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A Simple Clinical Risk Score (C_2HEST) for Predicting Incident Atrial Fibrillation in Asian Subjects

Derivation in 471,446 Chinese Subjects, With Internal Validation and External Application in 451,199 Korean Subjects

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BACKGROUND: The incidence of atrial fibrillation (AF) is increasing, conferring a major health-care issue in Asia. No risk score for predicting incident AF has been specifically developed in Asian subjects. Our aim was to investigate risk factors for incident AF in Asian subjects and to combine them into a simple clinical risk score.

METHODS: Risk factors for incident AF were analyzed in 471,446 subjects from the Chinese Yunnan Insurance Database (internal derivation cohort) and then combined into a simple clinical risk score. External application of the new score was performed in 451,199 subjects from the Korean National Health Insurance Service (external cohort).

RESULTS: In the internal cohort, structural heart disease (SHD), heart failure (HF), age ≥ 75 years, coronary artery disease (CAD), hyperthyroidism, COPD, and hypertension were associated with incident AF. Given the low prevalence and the strong association of SHD with incident AF (hazard ratio, 26.07; 95% CI, 18.22-37.30; $P < .001$), these patients should be independently considered as high risk for AF and were excluded from the analysis. The remaining predictors were combined into the new simple C_2HEST score: C_2: CAD/COPD (1 point each); H: hypertension (1 point); E: elderly (age ≥ 75 years, 2 points); S: systolic HF (2 points); and T: thyroid disease (hyperthyroidism, 1 point). The C_2HEST score showed good discrimination with the area under the curve (AUC) of 0.75 (95% CI, 0.73-0.77) and had good calibration ($P = .774$). The score was internally validated by bootstrap sampling procedure, giving an AUC of 0.75 (95% CI, 0.73-0.77). External application gave an AUC of 0.65 (95% CI, 0.65-0.66). The C_2HEST score was superior to $CHADS_2$ and CHA_2DS_2-VASc scores in both cohorts in predicting incident AF.

CONCLUSIONS: We have developed and validated the C_2HEST score as a simple clinical tool to assess the individual risk of developing AF in the Asian population without SHD.

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KEY WORDS: Asian; atrial fibrillation; cohort study; prediction model; risk factors; risk score

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Atrial fibrillation (AF) is the most prevalent arrhythmia worldwide and is associated with an increased risk of ischemic stroke (IS), heart failure (HF), coronary artery disease (CAD), and mortality.[1-3] The 2010 Global Burden of Disease Study[4] demonstrated that the worldwide age-adjusted prevalence of AF is 596 per 100,000 men and 373 per 100,000 women. The incidence of AF increases dramatically with the development of incident risk factors for AF, such as ageing, hypertension, HF, CAD, and COPD. Indeed, this arrhythmia confers a major health-care burden in Asia. For example, Japan will have 1 million patients with AF and China will have 9 million patients with AF by 2050.[5,6]

Given that many patients with incident AF are asymptomatic, a considerable number of patients are only diagnosed with AF when presenting with AF-related complications. Because of this underdiagnosis, the actual prevalence of AF could be considerably higher.[7,8] Hence, risk evaluation and early identification would be important for the targeting of early prevention strategies and improve prognosis.[9,10] Therefore, effective and cost-effective strategies should focus on identifying patients who are at higher risk of incident AF.

Several clinical risk scores have been developed to predict incident AF, including the Framingham Heart Study (FHS) score,[11] the Atherosclerosis Risk In Communities Study (ARIC) score,[12] and the Cohorts for Heart and Aging Research in Genomic Epidemiology-Atrial Fibrillation (CHARGE-AF) score.[13] These three scoring systems were all derived from large follow-up cohorts and have good predictive ability for incident AF.[11-13] However, they require many instrumental and laboratory variables to be calculated, being generally too complicated for everyday clinical application. Moreover, many of the previous scores were derived in Western populations, and a predictive score for incident AF in an Asian population has been never been developed. This is relevant, given that risk factors for AF may be different between Western and Asian populations.[14,15]

Our primary objective was to analyze risk factors for incident AF in a large cohort of Asian subjects, which were combined into a simple clinical risk stratification score, which would be easy and practical to apply in everyday practice.

Methods

Derivation Cohort

Details of the derivation database, the Yunnan Medical Insurance Database, have been described previously.[16] In brief, this is a medical insurance database in Yunnan Province, China, including > 10 million individuals from January 1, 2001, through December 30, 2012.[16] This medical insurance scheme covers urban residents in Yunnan Province, located in the far southwest of China, spanning approximately 394,000 km² and with a population of 46.3 million (2011 population statistics), representing 3% of the total Chinese population. It was part of a governmental medical insurance plan, ensuring all participants had a permanent and personal registration number, through which the information of medical history, drugs, and mortality data recorded could be collected. All medical information of participants was obtained from local 2A- and 3A-grade hospitals, which guaranteed the reliability of records regarding any medical service. Random sampling was performed on the enrolled individuals biennially, based on the periods of 2001 to 2002, 2003 to 2004, 2005 to 2006, 2007 to 2008, 2009 to 2010, and 2011 to 2012. A total of 1,228,539 people was selected. After excluding people with incomplete data (n = 2,611), readmission (n = 754,582), and prevalent AF at baseline (n = 30), 471,446 cases were entered in the final analysis.[16]

This derivation study was approved by the medical ethics committee of Chinese People's Liberation Army General Hospital (approval No. 13BJZ40). The definitions of AF and other risk factors were according to the *International Classification of Diseases, Ninth Revision/International Classification of Diseases, 10th Revision* (ICD-10) (e-Appendix 1). AF was defined based on an ECG or Holter recording. The inclusion criteria for an AF case were limited to inpatients with AF diagnosis confirmed on admission and discharge. The accuracy of AF diagnosis was validated previously using sensitivity analysis.[16]

Patients with paroxysmal AF were also included in the incident analysis. Patients with rheumatic heart disease were those who suffered from rheumatic fever and concomitant valvular heart disease (ie, mitral stenosis). Patients with structural heart disease (SHD) included those patients with rheumatic heart disease and dilated cardiomyopathy.

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External Application

The external cohort study was based on the Korean National Health Insurance Service (NHIS)-Health Screening cohort released in 2015, including subjects who participated in health screening programs provided by the NHIS in the Republic of Korea in 2002 and 2003. This external cohort consisted of 514,764 Korean subjects 40 to 80 years of age, who comprised a 10% simple random sample of all health screening participants. A total of 55.3% of the participants lived in nonmetropolitan areas, which covers some urban areas and all rural areas. The follow-up started from 2002 through 2013, with a mean duration of 87.3 ± 17.6 months. Detailed information and a profile of the NHIS-Health Screening cohort have been described in a previous report.[17] The baseline demographics for this external cohort are summarized in e-Table 1.

This study was approved by the institutional review board of Yonsei University Health System, and the informed consents were waived. We excluded the following subjects: (1) those diagnosed with AF before conducting the health check-ups (n = 5,019); (2) those with valvular heart disease (n = 935; with a diagnosis of mitral stenosis [ICD-10: I05.0, I05.2, and I34.2] or prosthetic heart valves [ICD-10: Z95.2-Z95.4], and insurance claims for valve replacement or valvuloplasty); and (3) those with cardiomyopathy (n = 357) (ICD-10: I42.0-I42.2). Finally, a population cohort of 451,199 patients was included for this analysis. Patients were defined as having incident AF (1) if there was a discharge diagnosis of AF for inpatients with no prior history of AF or (2) when an episode of AF was detected in an outpatient and confirmed by a specialist. This strategy of AF diagnosis has previously been validated in the NHIS database with a positive predictive value of 94.1%.[18,19]

Statistical Analysis

Continuous variables were reported as mean with SD, and categorical variables were expressed as number of patients (%). Annual incident rates were defined as the number of patients with incident AF divided by the number of person-years free of AF within a 1-year period.

Multivariable Cox regression analysis was used to identify independent risk factors for incident AF over 11 years of follow-up (mean ± SD, 4.1 ± 3.5 years) in the derivation cohort. The new predictive score was obtained with a stepwise model selection procedure based on Akaike information criterion. The pool of variables was also confirmed by a removal approach with a P value threshold of 10%. Risk factors in the final model were tested for interaction, but no further improvement was possible by including interactions.

The score was evaluated by means of the time-dependent (at follow-up at 11 years) area under the curve (AUC) for the receiver operating characteristic curve for predicting incident AF. Internal validation was obtained by means of 1,000 bootstrap replicates, and calibration was assessed by means of the Gronnesby and Borgan test.[20] Performance of the external application was also evaluated as the AUC in the whole Korean cohort.

The Kaplan-Meier curves were computed to present the survival rates free from AF during follow-up, after dividing patients into 3 groups (low-, medium-, and high-risk) according to the new score.

Given that the $CHADS_2$ (congestive HF, hypertension, age >75, diabetes mellitus, prior stroke or transient ischemic attack [2 points]), CHA_2DS_2-VASc (congestive HF, hypertension, age ≥75 [2 points], stroke/transient ischemic attack/thromboembolism [2 points], vascular disease, age 65-74, sex category), and HATCH (hypertension, age ≥75, transient ischemic attack or stroke [2 points], COPD, HF [2 point]) scores have been previously reported to be associated with incident AF,[21-23] we also performed an exploratory analysis to investigate how the C_2HEST score compares against these scores.

TABLE 1] Baseline Characteristics of 471,446 Subjects Included in the Internal Validation Cohort

Characteristics	Subjects Without AF (n = 470,525)	Subjects With Incident AF (n = 921)	P Value
Age, y	47 ± 16	62 ± 12	< .001
Male sex	247,752 (52.7)	574 (62.3)	< .001
Medical history			
Hypertension	45,444 (9.7)	236 (25.6)	< .001
Diabetes	18,900 (4.0)	29 (3.1)	.180
CAD	14,813 (3.1)	187 (20.3)	< .001
Hyperlipidemia	6,610 (1.4)	17 (1.9)	.198
Vascular disease	6,003 (1.3)	9 (1.0)	.486
COPD	1,687 (0.4)	25 (2.7)	< .001
Previous IS	1,608 (0.3)	7 (0.8)	.023
Renal dysfunction	1,423 (0.3)	8 (0.9)	.002
Hyperthyroidism	971 (0.2)	5 (0.5)	.025
HF	700 (0.1)	43 (4.7)	< .001
SHD	401 (0.1)	33 (3.6)	< .001
Hypothyroidism	203 (0.0)	1 (0.1)	.340
CHA_2DS_2VASc score	1 (0-1)	2 (1-3)	< .001

Values are mean ± SD, No. (%), median (interquartile range), or as otherwise indicated. AF = atrial fibrillation; CAD = coronary artery disease; HF = heart failure; IS = ischemic stroke; SHD = structural heart disease.

Results

Baseline characteristics of the derivation cohort are presented in Table 1. A total of 471,446 subjects were included in the final analysis, of whom 921 subjects developed AF during 11 years of follow-up (mean ± SD, 4.1 ± 3.5 years), with an incidence of 0.5 per 1,000 person-years. Compared with subjects without AF, patients who developed AF were older ($P < .001$), more frequently men ($P < .001$), and with higher rates of hypertension, CAD, COPD, previous IS, renal dysfunction, hyperthyroidism, HF, and SHD ($P < .001$, for all).

Risk Factors for Incident AF and Score Development

Univariate Cox regression analysis is shown in Table 2. On multivariable analysis, SHD, HF, age ≥ 75 years, CAD, hyperthyroidism, COPD, and hypertension were independent risk factors for incident AF (Table 2). Given the low prevalence and very strong association of SHD with incident AF (hazard ratio [HR], 26.07; 95% CI, 18.22-37.30; $P < .001$), this subgroup of patients should be considered as being at (very) high risk for incident AF independently from other risk factors. Therefore, this variable was not considered to build the score. The HRs of other independent risk factors for incident AF did not change after removal of SHD from the multivariable model (not shown).

We combined these risk factors into the new simple C_2HEST score (Table 3): C_2: CAD/COPD (1 point each); H: hypertension (1 point); E: elderly (age ≥ 75 years, 2 points); S: systolic HF (2 points); and T: thyroid disease (hyperthyroidism, 1 point). Total score ranged from 0 to 8 points.

The score showed a good discrimination with an AUC of 0.750 (95% CI, 0.730-0.771) (Fig 1A) and a good calibration ($P = .774$). The score was then internally validated by a bootstrap sampling procedure, which gave an AUC of 0.749 (95% CI, 0.729-0.769).

When applied to the external cohort, the score showed moderate discrimination with an AUC of 0.654 (95% CI, 0.649-0.659) (Fig 1B).

Incident Rates of AF and the C_2HEST Score

Table 4 shows incidence rates (IRs) and HRs at each point of the C_2HEST score. We divided patients in the derivation cohort into three groups according to the C_2HEST score: low (0-1 points, IR 0.34%/year), medium (2-3 points, IR 2.60%/year), and high risk (> 3 points, IR 15.98%/year). Kaplan-Meier curves

TABLE 2] HRs of Risk Factors for Incident Atrial Fibrillation

Risk Factors	Univariable Analysis			Multivariable Analysis		
	HR	95% CI	P Value	HR	95% CI	P Value
SHD	39.00	27.6-55.2	< .001	26.1	18.2-37.3	< .001
HF	34.66	25.5-47.1	< .001	7.95	5.76-11.0	< .001
Age ≥ 75 y	8.24	6.80-9.98	< .001	5.83	4.80-7.09	< .001
CAD	7.01	5.97-8.23	< .001	4.14	3.50-4.90	< .001
Hyperthyroidism	2.06	0.85-4.96	.107	3.20	1.33-7.71	.010
COPD	6.81	4.57-10.1	< .001	3.01	1.33-7.71	< .001
Hypertension	4.63	4.05-5.29	< .001	3.24	2.82-3.73	< .001
Renal dysfunction	2.91	1.45-5.83	.003	...	...	...
Previous IS	2.13	1.01-4.49	.046	...	...	...
Hyperlipidemia	1.12	0.71-1.79	.620	...	...	...
Male	1.22	1.07-1.40	.003	...	...	...
Hypothyroidism	1.79	0.25-12.7	.561	...	...	...
Diabetes	0.61	0.42-0.89	.009	...	...	...
Vascular disease	1.36	0.38-1.41	.355	...	...	...

HR = hazard ratio. See Table 1 legend for expansion of other abbreviations.

TABLE 3] C₂HEST Score for Incident Atrial Fibrillation

Acronym	Risk Factor	Points
C_2	CAD/COPD	1-2
H	Hypertension	1
E	Elderly (age ≥ 75 y)	2
S	Systolic HF	2
T	Thyroid disease (hyperthyroidism)	1
	Total points	0-8
	AUC (C index)	**95% CI**
C_2HEST score	0.749	0.729-0.769

AUC = area under the curve. See Table 1 legend for expansion of other abbreviations.

for risk categories (Fig 2) showed an increased risk of AF across the three groups (log-rank test $P < .001$).

Comparison of the C₂HEST Score With the CHADS₂, CHA₂DS₂-VASc, and HATCH Scores

Based on time-dependent prognostic models, the C_2HEST score had significantly better predictivity for incident AF compared with the $CHADS_2$, CHA_2DS_2-VASc, and HATCH scores in the derivation cohort from China (AUC $CHADS_2$, 0.632; 95% CI, 0.604-0.660; $P < .001$ vs C_2HEST; AUC CHA_2DS_2-VASc, 0.687; 95% CI, 0.659-0.716; $P < .001$ vs C_2HEST; AUC HATCH, 0.633; 95% CI, 0.598-0.667; $P < .001$ vs C_2HEST).

In the external cohort from Korea, the C_2HEST score also had significantly better predictivity for incident AF compared with the $CHADS_2$ and CHA_2DS_2-VASc scores (AUC $CHADS_2$, 0.637; 95% CI, 0.632-0.642; $P < .001$ vs C_2HEST; AUC CHA_2DS_2-VASc, 0.637; 95% CI, 0.632-0.642; $P < .001$ vs C_2HEST).

However, this difference was only marginally significant for the HATCH score (AUC HATCH, 0.646; 95% CI, 0.641-0.651; $P = .059$ vs C_2HEST).

Discussion

To our knowledge, this is the largest cohort study from an Asian population aimed at developing a simple risk assessment tool for incident AF. We investigated risk factors for incident AF and derived and validated the new C_2HEST score as a user-friendly clinical score to assess individual risk of developing incident AF.

In the multivariable analysis, we found that risk factors for incident AF were SHD, HF, ageing (≥ 75 years), CAD, hyperthyroidism, COPD, and hypertension. All these risk factors were also demonstrated to increase the risk of incident AF in previous studies.[5,24-26] Indeed, SHD dramatically increases the risk of incident AF such that patients
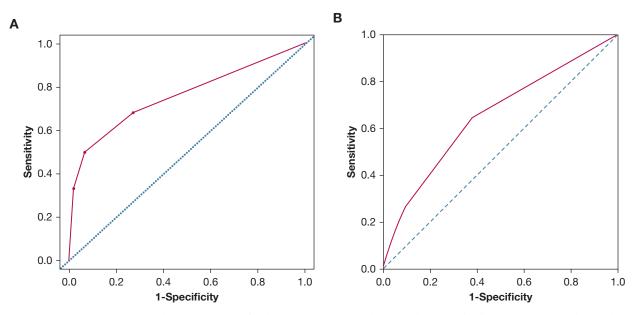

Figure 1 – A, B, Receiver operating characteristic curves for the C₂HEST score in predicting incident atrial fibrillation: (A) internal cohort and (B) external cohort.

TABLE 4] Annual Incidence of AF by C₂HEST Score

Score	No. of Subjects	No. of Incidents of AF	Incidence of AF[a]	Hazard Ratio	95% CI
0	310,117	246	0.18	1.00	…
1	88,825	378	0.82	4.31	3.67-5.06
2	19,270	148	2.31	12.8	10.4-15.6
3	8,253	68	3.73	22.6	17.2-29.6
4	1,373	68	16.1	97.0	74.1-127.0
5	90	6	28.7	187.4	83.3-421.6
≥ 6	45	7	59.8	332.0	156.6-704.0

See Table 1 legend for expansion of abbreviation.
[a]Per 1,000 person-years.

with SHD per se are very high risk of incident AF.[5] HF is also another significant and independent risk factor, with a two- to sixfold increase in the risk of incident AF.[24,25] The ARIC study showed that stable CAD was an independent risk factor for incident AF (HR, 2.21; 95% CI, 1.71-2.84).[12]

As previously highlighted, previous studies have proposed several predictive tools for incident AF, such as the FHS score, the ARIC score, and the CHARGE-AF score.[11–13] All these scoring systems were derived from large cohorts and showed good predictive values (C statistic, 0.75-0.78). However, these scores require many instrumental and laboratory variables to be calculated. Recently, the Suita study[27] in Japan has developed a risk score for
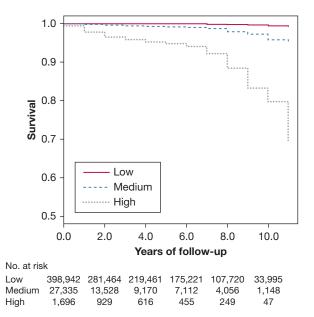

No. at risk
Low   398,942 281,464 219,461 175,221 107,720 33,995
Medium   27,335   13,528   9,170   7,112   4,056   1,148
High   1,696   929   616   455   249   47

Figure 2 – Kaplan-Meier curves for risk categories according to the C₂HEST score. Patients were divided into three groups: low (0-1 points), medium (2-3 points), and high risk (> 3 points).

incident AF with a good predictive power (C statistic, 0.75; 95% CI, 0.72-0.77). However, this score is complex (> 16 points), and we could not compare the C₂HEST score with the Suita study because our dataset did not have reliable data on cardiac murmur, which could be regarded as a subjective parameter based on physician auscultation.

As an exploratory analysis, we do show that the C₂HEST score had significantly better predictivity for incident AF compared with the CHADS₂, CHA₂DS₂-VASc, and HATCH scores in the derivation cohort. Similarly, in the external cohort, the C₂HEST confirmed higher predictivity for incident AF than the CHADS₂ and CHA₂DS₂-VASc scores, whereas it was only marginally significant compared with the HATCH score. These comparisons are with the caveat that these scores were not derived nor designed for the prediction of incident AF, but they were elaborated for stroke risk stratification[28,29] or arrhythmia progression from paroxysmal to persistent AF.[30]

In contrast, the C₂HEST was specifically designed to predict incident AF, and we used an established approach whereby a large Asian cohort was used to derive the score with internal validation using bootstrap and calibration methods. We then externally applied it in an independent Asian population sample for incident AF. The risk factors included in the C₂HEST score may be promptly deduced by a careful clinical evaluation of a patient with no need for any laboratory evaluation to calculate the individual risk of incident AF.

Strengths and Limitations

This is the first study aimed at developing a simple, user-friendly clinical risk score, the C₂HEST score,

from a large (n = 471,446) community-based Asian population with long follow-up. Also, we provided an external application using a nationwide cohort derived from another large Asian population dataset, the Korean NIHS dataset (n = 451,199). The C_2HEST score is easy to calculate and apply in clinical practice and allows for good identification of patients at risk for incident AF.

Nevertheless, this study has some limitations. There were some differences in the demographic characteristics and comorbidities between the Chinese and Korean cohorts, reflecting the different populations, the health-care system settings, and the nature of the cohorts per se (ie, health insurance scheme data from one single China province [Yunnan] from local 2A- and 3A-grade hospitals and a nationwide sample of Korean subjects).

The incidence of AF in the derivation cohort was also lower than that of Western populations, which may result from underdiagnosis and ethnic differences. Asymptomatic AF may be underrepresented, given that there was no opportunistic screening for AF performed in this study. Indeed, the lower incidence of AF in Asian populations compared with Western populations is in accordance with previous reports showing an incidence of AF of 0.50 to 1.37 per 1,000 person-years in Asians vs 3.04 to 3.68 per 1,000 person-years in Western populations.[31–34] The detection of asymptomatic AF is also problematic in large population studies considering the random pattern of AF onset. Nevertheless, it would generally be impossible to screen 0.5 million people for detecting asymptomatic AF, and such AF screening work could be done only in small highly selected samples (and possibly underpowered), which would again diminish the power of a large population-targeted study. Therefore, to do such a large population-based epidemiology study in developing countries, such as China and other Asian countries, we are using the most viable way, based on a simple clinical score-based approach. Another issue is that screening method selection could have a major impact on results.

Although we have excluded those patients with known AF at baseline according to available medical records, there may have been some patients with unknown AF (or transient AF) for which we could not confirm thorough AF screening at the patient level. However, this would not defeat the meaning of evaluating the subject's risk of developing incident AF during follow-up. Indeed, patients with AF occurring transiently are associated with high incidence of another AF episode in upcoming days,[35] and these patients usually have poor AF-related outcomes.[36,37]

The derivation cohort subjects of this study came from Yunnan Provence in the southwest of China and may not represent the whole scenario of China and Asia. We could not compare the C_2HEST score with other risk scores for incident AF, such as FHS and CHARGE-AF, because some variables from these scores were not collected for this dataset. However, the use of such complicated scoring systems relies on easily accessible computing and information systems, which are not applicable in the relatively underdeveloped Asia area. The simplicity of the C_2HEST score, which could be calculated by every clinical practitioner without relying on advanced information technology, may address the current unmet medical needs in Asia and help address the burden of AF in this part of the world. Although we have performed external application in another very large Asian cohort from Korea, further validation of the C_2HEST score is needed, especially in non-Asian cohorts (currently ongoing). Cultural health and environmental variations may be other factors which would have increased the complexity of any derived score (defeating the purpose of a simple clinical score for everyday practice), and are generally subordinated factors compared with clinical situations or disease conditions when making clinical decisions for risk assessment of incident AF.

Conclusions

We have developed and validated the C_2HEST score as a simple clinical tool to assess the individual risk of developing AF in the Asian population. This novel score may help identify patients without SHD who are at risk of incident AF and may be targeted for prevention strategies and screening programs.

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