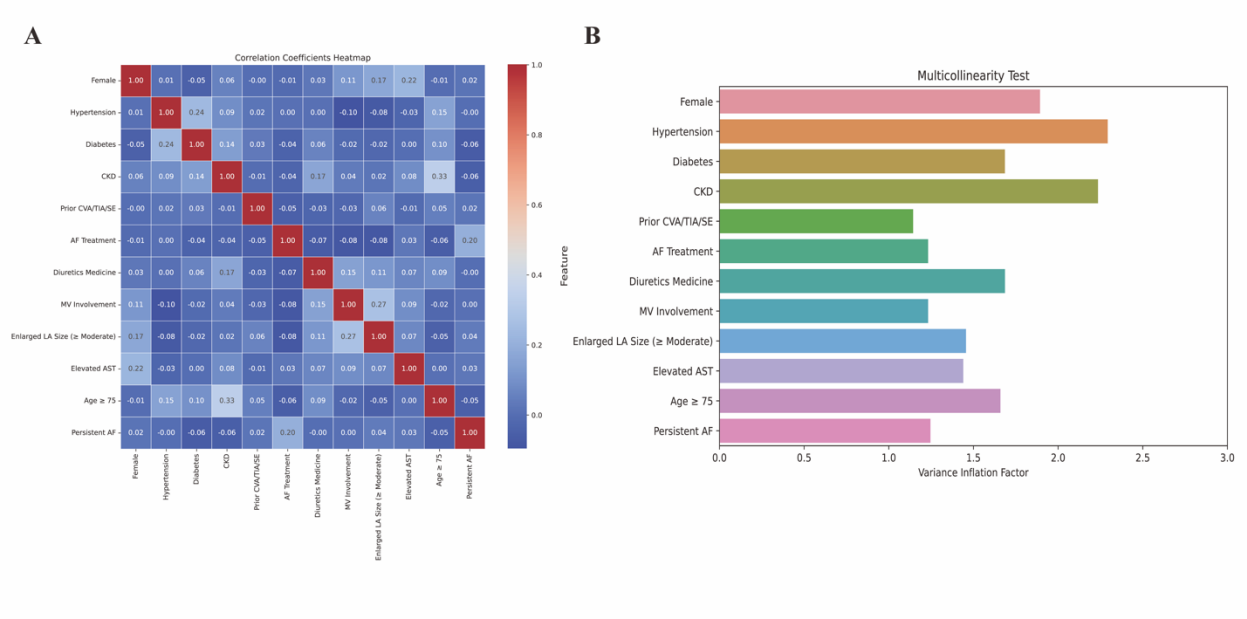
3. Using machine learning techniques, we explored the risk factors of stroke associated with atrial fibrillation in the South Asian atrial fibrillation population. Apart from the risk factors traditionally applied in some prediction models such as age, gender, hypertension, diabetes, and history of cerebrovascular disease/transient ischaemic attack/systemic embolism, other new risk factors were identified, including already accepted risk factors (chronic kidney disease, left ventricular dysfunction, mitral valve involvement, atrial fibrillation type) and several potential risk factors (atrial fibrillation treatment strategies, elevated aspartate transaminase, diuretics medicine).

4. This study is the first one within our knowledge to use several machine-learning algorithms and screened risk factors to construct models for predicting stroke associated with atrial fibrillation for the South Asian atrial fibrillation population, which performed much better than CHA2DS2-VASc (C-index: 0.821 vs. 0.665). When the model was applied to other Asian AF cohort, it (C-index: 0.670) performed better than CHA2DS2-VASc (C-index: 0.615) despite unsatisfactory performance, which triggers the important conclusion that for different ethnically atrial fibrillation populations, the prevalence of stroke associated with atrial fibrillation varies and that ethnically-specific machine-learning predictive models are required.

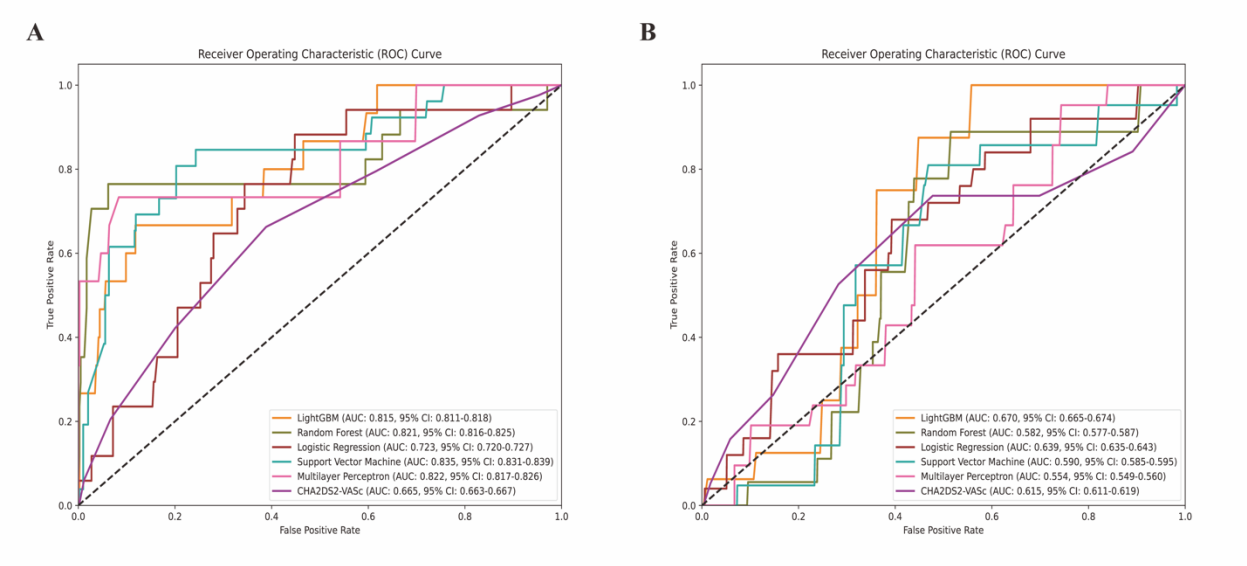
## Figure 1




## Figure 2



## Figure 3




## Figure 4

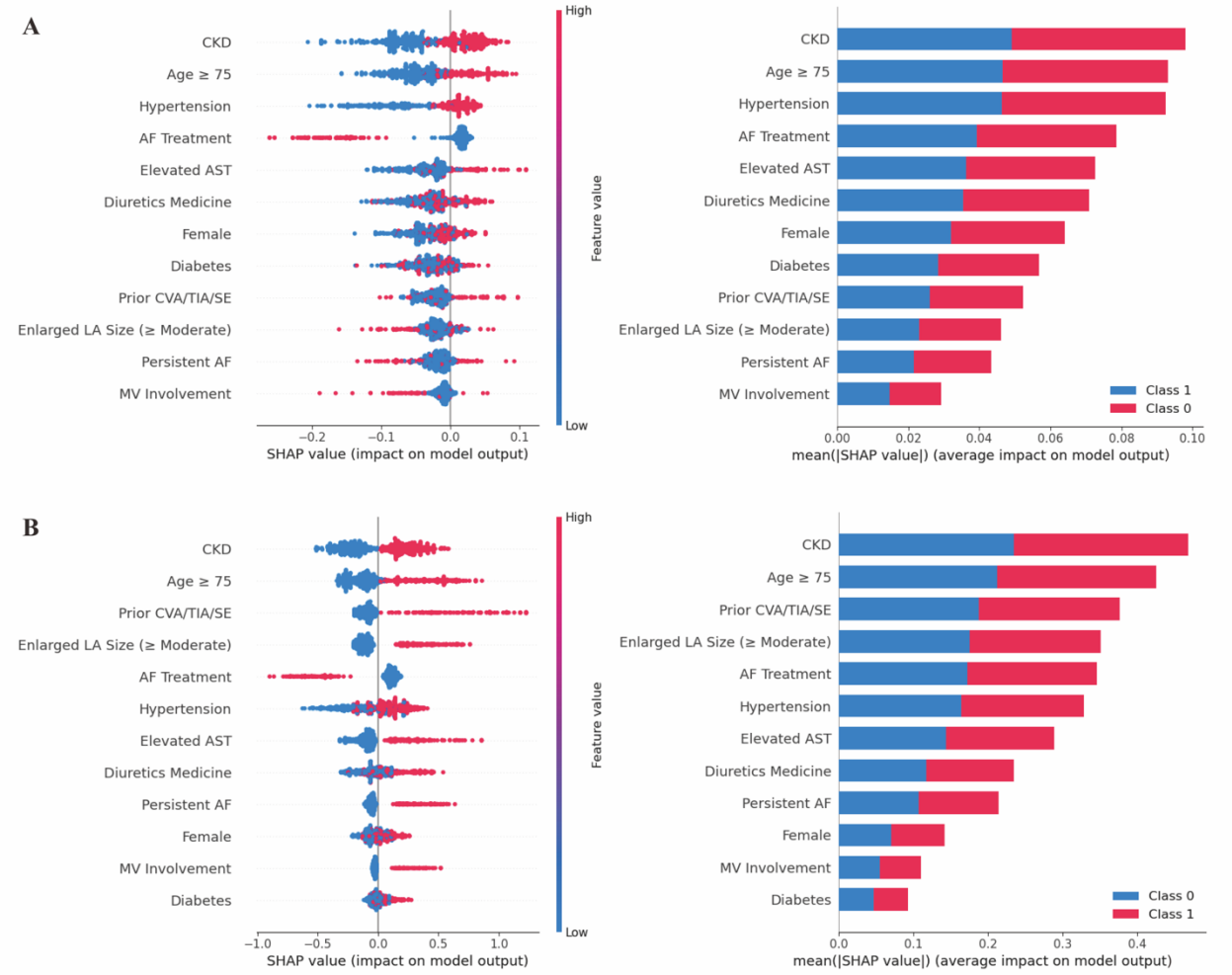
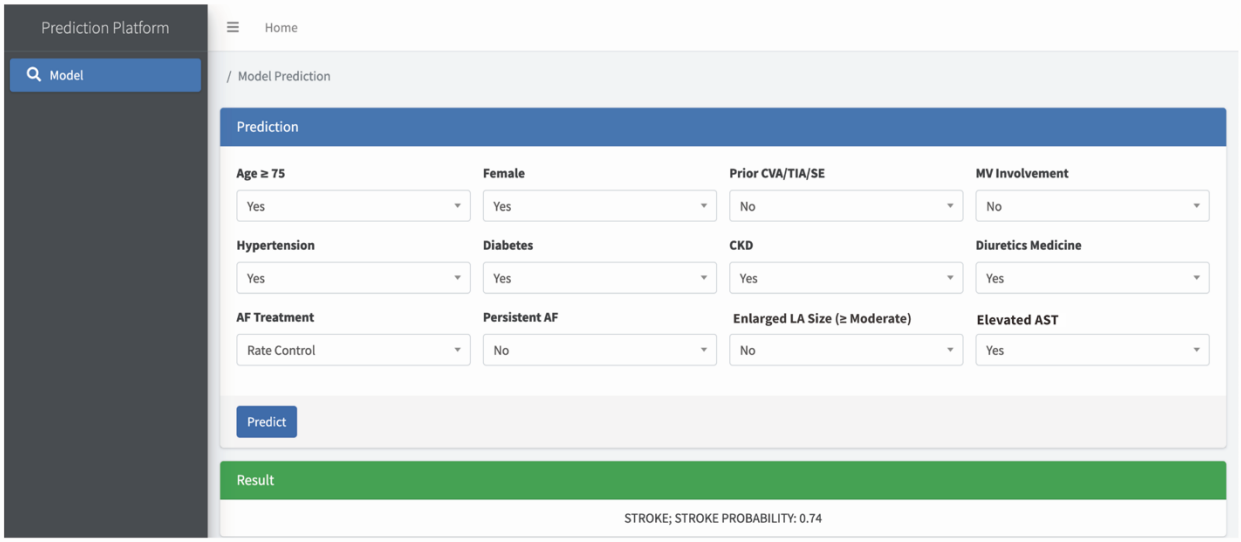


**Figure 5**


Prediction Platform
Model
Home
/ Model Prediction
Prediction
Age ≥ 75
Yes
Female
Yes
Prior CVA/TIA/SE
No
MV Involvement
No
Hypertension
Yes
Diabetes
Yes
CKD
Yes
Diuretics Medicine
Yes
AF Treatment
Rate Control
Persistent AF
No
Enlarged LA Size (≥ Moderate)
No
Elevated AST
Yes
Predict
Result
STROKE; STROKE PROBABILITY: 0.74

**Declarations Of Interest Statement**

G.Y.H.L. reports: Consultant and speaker for BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, Anthos. No fees are received personally. G.Y.H.L. is a National Institute for Health and Care Research (NIHR) Senior Investigator and co-principal investigator of the AFFIRMO project on multimorbidity in AF, which has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 899871. Other authors report no conflicts of interest.

Supplementary Table S1. Names and definitions of transformed categorical variables.

| Characteristic | Definition |
|---|---|
| Tachyarrhythmia | Heart Rate > 100 beats/min |
| Reduced LVEF (≥ Moderate) | LVEF < 40% |
| Enlarged LA Size (≥ Moderate) | Male: LA Diameter > 47 mm;<br>Female: LA Diameter > 43 mm |
| Elevated Haemoglobin | Male: Haemoglobin > 17 g/dl<br>Female: Haemoglobin > 15 g/dl |
| Reduced Haemoglobin | Male: Haemoglobin < 13 g/dl<br>Female: Haemoglobin < 12 g/dl |
| Elevated Total Cholesterol | Total Cholesterol > 200 mg/dl |
| Elevated LDL | LDL > 100 mg/dl |
| Reduced HDL | Male: HDL < 40 mg/dl;<br>Female: HDL < 50 mg/dl |
| Elevated AST | Male: AST > 50 U/l; Female: AST > 35 U/l |
| Elevated ALT | Male: ALT > 60 U/l; Female: AST > 45 U/l |
| Elevated FBS | FBS > 110 mg/dl |
| Reduced FBS | FBS < 70 mg/dl |
| Elevated INR | INR > 3 sec |
| Reduced INR | INR < 2 sec |
| Elevated Serum Creatinine | Male: Serum Creatinine > 1.2 mg/dl<br>Female: Serum Creatinine > 1.1 mg/dl |
| Elevated Bilirubin | Bilirubin > 1.2 mg/dl |
| Reduced GFR | GFR < 90 mg/dl |

Legend: ALT, alanine transaminase; AST, aspartate Transaminase; FBS, fasting blood sugar; GFR, glomerular filtration rate; HDL, high density lipoprotein; INR, international normalized ratio; LA, left atrium; LDL, low density lipoprotein; LVEF, left ventricular ejection fraction.

Supplementary Table S2. Transformed categorical variables between stroke and non-stroke in the KERALA-AF cohort.

| Characteristic, n (%) | All | Non-stroke | Stroke | *P*-value |
|---|---|---|---|---|
| Age ≥ 75 years | 628 (29.9%) | 585 (29.0%) | 43 (51.8%) | < 0.001 |
| BMI ≥ 30 kg/m$^2$ | 168 (8.0%) | 165 (8.2%) | 3 (3.6%) | 0.133 |
| Tachyarrhythmia | 755 (35.9%) | 720 (35.7%) | 35 (42.2%) | 0.227 |
| Reduced LVEF (≥ Moderate) | 192 (9.1%) | 185 (9.2%) | 7 (8.4%) | 0.820 |
| Enlarged LA Size (≥ Moderate) | 512 (24.4%) | 487 (24.1%) | 25 (30.1%) | 0.213 |
| Elevated Haemoglobin | 28 (1.3 %) | 27 (1.3%) | 1 (1.2%) | 1.000 |
| Reduced Haemoglobin | 1015 (48.3%) | 974 (48.3%) | 41 (49.4%) | 0.840 |
| Elevated Total Cholesterol | 419 (19.9%) | 407 (20.2%) | 12 (14.5%) | 0.202 |
| Elevated LDL | 984 (46.8%) | 941 (46.6%) | 43 (51.8%) | 0.354 |
| Reduced HDL | 1048 (49.9%) | 1004 (49.8%) | 44 (53.0%) | 0.560 |
| Elevated AST | 543 (25.8%) | 510 (25.3%) | 33 (39.8%) | 0.003 |
| Elevated ALT | 1721 (81.9%) | 1653 (81.9%) | 68 (81.9%) | 0.997 |
| Elevated FBS | 1046 (49.8%) | 1003 (49.7%) | 43 (51.8%) | 0.707 |
| Reduced FBS | 44 (2.1%) | 42 (2.1%) | 2 (2.4%) | 0.692 |
| Elevated INR | 152 (7.2%) | 146 (7.2%) | 6 (7.2%) | 0.998 |
| Reduced INR | 1562 (74.3%) | 1499 (74.3%) | 63 (75.9%) | 0.740 |
| Elevated Serum Creatinine | 849 (40.4%) | 811 (40.2%) | 38 (45.8%) | 0.309 |
| Elevated Bilirubin | 554 (26.4%) | 536 (26.6%) | 18 (21.7%) | 0.323 |
| Reduced GFR | 1875 (89.2%) | 1796 (89.0%) | 79 (95.2%) | 0.075 |

Legend: ALT, alanine transaminase; AST, aspartate Transaminase; BMI, body mass index; FBS, fasting blood sugar; GFR, glomerular filtration rate; HDL, high density lipoprotein; INR, international normalized ratio; LA, left atrium; LDL, low density lipoprotein; LVEF, left ventricular ejection fraction; NVAF, non-valvular atrial fibrillation.

Supplementary Table S3. Best hyperparameters of each classifier.

| Classifiers | Hyperparameters | |
|---|---|---|
| LightGBM | n_estimators | 150 |
| | max_depth | 7 |
| | learning_rate | 0.01 |
| | num_leaves | 95 |
| | max_bin | 255 |
| | min_data_in_leaf | 41 |
| | bagging_fraction | 0.8 |
| | bagging_freq | 45 |
| | feature_fraction | 0.9 |
| | lambda_l1 | 0.001 |
| | lambda_l2 | 0.1 |
| | min_split_gain | 0.0 |
| | class_weight | 'balanced' |
| Random Forest | n_estimators | 85 |
| | max_depth | 8 |
| | max_features | 1 |
| | min_samples_split | 2 |
| | criterion | 'gini' |
| | min_samples_leaf | 1 |
| | random_state | 19 |
| | class_weight | 'balanced' |
| Logistic Regression | C | 0.1 |
| | penalty | l2 |
| | solver | 'lbfgs' |
| | class_weight | 'balanced' |
| Support Vector Machine | C | 1 |
| | kernel | 'rbf' |
| | probability | True |
| | tol | 0.001 |
| | random_state | 90 |
| | class_weight | 'balanced' |
| Multilayer Perceptron | solver | 'lbfgs' |
| | activation | 'relu' |
| | hidden_layer_sizes | [50,] |
| | alpha | 0.001 |
| | random_state | 90 |

Legend: LightGBM, light gradient boosting machine.

Supplementary Table S4. The characteristics between stroke and non-stroke in the APHRS-AF cohort.

| Characteristic, n (%) | All | Non-stroke | Stroke | *P*-value |
|---|---|---|---|---|
| Age ≥ 75 years | 423 (27.5%) | 413 (27.2%) | 10 (52.6%) | 0.014 |
| Female | 533 (34.7%) | 524 (34.5%) | 9 (47.4%) | 0.242 |
| CHA2DS2-VASc Score, n (%) | | | | 0.246 |
| 0 | 168 (10.9%) | 165 (10.9%) | 3 (15.8%) | |
| 1 | 295 (19.2%) | 293 (19.3%) | 2 (10.5%) | |
| 2 | 335 (21.8%) | 335 (22.1%) | 0 (0%) | |
| 3 | 300 (19.5%) | 296 (19.5%) | 4 (21.1%) | |
| 4 | 210 (13.7%) | 205 (13.5%) | 5 (26.3%) | |
| 5 | 137 (8.9%) | 135 (8.9%) | 2 (10.5%) | |
| 6 | 64 (4.2%) | 2 (10.5%) | 62 (4.1%) | |
| 7 | 23 (1.5%) | 1 (5.3%) | 22 (1.4%) | |
| 8 | 4 (0.3%) | 0 (0.0%) | 4 (0.3%) | |
| 9 | 1 (0.1%) | 0 (0%) | 1 (0.1%) | |
| Diabetes | 333 (21.7%) | 328 (21.6%) | 5 (26.3%) | 0.581 |
| Chronic Kidney Disease | 123 (8.0%) | 121 (8.0%) | 2 (10.5%) | 0.660 |
| Prior CVA/TIA/SE | 171 (11.1%) | 170 (11.2%) | 1 (5.3%) | 0.713 |
| MV Involvement | 882 (57.4%) | 870 (57.3%) | 12 (63.2%) | 0.609 |
| Persistent AF | 556 (36.2%) | 550 (36.2%) | 6 (31.6%) | |
| AF Treatment Strategy | | | | 0.237 |
| Rhythm | 607 (39.5%) | 602 (39.7%) | 5 (26.3%) | |
| Rate | 930 (60.5%) | 916 (60.3%) | 14 (73.7%) | |
| Diuretics Medincine | 321 (20.9%) | 313 (20.6%) | 8 (42.1%) | 0.040 |
| Elevated AST | 76 (4.9%) | 75 (4.9%) | 1 (5.3%) | 0.949 |
| Enlarged LA Size (≥ Moderate) | 587 (38.2%) | 577 (38.0%) | 10 (38.2%) | 0.192 |

Legend: AST, aspartate Transaminase; CVA, cerebrovascular accident; LA, left atrium; MV, mitral valuvular; NVAF, non-valvular atrial fibrillation; SE, systemic embolism; TIA, transient ischaemic attack.