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Machine Learning Approaches to Predict Major Adverse Cardiovascular Events in Atrial Fibrillation

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Abstract: The increasing prevalence of atrial fibrillation (AF) and its association with Major Adverse Cardiovascular Events (MACE) presents challenges in early identification and treatment. Although existing risk factors, biomarkers, genetic variants, and imaging parameters predict MACE, emerging factors may be more decisive. Artificial intelligence and machine learning techniques (ML) offer a promising avenue for more effective AF evolution prediction. Five ML models were developed to obtain predictors of MACE in AF patients. Two-thirds of the data were used for training, employing diverse approaches and optimizing to minimize prediction errors, while the remaining third was reserved for testing and validation. AdaBoost emerged as the top-performing model (accuracy: 0.9999; recall: 1; F1 score: 0.9997). Noteworthy features influencing predictions included the Charlson Comorbidity Index (CCI), diabetes mellitus, cancer, the Wells scale, and CHA_2DS_2-VASc, with specific associations identified. Elevated MACE risk was observed, with a CCI score exceeding 2.67 ± 1.31 ($p < 0.001$), CHA2DS2-VASc score of 4.62 ± 1.02 ($p < 0.001$), and an intermediate-risk Wells scale classification. Overall, the AdaBoost ML offers an alternative predictive approach to facilitate the early identification of MACE risk in the assessment of patients with AF.

Keywords: atrial fibrillation; major adverse cardiovascular events (MACE); machine learning; artificial intelligence

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1. Introduction

Despite being the most prevalent cardiac arrhythmia, the early identification, diagnosis, and treatment of atrial fibrillation (AF) remain challenging. AF affects millions of individuals globally and is linked to a heightened risk of stroke, heart failure, and mortality [1–4]. These medical conditions collectively fall under the term Major Adverse Cardiovascular Events (MACE) and are subject to extensive research [5]. The diagnosis of AF is associated with a fourfold increase in heart failure incidence and an eightfold increase in MACE occurrence [6].

Risk factors for MACE in AF patients have been identified as age, gender, hypertension, diabetes (known as "traditional"), biomarkers, genetic variants, imaging parameters, and left atrial function [7–10]. In recent years, there has been growing interest in identifying new

predictors of MACE in AF patients [11] beyond traditional ones such as obesity, chronic obstructive pulmonary disease (COPD), or chronic renal failure [7,8,12]; this novel approach is associated with a reduced risk of MACE, including mortality and thromboembolism [13].

Several proposals for stroke risk assessment in AF have been developed, such as CHA_2DS_2-VASc [14], the Framingham score [15], Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) [16], Cohorts for Heart and Aging Research in Genomic Epidemiology for Atrial Fibrillation (CHARGE-AF) [17,18], and Atrial Fibrillation Research In CATalonia (AFRICAT) [19]. However, there are still challenges and limitations with clinical risk scores that restrict their applicability to certain populations. Moreover, the discriminatory ability of clinical risk scores in predicting stroke risk for an individual is at best moderate [20]. For MACE risk specifically, some studies [21,22] have proposed additional scoring systems or modifications to existing scores to better predict cardiovascular events in patients with AF. Leveraging artificial intelligence (AI) and machine learning (ML) techniques on electronic health record (EHR) data offers a potential avenue to further refine these risk prediction models. However, it is important to note that the extent of performance improvement achieved through AI and ML approaches can vary [23,24].

Therefore, more comprehensive risk prediction models incorporating a wider range of predictors or with more prognostic value are needed. Such models can be achieved using ML algorithms, which offer a promising approach in AF patients [2], as they can integrate large amounts of data from multiple sources and identify complex patterns and correlations that may not be evident using traditional statistical methods.

The heterogeneous mechanisms and risk factors associated with AF make it necessary to target personalized treatment approaches, requiring extensive patient data to identify specific patterns. AI algorithms are particularly suitable for handling high-dimensional data, predicting outcomes, and ultimately optimizing strategies for patient management [25]. Recent advances in ML have resulted in great success and have also been utilized to analyze electrocardiogram (ECG) data and predict the future occurrence of arrhythmias. Future Innovations in Novel Detection for Atrial Fibrillation (FIND-AF), an extensively scalable ML algorithm, is capable of analyzing routinely collected primary care data to identify individuals with an elevated risk of short-term AF [26]. Other studies have demonstrated the utility of machine learning-based models in AF for real-time identification of a variety of rhythms using 12-lead or single-lead ECG recordings, as well as for diagnosis, outcome prediction, disease characterization, and treatment assessment [2,27–33]. However, they do not address the discrimination of cardioembolic from noncardioembolic stroke among individuals with AF with high accuracy and surpassing traditional risk scores. These methods provide precise and efficient algorithms for data analysis, improving prediction accuracy, pattern identification, and task automation. If patients at higher risk of MACE could be identified, treatment strategies could be developed to potentially reduce incidence and associated complications.

The primary objectives of this study encompassed the identification of noteworthy clinical indicators associated with MACE in patients with new AF. It further aimed to assess the prognostic impact of these predictors within a community cohort, aged 65–95 years, tracked from 2015 to 2021.

2. Materials and Methods

2.1. Study Design

This was an observational study, and the data were retrospectively collected where possible, or manually collected otherwise. The specific codes of the International Classification of Diseases (ICD-10) were used. The project encompassed the broader demographic of individuals aged 65–95 years (n = 40,297) who did not have AF as part of their inclusion criteria and was conducted within the Primary Care facilities of Terres de l'Ebre, located in Catalonia, Spain, during the period spanning from 1 January 2015 to 31 December 2021.

The data were available from the electronic medical datasets (E-CAP and SAP) managed by the Catalan Health Institute (ICS), which collect information from primary care

centers and hospitals in the health region anonymously and without contact with the cases included, as follows:

1. The Health Plan [33] outlines healthcare priorities in the "Terres de l'Ebre" Healthcare Region (Catalonia, Spain) from 2021 to 2025.
2. The HC3 Patient Episode Dataset provides clinical information of care on inpatient and outpatient care in Catalan hospitals.
3. The clinical database of 11 primary care teams includes comprehensive health data for 97.7% of residents, covering symptoms, tests, diagnoses, comorbidities, prescribed medication, and referrals.
4. The Integrated System of Electronic Prescription (SIRE) captures information on prescribed medications.
5. The Statistics Institute of Catalonia includes demographic information [34–36].

The datasets generated, used, and analyzed during the current study are available from the corresponding author on reasonable request.

2.2. Eligibility Criteria

All patients over 65 years of age from Terres de l'Ebre (N 55,459) without AF or MACE in their clinical history were considered, and the following criteria were defined:

1. Outcomes: AF patients who had a MACE.
2. Inclusion criteria: Subjects aged 65–95 years who met the inclusion criteria: high risk-AF (according to the risk model and belonging to Q4) [19], active clinical history in any of the health centers of the territory with information accessible through the shared history (HC3), without previous AF or MACE, residing in the territory, and attached to any of the Primary Care Teams (EAP) of the territory.
3. Exclusion criteria: under 65 years of age or over 95 years of age, living outside Terres de l'Ebre, a previous diagnosis of AF, treatment with anticoagulants, impaired cognitive status, Barthel score < 55 points, or pacemaker or defibrillator wearer. Non-availability or loss of accessibility to the information necessary for the study was considered a reason for exclusion.

2.3. Data and Preprocessing

The overall composition of the dataset for MACE prediction is given in Table 1 Numerical calculations and data analysis were performed using Python library version 3. Code and models used for the analysis are available online (https://github.com/vmalonsobarberan/MACE) (accessed on 15 December 2023).

Table 1. Comparison of the performance of different models.

Machine Learning Model	Accuracy	Precision	Recall	F1 Score	Sensitivity	Specificity	PPV	NPV	AUC
Random Forest	96.78%	0.8456	0.9263	0.8841	0.9885	0.8456	0.9741	0.9263	96.78%
Extra Trees	98.82%	0.9641	0.9554	0.9597	0.9923	0.9641	0.9938	0.9554	98.82%
AdaBoost	99.99%	0.9994	1	0.9997	1	0.9994	0.9999	1	99.99%
XGBoost	99.95%	1	0.9971	0.9985	0.9995	1	1	0.997	99.95%
LightGBM	99.96%	1	0.9977	0.9988	0.9996	1	1	0.9977	99.96%

2.4. Model Development

To develop ML models for estimation, we took features of the individuals with newly diagnosed AF who developed MACE, following the eligibility criteria. ML model development was performed using the SKLearn and TensorFlow libraries due to their versatility and ease of programming. For each fold, hyperparameters were tuned on training data using a randomized search after the determination of a candidate hyperparameter set. Evaluation of validation data was performed using the metrics described in the next section.

Five different ML models were implemented based on the following algorithms: Random Forest, Extra Trees, AdaBoost, XGBoost, and LightGBM. They were trained on all the features (variables) used in the study to predict the development of MACE within one year as well as to predict the development of AF.

A fundamental part of the study, prior to the construction of the learning models, consisted of "Feature Engineering", which consists of the analysis and selection of the variables, as well as the processing of the data they contain. To this end, those that only contribute noise and/or are correlated with others that have a greater influence on the objective we aimed to predict were eliminated.

The performance of MACE prediction was quantified using the following metrics: precision, recall, accuracy, and F1 score (combination of precision and recall). Two thirds of the data (36,973) were randomly selected for training and model building using different approaches and optimized to reduce the prediction error. The remaining 1/3 (18,486) was used for testing and validation. The models underwent testing using this separate test data to assess their performance on data that had not been utilized during the training phase. This evaluation aimed to determine whether the models could effectively generalize and make accurate predictions on unseen data.

2.5. Model Performance Analysis

Several metrics were used to evaluate the algorithms, including prediction robustness, completeness, sensitivity, specificity, precision, recall, accuracy, and F1 score (combination of precision and recall). Evaluation of these metrics allowed us to adjust the hyperparameters of the model to improve the most desirable aspect of the model. The model with the highest and most robust performance was chosen after evaluating the performance of the different models using the mean value of the area under the ROC curve. The assessment of our models included consideration of the standard deviation of the results to evaluate their stability, along with an analysis of sensitivity, specificity, and accuracy. After fitting and evaluating different models, the best model was selected, and the hyperparameters were adjusted to obtain the optimal results.

2.6. Model Interpretability

The Shapley Additive exPlanations (SHAP) method was used to analyze which factors were the most important and to what extent they contribute to the model's predictions. An individual automatic explainability model was also created to allow an analysis to be made for each individual patient. The latter allows, after analyzing a patient's variables, to explain how likely a patient with AF is to have a MACE and which factors contribute to this prediction and to what extent.

2.7. Statistical Analysis

The traditional statistical analysis of the baseline data was previously documented [6].

3. Results

3.1. Study Population Patient Characteristics

The study encompassed a cohort of 2574 individuals devoid of prior MACE incidents, with a mean age of 81.22 $\pm$ 7.91 years and a gender distribution of 52.01% women. A detailed analysis of baseline characteristics, as outlined previously [6], revealed notable distinctions among the study groups. Notably, women who experienced MACE exhibited a higher mean age (82.23 $\pm$ 7.59 years, compared to 80.53 $\pm$ 8.05 years for males, $p < 0.001$) and a higher prevalence of cardiovascular risk factors and comorbidities. Refer to Table 2 for a comprehensive overview of the selected variables instrumental in model construction.

Table 2. Distribution of AF patients according to the presence of MACE.

Variables	No MACE	(%)	MACE	(%)	*p*	All
All	1527	59.32%	1047	40.68%		2574
Woman	785	51.41%	558	53.30%	0.356	1343
Age average	80.53 ± 8.05		82.23 ± 7.59		<0.001	81.22 ± 7.91
Hypertension, arterial	1112	72.82%	833	79.56%	<0.001	1945
Diabetes mellitus	406	26.59%	363	34.67%	<0.001	769
Dyslipemia	692	45.32%	524	50.05%	0.020	1216
Vascular disease	59	3.86%	286	27.32%	<0.001	345
Dementia/cognitive impairment	174	11.39%	136	12.99%	<0.001	310
Liver disease	6	0.39%	4	0.38%	1.000	10
Renal failure	339	22.20%	337	32.19%	<0.001	676
Cancer	516	33.79%	340	32.47%	0.496	856
Thyroid disease	109	7.14%	106	10.12%	0.018	215
OSAHS [1]	60	3.93%	66	6.30%	0.007	126
COPD [2]	225	14.73%	222	21.20%	<0.001	447
Inflammatory disease (Crohn's and Colitis)	9	0.59%	7	0.67%	0.804	16
Deep vein thrombosis	20	1.31%	17	1.62%	0.506	37
Weight (kg)	77.47 ± 5.7		78.03 ± 16.51		0.038	77.69 ± 16.04
BMI [3]	29.32 ± 5.28		29.75 ± 5.51		0.041	29.49 ± 5.38
Heart rate/min	76.05 ± 1847		75.71 ± 18.47		0.625	75.91 ± 18.47
Cholesterol mg/dL	184.23 ± 38.07		164.98 ± 38.14		<0.001	176.4 ± 39.24
ProBNP (pg/mL)	1550		3301.75 ± 2882.7		0.625	2951.4 ± 2616.52
Dimer D (ng/mL)	1753.59 ± 2714.47		1319.72 ± 2954.13		0.337	1532.56 ± 2838.47
Glomerular filtration rate (mL/min/1.73 m^2)	66.11 ± 19.8		59.85 ± 20.74		<0.001	63.48 ± 20.43
Serum albumin (g/dL)	4.94 ± 5.43		5.04 ± 14.85		0.835	4.98 ± 10.68
Lymphocytes ($\times 10^3/\mu L$)	2.12 ± 1.11		2.02 ± 1.62		0.072	2.08 ± 1.34
Statins	505	33.07%	607	57.98%	<0.001	945
Anticoagulation	1207	79.04%	787	75.16%	0.021	1994
Antivitamin-K	613	40.14%	331	31.61%	<0.001	944
NOAC [4]	595	38.96%	458	43.74%	0.015	1053
Anti-aggregants	67	4.38%	74	7.06%	0.003	141
Pfeiffer score ± SD	2.91 ± 3.1		2.61 ± 2.8		0.218	2.75 ± 2.94
CHA_2DS_2-VASc ± SD	3.26 ± 0.95		4.62 ± 1.02		<0.001	3.81 ± 1.20
CCI [5] ± SD	1.24 ± 1.19		2.67 ± 1.31		<0.001	1.82 ± 1.43
CONUT score ± SD	1.31 ± 0.54		1.48 ± 0.61		<0.001	1.38 ± 0.58
Wells score ± SD	1.35 ± 0.48		1.33 ± 0.47		0.415	1.34 ± 0.47
COVID-19	150	9.82%	110	10.51%	0.573	260
Death	1279	83.76%	777	74.21%	<0.001	2056

[1]. OSAHS: obstructive sleep apnea-hypopnea syndrome; [2]. COPD: chronic obstructive pulmonary disease; [3]. BMI: Body Mass Index; [4]. NOAC: new oral anticoagulants; [5]. CCI: Charlson Comorbidity Index.

3.2. Machine Learning Model

3.2.1. Comparison between the Different Models

In the comparative analysis of various pre-trained models, AdaBoost emerged as the top-performing model, showcasing exceptional metrics, with an accuracy of 0.9999, recall of 1, and an F1 score of 0.9997. This marked superiority was evident, making AdaBoost the optimal choice, balancing both sensitivity and specificity (Figure 1).

Following closely behind, XGBoost (accuracy: 0.9995; recall: 0.9971; F1: 0.9985) and LightGBM (accuracy: 0.9996; recall: 0.9977; F1: 0.9988) emerged as the second-best models in our evaluation (Table 1). Notably, Random Forest and Extra Trees, while achieving commendable Area Under the Curve values (Figure 2), did not match the performance levels achieved by AdaBoost.

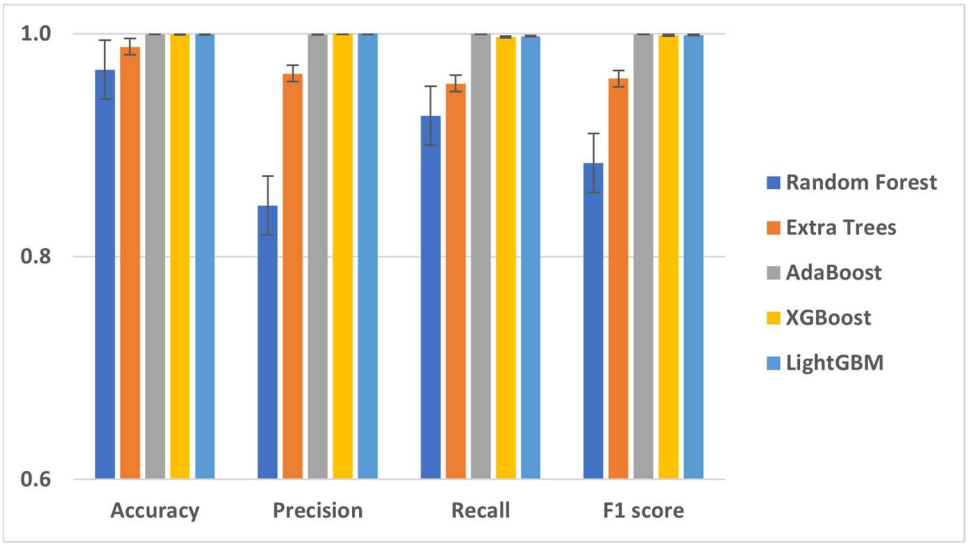

Figure 1. Comparison of the performance of different models.

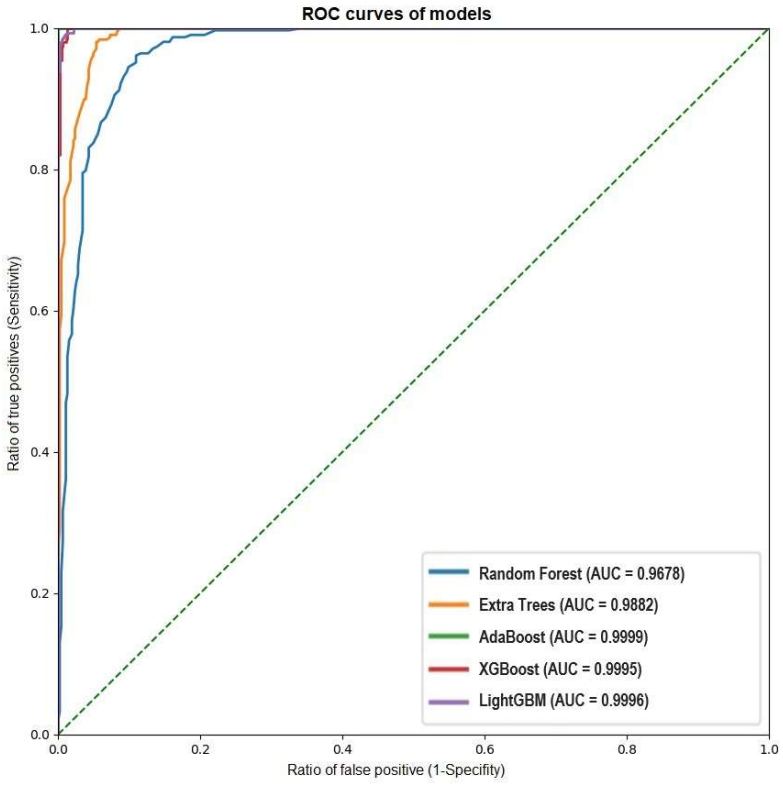

Figure 2. Comparison of AUC results between the machine learning models.

The confusion matrices of the different models and cross-validation were calculated. Each model has a confusion matrix. The models were ranked by true positive rates (Table 2).

3.2.2. Predictors by Outcomes

Figure 3 shows the main prognostic factors for MACE in AF patients. From most to least important were an elevated CCI, cancer, diabetes mellitus, COPD/asthma/bronchitis, cognitive impairment, vascular disease, high values of the CHA_2DS_2-VASc, and Wells scale.

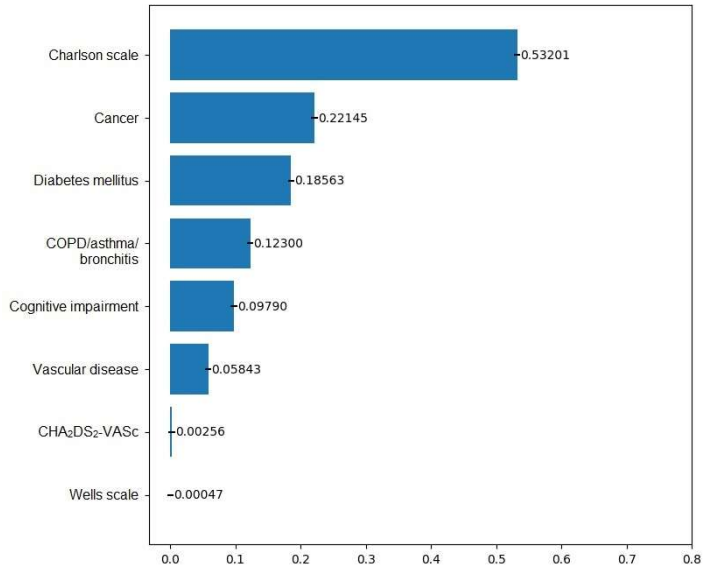

Figure 3. Strength of the main prognostic factors for MACE.

3.2.3. Model Interpretation

Figure 4 encapsulates a comprehensive overview of the feature contributions within the optimal model, AdaBoost. The SHAP (SHapley Additive exPlanations) summary chart delineates the significance of various characteristics, with the following five features emerging as the most influential: CCI, diabetes mellitus, cancer, Wells scale, and CHA_2DS_2-VASc. This SHAP summary chart not only identifies the primary features impacting the prediction but also quantifies their respective magnitudes through the SHAP values. The figures provide valuable insights into the relative importance of each feature, aiding in a nuanced understanding of the predictive dynamics within the AdaBoost model.

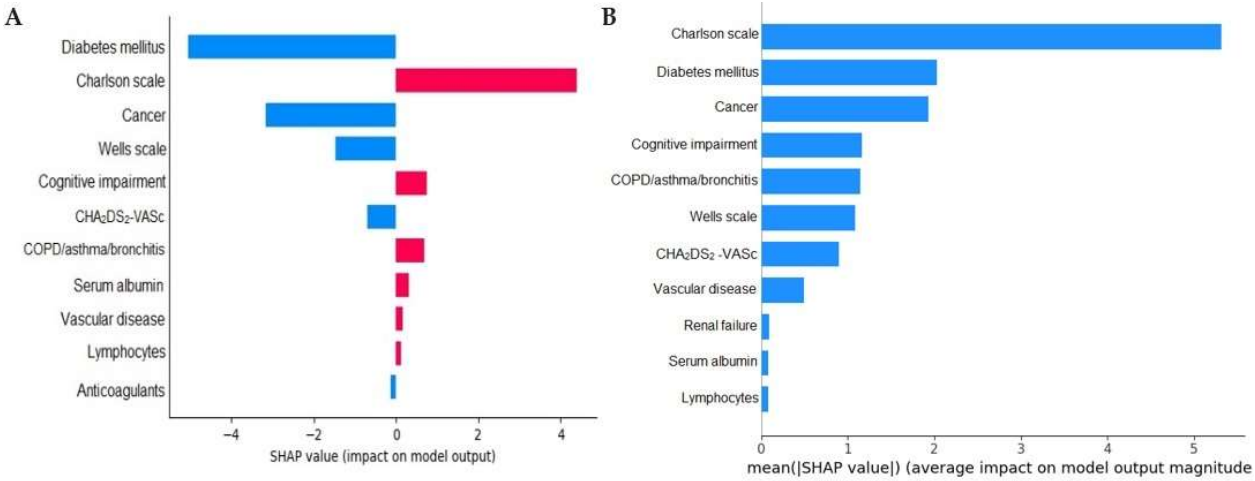

Figure 4. SHAP summary plot of optimum model. (**A**) The warm SHAP plot shows the distribution of SHAP values for each characteristic. (**B**) Bar chart according to feature importance.

Figure 5, the SHAP bar plot, serves as a visual representation elucidating the overall significance of each feature in predicting the occurrence of MACE. The height of the bars directly correlates with the importance of each feature to the model—higher bars denote greater importance. This graphical representation offers a clear and straightforward depiction of the overall magnitude and relevance of individual features in influencing the predictive outcome of MACE within the model. The visual emphasis on bar height

facilitates an immediate understanding of the relative contributions of different features, enhancing the interpretability of the model's decision-making process.

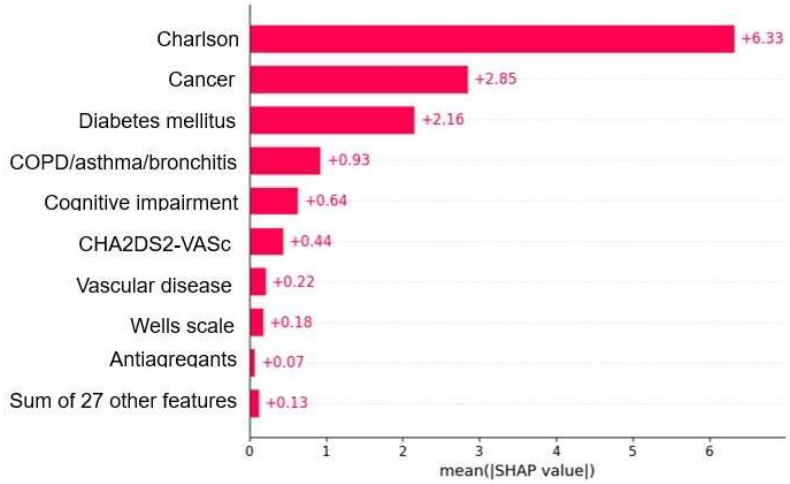

Figure 5. SHAP bar plot showing the overall magnitude and importance of the features.

The analysis delved into the influence of specific diseases, as outlined in the model, as predictors of MACE in AF patients. A CCI score exceeding 2.67 ± 1.31 ($p < 0.001$), a CHA_2DS_2-VASc score of 4.62 ± 1.02 ($p < 0.001$), and an intermediate-risk classification in the Wells scale were all observed to significantly elevate the risk of MACE. These findings underscore the nuanced interplay of individual patient characteristics, providing valuable insights into the factors contributing to the heightened risk of MACE in AF patients.

In Figure 6, the force chart dynamically illustrates the contributions of each feature in directing the model prediction from the base value to the ultimate result. The length of the colored bars within the chart serves as a visual indicator of the magnitude of each feature's contribution. This graphical representation offers a dynamic and insightful portrayal of how individual features influence the model's predictions, emphasizing the varying degrees of impact that contribute to the final outcome. The length of each bar provides a quick and intuitive assessment of the relative importance of each feature in shaping the model's decision-making process.

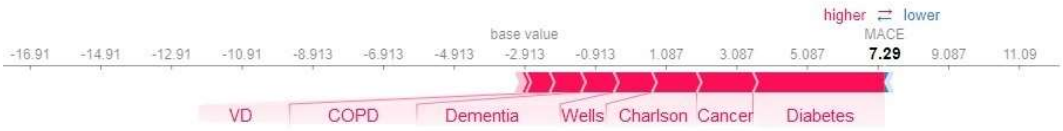

Figure 6. Dynamic force chart.

4. Discussion

The study identified AdaBoost as the best-performing model for MACE prediction in AF patients. Additionally, the CCI, concurrent cancer diagnosis, diabetes mellitus, and Wells and CHA_2DS_2-VASc scores emerged as primary predictors of MACE among patients newly diagnosed with AF. In a previous investigation [6], subsequent adjustments for age, gender, body mass index, cardiovascular risk factors, antiplatelets, and anticoagulants revealed that only the CHA_2DS_2-VASc, CCI, and CONUT scores remained as independent prognostic factors for MACE in individuals with a recent diagnosis of AF [6].

The various potential benefits of the results can be described in the different sections included in the flowchart for the approach and treatment of AF [14] as risk stratification, the prevention of thromboembolism among patients with silent AF and stroke without a previous diagnosis of AF, and for specific comorbidities such as chronic coronary disease, peripheral artery disease, heart failure, chronic kidney disease, and cognitive impairment.

AF almost quintuples the risk of MACE [6], especially ischemic stroke and heart failure. The 23.5% with known AF were not receiving oral anticoagulant therapy [37]. The AF was associated with more severity, disability, and a 20% increase in stroke-related costs. The clinical benefits of appropriate anticoagulation are widely recognized, and clinicians should be aware of the importance of anticoagulation therapies in stroke prophylaxis, the occurrence of stroke, and the downstream economic burden on an increasingly aging population [38]. Patients with AF may benefit from evaluating factors such as the AdaBoost model. This information can assist in making informed decisions about treatment.

The decision to prescribe oral anticoagulants for preventing MACE in patients with intermediate annual risk of thromboembolic events, as determined by classic risk scores like CHA_2DS_2-VASc or an equivalent, and who are uncertain about the benefits of anticoagulation, may require additional discussion. This is due to the diverse magnitude of risk associated with each factor across different populations. Managing specific patient groups, particularly those with risk factors for MACE, can improve risk discrimination by incorporating additional factors, as seen with the AdaBoost model.

Moreover, it addresses the optimization of treatment decisions concerning the burden of AF in relation to the associated risks of thromboembolism and ischemic stroke. This involves assessing the need for anticoagulant treatment decisions in individuals experiencing either paroxysmal or persistent AF because of the predictive significance of the AF burden [39,40]. A pioneering aspect of this approach involves the comprehensive analysis of large patient cohorts and the integration of diverse data sources, including blood biomarkers, electrical signals, and medical images [41]. The significance of this research extends into the domain of Personalized Risk Assessment, providing a promising approach for the early non-invasive detection of AF. This extends to optimizing treatment approaches and anticipating long-term clinical trajectories.

The algorithm emphasizes the CCI as the primary predictor, a widely utilized tool in the medical field for predicting the risk of mortality linked to chronic health conditions. It encompasses various factors such as heart disease, diabetes, and cancer and assigns specific weights to each based on their impact on mortality. The cumulative score is then employed to estimate an individual's overall health status and prognosis. A higher CCI score correlates with an elevated risk of adverse outcomes or mortality. Remarkably, until now, the CCI has not been previously associated with the risk of thromboembolism in patients recently diagnosed with AF. Notably, there have been instances where the use of anticoagulant therapy was linked to a lower CCI score [42]. While the CCI has undergone extensive validation and widespread use in predicting outcomes across various medical contexts, its application in specific situations, such as predicting outcomes in patients with AF [6], may not have been as comprehensively explored.

The presence of cancer emerges as the second-ranking predictor of MACE. While the algorithm does not specify the type of cancer, numerous studies have explored the connection between cancer and thromboembolism in patients with AF. Some of these studies not only identify cancer as a significant predictor of MACE, encompassing thromboembolic events [43], but also suggest that the onset of new AF is associated with an elevated risk of developing cancer [44,45]. These findings underscore the intricate interplay between AF, cancer, and thromboembolic complications, as well as the importance of considering both conditions in clinical assessment and management [46].

The Wells score has not been widely recognized as a prognostic factor for thromboembolism among patients with AF; it is typically used to assess the likelihood of deep vein thrombosis and pulmonary embolism. AF and venous thromboembolism share several common risk factors. Moreover, the presence of AF may be linked to a higher risk of developing VTE, and individuals with a high risk of experiencing VTE may also face an elevated risk of developing AF [47]. This bidirectional association highlights the potential interplay between these two conditions, suggesting that they may influence each other's occurrence and progression. Further research is warranted to fully understand the com-

plex relationship between AF and VTE and its implications for clinical management and preventive strategies.

Diabetes mellitus and peripheral artery disease play an important role as a predictor of MACE [7,48]. Although they are also variables included in the CHA_2DS_2-VAS_c and CCI scales, they alone are also an important variable for the development of MACE, and the significance of CHA_2DS_2-VAS_c is widely recognized among patients with nonvalvular AF receiving oral anticoagulants [6,14,49,50]. In a recent study [51], machine learning models demonstrated satisfactory performance in forecasting MACE among patients with Type 2 diabetes mellitus. Notably, these models exhibited a higher accuracy in predicting strokes than myocardial infarction and heart failure.

Eventually, the study shed light on the significant role of COPD in the development of MACE among patients with AF, in alignment with existing evidence [8,12,50,52]. Prolonged P-wave duration acts as a potent precursor to AF, a condition that may be triggered by obstructive sleep apnea [53]. The presence of COPD in AF patients may contribute to an increased risk of MACE, emphasizing the importance of considering and managing this comorbidity when evaluating cardiovascular outcomes in this patient population.

While simpler models, such as logistic regression and decision trees, are more straightforward to interpret, they frequently exhibit inferior predictive performance compared to more sophisticated algorithms, including ensembles of decision trees like XGBoost and random forests [54]. Harnessing ML [53] algorithms facilitates the early identification of subtle indicators of thromboembolism risk from intricate datasets, thereby uncovering latent relationships among the risk factors associated with AF. The LightGBM model revealed associations between ischemic stroke and various peripheral blood biomarkers (such as creatinine, glycated hemoglobin, and monocytes) not considered by CHA_2DS_2-VASc and demonstrated significance in predicting ischemic stroke among AF patients [55,56]. These algorithms not only facilitate the analysis and correction of potential confounding factors but also serve as powerful tools to identify and mitigate bias in the AI system. Continuous monitoring using ML algorithms offers ongoing assessment of thromboembolic risk among AF patients, contributing to the tracking of disease progression, monitoring treatment response, and promptly detecting any sudden changes in health status. Additionally, by enhancing follow-up through the prediction of patient-specific risks, these algorithms can prioritize follow-up visits and interventions, ultimately leading to improved patient outcomes.

Using the Deep Learning methodology, the results were slightly inferior to those achieved with Machine Learning (accuracy of 0.9678). The primary reason for this discrepancy may be the fact that neural networks demand a substantial amount of data to effectively learn. They are characterized by an abundance of parameters that require tuning, allowing them to grasp intricate, high-dimensional patterns. However, this proves to be a disadvantage when the dataset is limited. In instances of small datasets, these models become prone to overfitting, essentially 'memorizing' the training data rather than 'learning' the underlying pattern. Consequently, this results in suboptimal generalization performance when applied to unseen data.

The strengths of the study include the models of prediction, the high-quality datasets, and strict adherence to data privacy regulations, as well as clinical context and domain knowledge, making it easy to interpret the reasons behind their predictions. In summary, incorporating machine learning algorithms into the clinical management of individuals at high risk of AF and those with AF yields potential benefits, including personalized risk assessment, data-driven decision support, and improved patient care. However, further validation in independent studies is required.

Some limitations should be considered, as external validation is essential before effectively adopting and integrating AI systems into patient care. One crucial factor that largely determines the efficiency and accuracy of these models is the quantity of data available. For small datasets, like in our case, traditional machine learning models tend to outperform their deep learning counterparts, contrary to popular belief. AI models trained

on specific datasets might not generalize well to different populations or healthcare settings, and overfitting could limit their applicability. Additionally, it is important to note that correlation does not necessarily imply causation. Establishing causal relationships between risk factors for AF and thromboembolism requires further research and experimentation. By addressing these limitations and maintaining responsible and effective AI use, we can enhance our understanding beyond not only the early detection of AF but also the risk associated with the incidence of MACE, providing opportunities to intervene in modifiable risk factors, and including aspects such as monitoring methods, detection technologies, and biomarkers linked to the association between AF and thromboembolism, ultimately leading to enhanced patient care outcomes.

Artificial intelligence-based clinical decision support systems may improve the outcomes among patients who have AF, but the efficacy of the tool in the real world is seldom reported. Future research could explore additional advantages, such as personalized risk assessment. By analyzing extensive datasets, including social determinants of health [18,57,58], biomarkers [59], multimodality imaging parameters [60,61], and nutritional status associated with AF risk [57,62], a comprehensive assessment can be made. This integration facilitates a more comprehensive and personalized risk assessment for each individual, allowing the identification of distinctive patterns and factors specific to the patient. This approach leads to more accurate risk predictions compared to traditional statistical models [6,23,63] and, consequently, may improve treatment decision making.

5. Conclusions

The application of Machine Learning, employing multiple models, indicates that the AdaBoost model is the most effective in predicting MACE in patients with newly diagnosed AF, with an accuracy of 0.9999, recall of 1, and an F1 score of 0.9997. The primary prognostic factors identified included an elevated Charlson Comorbidity Index, cancer, diabetes mellitus, COPD, cognitive impairment, vascular disease, and high values on the CHA_2DS_2-VASc and Wells scale. This finding contributes to the optimization of treatment decisions concerning the burden of AF in relation to the associated risks of thromboembolism and ischemic events.

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Institutional Review Board Statement: This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Approval was obtained from the Ethics Committee of the Institut Universitari d'Investigació en Atenció Primària Jordi Gol with the registration number 22/243-P (30 November 2022). Registry information was collected from the government-run healthcare provider responsible for all inpatient care in the county, without contact with participants, in order to gather data from the study. The manuscript does not contain clinical studies or patient data that might disclose the identity of the people under study.

Informed Consent Statement: Not applicable. For this type of study, formal consent is not required, and the requirement for the informed consent of patients was waived prior to the inclusion of their medical data in this study.

Data Availability Statement: Numerical calculations and data analysis were performed using Python library version 3. The code and models used for the analysis are available online (https://github.com/

vmalonsobarberan/MACE) (15 December 2023). The datasets generated, used, and analyzed during the current study are available from the corresponding author (P.M.-B.) upon reasonable request.

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