

Prediction of Incident Atrial Fibrillation and Association With Outcomes Using Routine Electronic Health Records in a Western Pacific Population

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Background and Aim

Atrial fibrillation (AF) affects over 37 million people internationally and confers increased risk of cardiovascular conditions. Prediction algorithms have attempted to predict incident AF, but other cardio-renal diseases could also provide targets for earlier intervention.

Method

We derived a random forest classified for incident AF within 5 years (Future Innovations in Novel Detection of Atrial Fibrillation [FIND-AF] Taiwan) using routinely collected data from the National Taiwan University Hospital database. We compared this to congestive heart failure, hypertension, age >75 years (two points), diabetes mellitus, stroke/transient ischaemic attack/thromboembolism (two points), vascular disease, age 65–74 years, sex category (CHA₂DS₂-VASc) and coronary artery disease/chronic obstructive pulmonary disease (one point each), hypertension, elderly (age ≥75 years, two points), systolic heart failure, thyroid disease (hyperthyroidism) (C₂HES_T). Youden's Index was calculated to determine optimal threshold for higher versus lower predicted AF risk. We calculated cumulative incident curves and hazard ratios for incident AF, heart failure hospitalisation, or development of moderate-to-severe renal impairment, stroke or transient ischaemic attack and cardiovascular and all-cause mortality.

Results

Overall, 103,321 patients were included, with an average age of 64.6 years and 52.8% women. Overall, 4.4% had incident AF over the 5-year follow-up period. FIND-AF Taiwan had better discrimination (area under received operating characteristic 0.792, 95% confidence interval [CI] 0.777–0.807) than CHA₂DS₂-VASc (0.737; 0.721–0.754) and C₂HES_T (0.750; 0.733–0.766). After adjustment, individuals at higher risk were at increased hazard for heart failure hospitalisation (hazard ratio 15.32; 95% CI 9.19–25.54), transient ischaemic attack or ischaemic stroke (28.4; 21.01–38.47), progression to moderate or severe chronic kidney disease (1.18; 1.09–1.27), cardiovascular mortality (1.32; 0.88–1.98), and all-cause mortality (1.23; 1.11–1.36).

Conclusions

We derived a supervised machine learning algorithm for AF in a Western Pacific population and demonstrated that higher risk was associated with hospitalisation for other cardio-renal diseases and death. This tool could be used to target interventions to reduce hospitalisation.

Keywords

Atrial fibrillation • Electronic health records • Prediction • Mortality

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Introduction

Atrial fibrillation (AF) is a global epidemic affecting more than 37 million people worldwide [1], and confers an increased risk of stroke, heart failure (HF), renal disease, and death [2]. However, it is estimated that up to 35% of disease burden remains undiagnosed [3]. Accordingly, identifying patients at risk of undiagnosed AF is seen as an important public health issue.

To achieve this prediction, algorithms have been developed and/or validated to identify individuals at risk of AF in the community [4], including through the use of machine learning (Future Innovations in Novel Detection of Atrial Fibrillation [FIND-AF]) [5]. However, FIND-AF was developed in a western Caucasian predominant population, and therefore identification of high-risk Western Pacific patients may be best served by a tool developed using machine learning in this population. Individuals at risk of AF may also be at increased risk of cardio-renal outcomes [6], which may be modifiable through the use of currently available cardio-renal-metabolic pharmacological therapies [7]. Therefore, understanding if high AF risk in Western Pacific patients translate to increased occurrence of cardio-renal outcomes could enable interventions based on AF risk to extend beyond oral anticoagulation for stroke prophylaxis.

We sought to explore if machine learning could be used in Taiwanese routine health data to achieve better AF prediction, and to determine if AF risk was associated with increased cardio-renal events.

Methods

Study Design and Population

The study population was derived from the National Taiwan University Hospital (NTUH) Integrated Medical Database, which contains comprehensive medical records from a tertiary medical centre in Taiwan. Ethical approval for the study was granted by the institutional review board of NTUH, Taiwan (202410100RINA).

Given the higher prevalence of AF in older adults, we included patients aged ≥ 50 years who were diagnosed at NTUH between 1 January 2014 and 31 December 2019. The index date for each outcome was defined as the first recorded diagnosis in the electronic health records (EHRs). The cohort consisted of individuals with at least one outpatient visit or hospitalisation during the study period. Patients with a prior history of AF were excluded. Patients were assumed lost to follow-up if there were no repeat prescriptions or coded outpatient visits between 1 October and 31 December 2019—and were excluded. Patients were followed until their last clinical visit or death.

The cohort was constructed using data from the NTUH Integrated Medical Database, which includes only inpatient and outpatient records from the NTUH main hospital (Taipei branch). Patients who presented only to the

emergency department, with no subsequent healthcare follow-up, for one of our outcomes of interest were not included in this study. Consequently, healthcare encounters from other NTUH branches (e.g., Hsinchu, Yunlin, Jinshan) or external medical institutions were not captured. Patients without diabetes and with diabetes and prescribed a sodium-glucose cotransporter 2 inhibitor (SGLT2i) were included. SGLT2i have been demonstrated to reduce cardio-renal outcomes in meta-analysis of randomised clinical trials [7], and may be protective of incident AF [8]. This analysis is a subsequent analysis of a dataset gathered for a different initial analysis. Additionally, this could be considered a retrospective analysis of this cohort.

Outcome

The primary outcome was incident AF within 5 years, defined by International Classification of Diseases, Tenth Revision (ICD-10) diagnostic codes for AF or atrial flutter or confirmation via a 12-lead electrocardiogram. Secondary outcomes included highly prevalent and morbid diseases, associated with the consequence of AF [2], including: HF hospitalisation, new-onset transient ischaemic attack (TIA) or ischaemic stroke, moderate-to-severe renal impairment, cardiovascular mortality, and overall mortality. AF and HF were considered diagnosed if listed in any of the top three diagnostic positions after discharge. The top three diagnostic positions were selected as this is most likely to represent the principal cause of admission, as later diagnostic conditions could denote comorbid conditions. New-onset stroke/TIA or moderate-to-severe renal impairment were considered in any diagnostic position as this was new to prior coded diagnoses. Mortality events were adjudicated by a central committee and classified as cardiac or non-cardiac causes. Outcomes were identified by ICD-10 diagnostic codes. Mortality data were linked to the mortality registry database.

FIND-AF Algorithm

The original FIND-AF algorithm was developed using primary care EHRs from the United Kingdom (UK) Clinical Practice Research Datalink (CPRD) dataset [5]. CPRD is considered representative of the UK population in terms of age, sex and ethnicity. All adults registered at practices within CPRD who were ≥ 30 years at entry with no history of AF with at least 1 year of follow-up between 2 January 1998 and 30 November 2018 were included. Individuals were censored to a diagnosis of AF, withdrawal from CPRD or 6 months, whichever came first.

The FIND-AF model was a random forest (RF) classifier to determine risk of developing AF in 6 months. RF is a machine learning method consisting of many individual decision trees that operate as an ensemble. To ensure future ability to implement, candidate variables were restricted only to ethnicity and comorbidities. Candidate variables were identified from a prior systematic review, including 72 binary variables and six ethnicity categories [9]. The RF classifier

was trained using 10-fold cross-validation on the full training set [5].

Development of FIND-AF Taiwan Algorithm

Predictor variables

We used the variables identified as important to incident AF in the FIND-AF studies [5,10]. These included age, sex, diabetes mellitus, HF, hypertension, stroke or systemic embolism, ischaemic heart disease, chronic obstructive pulmonary disease, valvular heart disease, chronic kidney disease (CKD), and rheumatoid arthritis. Predictor variables were identified by ICD-10 diagnostic codes.

Timeline Definition and Exposure/Outcome Assignment

Day 0 was defined as the date of first clinical encounter. The index date (day 180) marked the beginning of the observation window, allowing for a 180-day run-in period to exclude early-onset AF cases. This 180-day run-in period was to avoid misclassifying pre-existing AF as incident cases, on the assumption that these cases were likely prevalent. Outcomes (incident AF) and exposures were tracked prospectively from the index date, minimising temporal overlap or misclassification.

Statistical analyses

The baseline characteristics are summarised by incident AF status. Continuous variables were reported as mean $\pm$ standard deviation. Categorical variables were reported as frequencies with corresponding percentages.

The data were partitioned into a training and testing dataset (8:2) using the Mersenne twister pseudorandom number generator. A RF classifier was trained to predict AF at 5 years using the predictor variables using 10-fold cross-validation (FIND-AF-Taiwan). We calculated the mean decrease in Gini coefficients for the variables to determine the weighting of importance in prediction by FIND-AF-Taiwan. Machine learning approaches such as tree-based ensembles can be advantageous over conventional regression approaches as they can accommodate nonlinear relationships and interactions among predictors without prespecifying interaction or higher order terms [11].

We tested the performance of FIND-AF-Taiwan in comparison to the congestive HF, hypertension, age >75 years (two points), diabetes mellitus, stroke/transient ischaemic attack/thromboembolism (two points), vascular disease, age 65–74 years, sex category (CHA₂DS₂-VASc) and coronary artery disease/chronic obstructive pulmonary disease (one point each), hypertension, elderly (age ≥ 75 years, two points), systolic HF, thyroid disease (hyperthyroidism) (C₂HES₂) scores. The CHA₂DS₂-VASc score was originally developed to predict stroke risk in individuals with AF. The C₂HES₂ score for incident AF in Asian people without structural heart disease [9]. These algorithms are robust to

missing data in EHRs as they only require age, sex and comorbidity data.

The area under the receiver operating characteristic curve (AUC) was used to evaluate predictive ability (concordance index) with 95% confidence intervals (CIs) calculated using the DeLong method. Calibration was assessed by plotting predicted AF risk against observed AF incidence and by the calibration slope. We calculated the Brier score, a measure of both discrimination and calibration, by taking the mean squared difference between predicted probabilities and the observed outcome.

Youden's Index was calculated for the FIND-AF-Taiwan algorithm to identify the optimum threshold for differentiating higher and lower risk. We plotted Kaplan–Meier plots for individuals identified as higher and lower FIND-AF-Taiwan predicted risk of AF to assess the hospitalisation rate for HF, stroke, CKD or cardiovascular death and all-cause mortality, censored at 5 years. We calculated the hazard ratio for these outcomes between higher and lower predicted risk of AF using the Cox proportional hazard algorithm. Multivariable Cox proportional hazards models were used to estimate hazard ratios. Adjustments were performed using linear covariate terms, and the proportional hazards assumption was verified using Schoenfeld residuals. A sensitivity analysis was conducted to account for possible ascertainment bias by earlier diagnostic coding leading to an artificially inflated incident risk estimate. This was done by having a period of censoring of 3 months following entry into the study cohort.

We used R version 4.1.0 for all analyses. We followed the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) reporting guideline and the CODE-EHR best-practice framework for using structured electronic healthcare records in clinical research [12].

Results

Patient Population and Baseline Characteristics

The initial population with at least one healthcare encounter between 2014 and 2019, totalling 174,835 (comprising 100,000 patients without diabetes, and 74,835 with diabetes receiving at least SGLT2i as treatment) were included. Patients with only emergency department records (n=3,494) were excluded to ensure adequate follow-up potential and completeness of data. Among patients with at least one outpatient or inpatient visit (n=171,341) and 1 year of follow-up, the following were excluded: follow-up duration less than 365 days (i.e., from first to last clinical visit) (n=64,304); developed AF within the initial 180 days after the first visit (n=3,716), to avoid inclusion of prevalent AF cases. This led to a final cohort of 103,321 patients who attended NTUH between 2014 and 2019 (Supplementary Figure 1). The average age of the cohort was 64.5 $\pm$ 10.5 years, with 51.3% of the participants being women. Over 5 years of follow-up, 4,544 (4.4%) had incident AF. Those who

Table 1 Baseline characteristics of the analytical cohort with and without atrial fibrillation (total n=103,321).

	Full cohort n=103,321	No incident AF n=98,777 (95.6%)	Incident AF n=4,544 (4.4%)	p-value
<i>Demographics</i>				
Age, years (SD)	64.5±10.5	64.1±10.4	72.5±10.6	<0.001
Sex, female (%)	54,839 (51.3)	52,884 (53.5)	1,955 (43.0)	<0.001
<i>Comorbidities</i>				
Diabetes mellitus (%)	53,048 (51.3)	49,885 (50.5)	3,163 (69.6)	<0.001
Stroke or TIA (%)	5,534 (5.4)	4,732 (4.8)	802 (17.6)	<0.001
Ischaemic heart disease (%)	22,049 (21.3)	19,929 (20.2)	2,120 (46.7)	<0.001
Hypertension (%)	47,365 (45.8)	44,101 (44.6)	264 (71.8)	<0.001
Heart failure (%)	2,445 (2.4)	1,619 (1.2)	826 (18.2)	<0.001
COPD (%)	6,532 (6.3)	5,851 (5.9)	681 (15.0)	<0.001
Chronic kidney (%) disease	3,523 (3.4)	3,052 (3.1)	471 (10.4)	<0.001
Valvular heart disease (%)	3,124 (3.0)	2,534 (2.6)	590 (13.0)	<0.001
Rheumatoid arthritis (%)	635 (0.6)	603 (0.6)	32 (0.7)	0.488
Hyperthyroidism (%)	4,645 (4.5)	4,396 (4.5)	249 (5.5)	0.001

Abbreviations: AF, atrial fibrillation; SD, standard deviation; TIA, transient ischaemic attack; COPD, chronic obstructive pulmonary disease.

developed AF were older, more commonly men, and had a higher prevalence of baseline comorbidities than those who did not develop AF (Table 1).

Prediction Factors and Algorithm Accuracy

According to mean decrease in the Gini coefficient, age and HF contributed the most to the prediction (both weighted importance >250) of AF by FIND-AF-Taiwan followed by valvular heart disease and ischaemic heart disease (Figure 1).

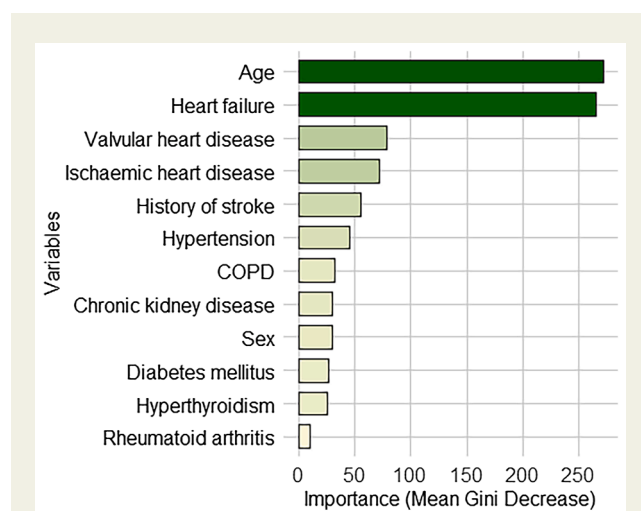


Figure 1 The importance of variables for FIND-AF-Taiwan ranked by mean decrease in Gini coefficient. Abbreviations: COPD, chronic obstructive pulmonary disease; FIND-AF, Future Innovations in Novel Detection of Atrial Fibrillation.

AF discrimination and accuracy of predictions, by area under received operating characteristic (AUROC) and Brier scores, were better using FIND-AF-Taiwan than the CHA₂DS₂-VASc and C₂HEST algorithms (Table 2, Figure 2). Sensitivity was highest for CHA₂DS₂-VASc, but specificity was lowest (Table 2). Of the algorithms, FIND-AF-Taiwan was the best calibrated (calibration slope 1.022 [95% CI 0.986–1.057]) (Supplementary Figures 2–5). FIND-AF-Taiwan discrimination performance was best in both men and women in sex-stratified analysis, and performance was better in women than men (a pattern also seen for CHA₂DS₂-VASc and C₂HEST) (Supplementary Table 1). FIND-AF-Taiwan also performed best when applied to both older-individual cohorts. For those aged ≥65 years or ≥75 years, FIND-AF-Taiwan performed best (AUROC 0.744; 95% CI 0.724–0.764 and AUROC 0.701; 95% CI 0.672–0.731; respectively) when compared to both C₂HEST and CHA₂DS₂-VASc (Supplementary Table 2).

Association of Predicted AF Risk and Cardio-Renal Events and Death

According to the Youden Index, the optimal cut off was 0.039, which led to the sensitivity of 0.735 (0.705–0.763) and specificity of 0.693 (0.656–0.699) for FIND-AF-Taiwan (Table 2). The incidence rate of AF for the higher-risk cohort was 5.7-fold higher than the lower risk cohort (12.5% vs 2.2%).

Higher FIND-AF-Taiwan risk was associated with increased occurrence of the prespecified outcomes (HF hospitalisations, stroke/TIA, moderate-to-severe CKD, both all-cause and cardiovascular mortality) at 5 years of follow-up (Table 3). Relative to individuals at lower risk, those

Table 2 Performance for 5-year incident AF with optimal threshold determined by Youden Index.

	Algorithm		
	FIND-AF-Taiwan	CHA ₂ DS ₂ -VASc	C ₂ HEST
AUROC (95% CI)	0.792 (0.777–0.807)	0.737 (0.721–0.754)	0.750 (0.733–0.766)
Calibration slope ^a	1.022 (0.986–1.057)	0.972 (0.930–1.014)	0.951 (0.913–0.989)
Brier score	0.0381	0.0400	0.0394
Sensitivity	0.735 (0.705–0.763)	0.784 (0.756–0.810)	0.685 (0.654–0.715)
Specificity	0.693 (0.656–0.699)	0.564 (0.557–0.571)	0.692 (0.686–0.699)

^aCalibration slope was derived from linear regression models by forcing the intercept through origin (0,0).

Abbreviations: AF, atrial fibrillation; FIND-AF, Future Innovations in Novel Detection of Atrial Fibrillation; CHA₂DS₂-VASc, congestive heart failure, hypertension, age >75 years (two points), diabetes mellitus, stroke/transient ischaemic attack/thromboembolism (2 points), vascular disease, age 65–74 years, sex category; C₂HEST, coronary artery disease/chronic obstructive pulmonary disease (one point each), hypertension, elderly (age ≥75 years, two points), systolic heart failure, thyroid disease (hyperthyroidism); AUROC, area under the receiver operating characteristic curve; CI, confidence interval.

with higher risk had 49-fold increased hazard for HF hospitalisation (unadjusted hazard ratio [HR] 49.2; 95% CI 31.1–77.8) for, 17-fold increased hazard for TIA or ischaemic stroke (17.2; 95% CI 13.6–21.8), four-fold increased hazard of progression to moderate or severe CKD (4.0; 95% CI

3.8–4.2), six-fold increased hazard of cardiovascular death (6.40; 95% CI 4.86–8.41), and three-fold increased hazard for death of any cause (3.2; 95% CI 2.95–3.47) (Figure 3).

After adjustment for age, sex, and comorbidities higher FIND-AF-Taiwan risk was still associated with at increased hazard across outcomes including 15-fold (15.32; 95% CI 9.19–25.54) for HF hospitalisation, 28-fold (28.4; 95% CI 21.01–38.47) for TIA or ischaemic stroke, 1.2-fold (1.18; 95% CI 1.09–1.27) for moderate-to-severe CKD and 1.3-fold 1.33; 95% CI 0.88–2.01) for cardiovascular death and 1.2 fold (1.21; 95% CI 1.07–1.38) for all-cause death (Table 4).

The proportional hazards assumption was not violated for HF, TIA/stroke, and cardiac death. Mild time-varying effects were noted for CKD and all-cause death, but the associations remained directionally consistent over time.

Sensitivity Analysis

After censoring events for the first 3 months after entry into the cohort, Higher FIND-AF-Taiwan risk was associated with increased occurrence of the prespecified outcomes (HF hospitalisations, stroke/TIA, moderate-to-severe CKD, both all-cause and cardiovascular mortality) at 5 years of follow-up (Supplementary Table 3). Relative to individuals at lower risk, those with higher risk had 51-fold increased hazard for HF hospitalisation (unadjusted HR 51.17; 95% CI 31.04–84.37) for, 12-fold increased hazard for TIA or ischaemic stroke (12.35; 95% CI 8.97–17.00), 2.7-fold increased hazard of progression to moderate or severe CKD (2.72; 95% CI 2.57–2.89), six-fold increased hazard of cardiovascular death (6.21; 95% CI 4.69–8.21), and three-fold increased hazard for death of any cause (3.30; 95% CI 3.03–3.58) (Supplementary Figure 5).

After censoring events for the first 3 months after entry into the cohort and adjustment for age, sex, and comorbidities higher FIND-AF-Taiwan risk was still associated with at increased hazard across outcomes including 17-fold (17.82; 95% CI 10.23–31.05) for HF hospitalisation, 17-fold (17.23; 95% CI 11.18–26.54) for TIA or ischaemic stroke,

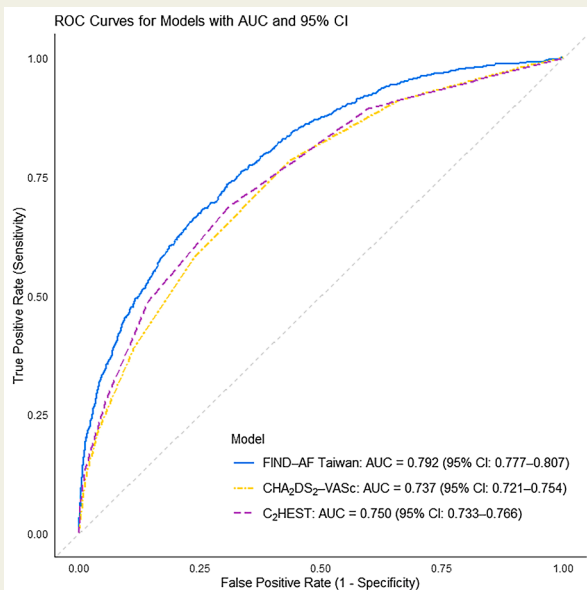


Figure 2 Receiver operating characteristic curves for FIND-AF-Taiwan, CHA₂DS₂-VASc, C₂HEST, and FIND-AF algorithms.

Abbreviations: C₂HEST, coronary artery disease/chronic obstructive pulmonary disease (one point each), hypertension, elderly (age ≥75 years, two points), systolic heart failure, thyroid disease (hyperthyroidism); CHA₂DS₂-VASc, congestive heart failure, hypertension, age >75 years (two points), diabetes mellitus, stroke/transient ischaemic attack/thromboembolism (two points), vascular disease, age 65–74 years, sex category; CI, confidence interval; FIND-AF, Future Innovations in Novel Detection of Atrial Fibrillation.

Table 3 Cumulative incidence of cardio-renal outcomes stratified by FIND-AF Taiwan risk.

Cumulative incidence, 95% CI (per 1,000 persons)				
Outcome	Predicted lower risk		Predicted higher risk	
	1 year	5 years	1 year	5 years
AF	4.09 (3.10–5.30)	17.30 (15.20–19.61)	25.09 (21.49–29.11)	99.03 (92.00–106.42)
HF hospitalisation	0.36 (0.12–0.84)	1.29 (0.77–2.04)	22.57 (19.16–26.40)	65.78 (59.97–71.96)
Moderate-to-severe CKD	105.04 (100.00–110.25)	211.95 (205.18–218.83)	411.88 (400.09–423.74)	603.71 (591.91–615.42)
Stroke/TIA	3.52 (2.60–4.65)	5.67 (4.49–7.06)	68.60 (62.67–74.90)	94.43 (87.55–101.67)
Cardiovascular mortality	0.72 (0.34–1.32)	4.96 (3.86–6.27)	5.37 (3.77–7.43)	29.56 (25.63–33.90)
All-cause mortality	16.10 (14.07–18.33)	71.28 (67.06–75.69)	38.51 (34.03–43.40)	211.97 (202.24–221.96)

Abbreviations: AF, atrial fibrillation; CI, confidence interval; CKD, chronic kidney disease; FIND-AF, Future Innovations in Novel Detection of Atrial Fibrillation; HF, heart failure; TIA, transient ischaemic attack.

1.0-fold (1.02; 95% CI 0.96–1.16) for moderate-to-severe CKD and 1.3-fold (1.36; 95% CI 0.90–2.07) for cardiovascular death and 1.2 fold (1.23; 95% CI 1.08–1.41) for all-cause death (Supplementary Table 3).

Discussion

This study has three key findings. First, the FIND-AF-Taiwan algorithm outperforms other recognised algorithms (CHA₂DS₂-VASc and C₂HES₂) for the prediction of incident AF. Second, individuals at higher AF risk were at high risk of subsequent hospital attendances with cardio-renal-metabolic diseases beyond AF. Third, after adjustment for variables contained in the newly developed algorithm, individuals were still at an increased risk of adverse events which suggests that there are underlying changes and interactions identified by the algorithm beyond the number of comorbidities.

Identifying patients at higher risk of incident AF, who are subsequently screened and diagnosed with AF earlier in the disease course, enables clinicians to decide on anti-coagulation earlier and potentially avoid ischaemic strokes, alongside other cardiovascular diseases as a consequence of AF [13,14]. The STROKESTOP II trial (Randomized Invitation to Systematic NT-proBNP and ECG Screening in 75-Year-Olds to Detect Atrial Fibrillation) investigated B-type natriuretic peptide-guided AF screening in older patients; however, this adds expense and inconvenience [15]. The advantage of this algorithm is that it can run cheaply, avoids unnecessary patient journeys or tests, and is fully implementable using routinely collected healthcare data. This could prove to be the additional step required to ensure that AF detected earlier improves clinical outcomes [13].

Additionally, we found that higher predicted AF risk was associated with cardio-renal outcomes beyond AF. This is not surprising as predictors within the FIND-AF-Taiwan

model are independently associated with these outcomes. Therefore, it is difficult to distinguish whether AF is a precursor condition or not, as lifestyle, smoking, obesity, hypertension and diabetes mellitus are shared risk factors for development of all investigated outcomes in this study. However, considering that these findings are mirrored across other studies—it is likely that AF lies on a cardio-renal-metabolic-pulmonary morbidity axis and that risk of one disease is associated with increased risk of other diseases [6]. FIND-AF-Taiwan could be used in Western Pacific hospital data to identify higher-risk individuals for a targeted multi-component intervention beyond screening for AF. Prospective studies could identify the proportion of patients eligible for pharmacological interventions that are protective of AF and cardio-renal outcomes, such as SGLT2i [7,8]. A prospective randomised clinical trial could then test a targeted intervention for higher-risk individuals to determine if there is a benefit for cardiovascular outcomes. Importantly the algorithm is not limited by missing data due to the variables included and so it could be translated to clinical records systems if the requisite data architecture is available.

CKD and stroke/TIA outcomes were found to occur earlier than other conditions in the cardio-renal-metabolic-pulmonary axis. This could in part be explained by higher-intensity healthcare utilisation and more regular follow-up visits (e.g., nephrology or neurology clinics), which increases the likelihood of early diagnostic coding. This may create an apparent earlier onset of these events. Furthermore, stroke/TIA and CKD outcomes were included in any diagnostic position (as opposed to HF and AF outcomes) which might further explain an apparent earlier onset of events. Our sensitivity analysis with censoring of events within the first 3 months of entering the study cohort produced similar findings. Additionally, there was a lower-than-expected rate of cardiovascular death in this study. In Taiwan, cause-of-death registration is often limited by

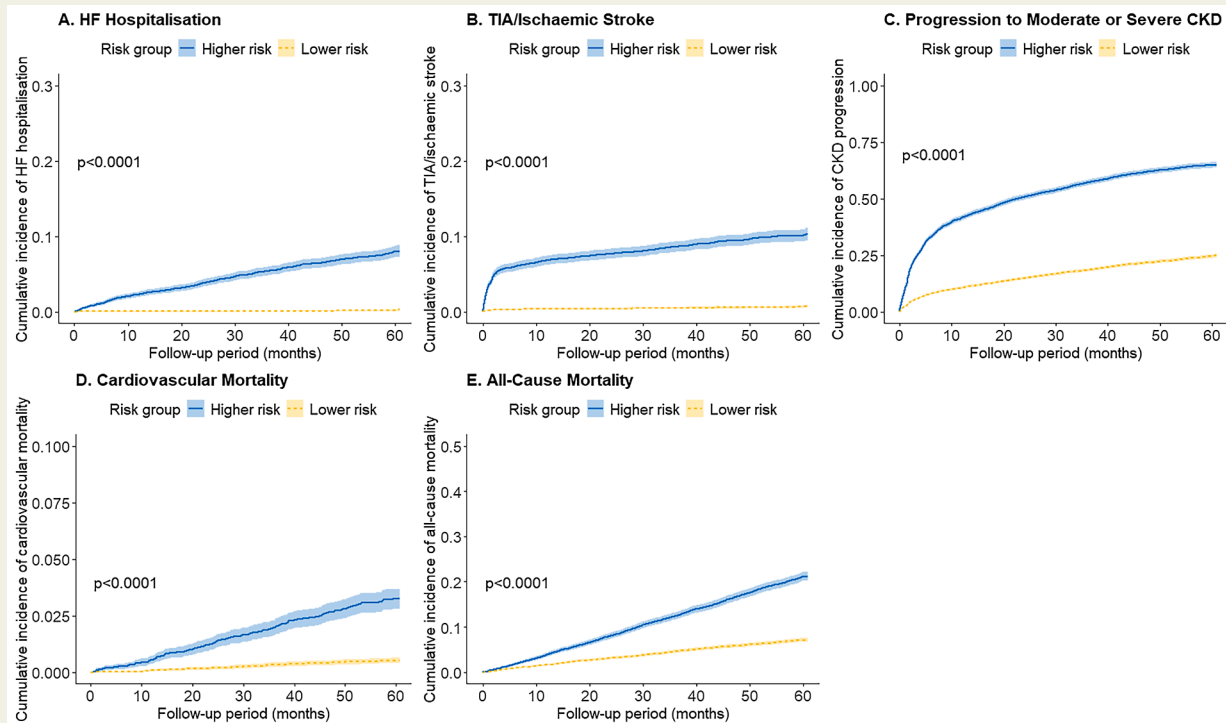


Figure 3 Kaplan–Meier plots for hospitalisation for HF, cardio–renal events, and death, by predicted AF risk from FIND-AF-Taiwan.

Abbreviations: AF, atrial fibrillation; HF, heart failure; FIND-AF, Future Innovations in Novel Detection of Atrial Fibrillation.

the subjective reporting of physicians and the simplification of ICD coding. Certain cardiovascular deaths, such as sudden cardiac death or aortic dissection, may be misclassified under other categories, such as “unspecified causes.” Additionally, while institutional death reports (e.g., NTUH’s internal mortality records) may classify cardiovascular deaths based on five cause-of-death keyword fields—including terms like “hypertension”—the national death registry does not categorise hypertensive diseases as cardiovascular deaths. This discrepancy may contribute to an underestimation of cardiovascular death in our dataset.

There are some limitations to our study. First, the NTUH database is routinely collected, retrospective primary care data and an underestimation of incidence of outcomes in this study is possible, as the cohort is based on administrative data collected in the Taipei branch only. This limitation may affect the completeness of outcome ascertainment, particularly for events such as AF diagnosis or cardiovascular death that may occur outside the main hospital system. Second, it is possible that AF risk is associated with increased risk of diseases outside of those we investigated (for example, different cancers). Here we sought to assess association with diseases where there was an underlying pathophysiological rationale and available

treatment options [2], rather than take a data-driven approach. Third, this study was based in Taiwan. In order to achieve a similar purpose in another geographic location, a version of FIND-AF may have to be re-trained on local data. This would limit the external validity of this algorithm when further expanded to other Western Pacific populations. This algorithm should undergo further external validation in an independent Taiwan-specific, or another independent Western Pacific dataset. Fourth, ICD-10 codes do not capture ejection fraction and so we could not distinguish between different HF subtypes. However, it is established that all subtypes of HF are associated with an increased mortality risk [16]. Fifth, there are other AF prediction algorithms that were not compared against, such as the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) AF score [17]. However, these other risk scores often require data variables that are not regularly completed in EHRs. An external validation study in the Netherlands found that CHARGE-AF could only be utilised in 17.2% of the population [18]. Therefore, we chose risk scores that are shown to have a high completeness in EHRs to enable meaningful comparison with FIND-AF Taiwan. Sixth, we included patients without diabetes, and those with diabetes and prescribed a SGLT2i. Though this is relevant to prediction and prevention of incident AF and

Table 4 Cox Regression for cardio-renal outcomes between high- and low-risk individuals in the hold-out testing dataset of the analytical cohort.

	Algorithm 1 (unadjusted) ^a	p-value	Algorithm 2 (adjusted age, sex comorbidities) ^b	p-value
	HR (95% CI)		HR (95% CI)	
HF hospitalisation, event n=463				
Lower risk	1		1	
Higher risk	49.17 (31.07–77.83)	<0.001	15.32 (9.19–25.54)	<0.001
TIA/ischaemic stroke, event n=718				
Lower risk	1		1	
Higher risk	17.24 (13.66–21.75)	<0.001	28.42 (21.01–38.47)	<0.001
Moderate-to-severe CKD; event n=7,026				
Lower risk	1		1	
Higher risk	4.01 (3.83–4.21)	<0.001	1.18 (1.09–1.27)	<0.001
Cardiovascular mortality, event n=269				
Lower risk	1		1	
Higher risk	6.40 (4.86–8.41)	<0.001	1.33 (0.88–2.01)	0.185
All-cause mortality, event n=3,714				
Lower risk	1		1	
Higher risk	3.20 (2.95–3.47)	<0.001	1.21 (1.07–1.38)	<0.001

^aCrude algorithm.^bAdjust age, sex, hypertension, diabetes mellitus, ischaemic heart disease, chronic obstructive pulmonary disease, valvular heart disease, hyperthyroidism. Abbreviations: CI, confidence interval; CKD, chronic kidney disease; HF, heart failure; HR, hazard ratio; TIA, transient ischaemic attack.

cardio-renal outcomes, it does not represent an all-comer population, and FIND-AF-Taiwan may perform differently in populations with a lower prevalence of diabetes.

Conclusions

To our knowledge, we derived the first supervised machine learning algorithm for incident AF and demonstrated that higher predicted AF risk was associated with hospitalisation for other cardio-renal-metabolic diseases and death. Importantly this algorithm is accurate in a Western Pacific population and affords the opportunity to intervene in high-risk people with diagnostics and prevention strategies to reduce hospitalisation and death.

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Declaration of Competing Interests

C.P.G. has received grants for research from British Heart Foundation, National Institute for Health Research, Horizon 2020, Abbott Diabetes, Bristol Myers Squibb and European Society of Cardiology; consulting fees from AstraZeneca, Bayer, Bristol Myers Squibb, Boehringer-Ingelheim, Boston Scientific, Chiesi, Daiichi Sankyo, Menarini and Organon; honoraria for speaking at meetings and educational events from AstraZeneca, Menarini, Novartis, Raisio Group, Wondr Medical, and Zydus; support for attending meetings from Bayer and Bristol Myers Squibb; and has acted as an advisory board member for Amgen, AstraZeneca, Bayer, Bristol Myers Squibb, Boehringer-Ingelheim, Chiesi, Daiichi Sankyo, Menarini, Novartis, and iRhythm. All other authors declare no competing interests, or activities that could appear to have influenced the submitted work.

Author Contributions

R.N. conceived the idea of the study. J.C.H. undertook data extraction and J.C.H. and C.J.H. undertook statistical analysis. R.N. and J.C.H. interpreted the findings and drafted the manuscript. T.J. helped further draft the manuscript. C.J.H. critically reviewed the manuscript, and R.N. revised the manuscript for final submission. All authors accept responsibility to submit for publication.

Data Availability

Data may be available from the corresponding author upon reasonable request.

Appendices

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.hlc.2026.03.062>

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