Use of CHA₂DS₂-VASc Score to Predict New-Onset Atrial Fibrillation in Chronic Obstructive Pulmonary Disease Patients — Large-Scale Longitudinal Study —

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Background: The aim of this study was to assess the accuracy of CHA₂DS₂-VASc score in predicting new-onset atrial fibrillation (AF) in patients with chronic obstructive pulmonary disease (COPD).

Methods and Results: A total of 50,430 COPD patients were enrolled in this study. The area under the receiver operating characteristic curve (AUC) and the Cox model c-statistic were used to assess the association between new-onset AF risk and CHA₂DS₂-VASc score in COPD patients. After adjustment for comorbidities other than the components of CHA₂DS₂-VASc score, risk of new-onset AF in COPD patients increased from 1.24 (95% confidence interval (CI): 1.01–1.52) for a score of 1, to 2.15 (95% CI: 1.62–2.86) for score ≥ 6 (trend test, $P < 0.001$), compared with CHA₂DS₂-VASc score 0. The AUC for CHA₂DS₂-VASc score in predicting new-onset AF in COPD patients was 0.69 (95% CI: 0.68–0.70). The c-statistic of Cox model in predicting incident AF was 0.73.

Conclusions: Risk of new-onset AF in COPD patients increased with increasing CHA₂DS₂-VASc score. The predictive ability of the score was moderate. CHA₂DS₂-VASc score might be used as a screening tool for AF in COPD patients.

Key Words: Atrial fibrillation; CHA₂DS₂-VASc score; Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD), one of the leading causes of death in the world, is associated with cardiovascular disease (CVD).^{1–4} Atrial fibrillation (AF) is a common arrhythmia and is associated with several cardiovascular morbidities.^{5–8} The connection between COPD and AF has been proposed; indeed, the negative prognostic impact of AF on patients with COPD has also been reported.^{9–14}

CHA₂DS₂-VASc score, the clustering of several CVD-related risk factors, was initially proposed for stroke prediction in non-valvular AF.^{15–17} Recently, the role of CHA₂DS₂-VASc score has been expanded to predict different adverse cardiac and cerebrovascular outcomes in different populations.^{18–21} In order to reduce AF-related adverse cardiovascular events in COPD patients, it is essential to construct an accurate, convenient and easy-to-use risk stratification model for prediction of new-onset AF in COPD patients. Using a nationwide cohort, this study assessed the accuracy of CHA₂DS₂-VASc score in predicting incident AF in this population.

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Methods

Data Source

Since 1995, Taiwan's National Health Insurance (NHI) Bureau has provided a single-payer health insurance program with a coverage rate of >99% of residents in Taiwan.²² The Longitudinal Health Insurance Database 2000 (LHID 2000) of the NHI program was obtained. Detailed descriptions of the LHID 2000 have been reported previously.^{23,24} The diagnosis of the disease was coded based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). This study was approved by the Institutional Review Board (IRB) of China Medical University and Hospital (CMUH104-REC2-115).

Sampled Participants

The subject selection procedure is shown in **Figure 1**. Between 1 January 2000 and 31 December 2011, the date of diagnosis of COPD (ICD-9-CM codes 491, 492, 496)

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was defined as the index date. Patients aged ≥ 18 years at the index date were included in the present study. We excluded patients who had a diagnosis of AF or atrial flutter (ICD-9-CM code 427.31, 427.32) before the index date. CHA₂DS₂-VASc score was used to estimate the risk of incident AF in patients with COPD.^{25,26} Comorbidities associated with AF development, such as cancer (ICD-9-CM codes 140–208), hyperlipidemia (ICD-9-CM code 272), chronic kidney disease (ICD-9-CM code 585), hyperthyroidism (ICD-9-CM code 242) and valvular heart disease (ICD-9-CM code 424) were noted. All subjects were followed up until occurrence of new-onset AF, censoring because of death, withdrawal from the NHI program, or at the end of 2011 (whichever occurred first).

Statistical Analysis

Demographic data are presented as mean $\pm$ SD for continuous variables and as number and percentage for categorical variables. The categorical variables and the continuous variables were compared using chi-squared test

Table 1. Baseline COPD Patient Characteristics vs. Presence of AF

Variable	AF		P-value
	No (n=47,980)	Yes (n=2,450)	
Age (years)			<0.001 [†]
≤64	28,378 (59.2)	581 (23.7)	
65–74	11,218 (23.4)	891 (36.4)	
≥75	8,384 (17.5)	978 (39.9)	
Mean $\pm$ SD	59.1 $\pm$ 16.3	71.6 $\pm$ 10.7	<0.001 [‡]
Sex			<0.001 [†]
Male	27,298 (56.9)	1,489 (60.8)	
Female	20,682 (43.1)	861 (39.2)	
Underlying disease (components of CHA₂DS₂-VASc score)			
CHF	2,238 (4.66)	406 (16.6)	<0.001 [†]
Diabetes mellitus	5,825 (12.1)	328 (13.4)	0.07 [†]
CVA or TIA	3,127 (6.52)	235 (9.59)	<0.001 [†]
Vascular disease	2,347 (4.89)	175 (7.14)	<0.001 [†]
Hypertension	22,792 (47.5)	1,795 (73.3)	<0.001 [†]
Other underlying disease			
Cancer	1,676 (3.49)	83 (3.39)	0.78 [†]
Hyperlipidemia	12,203 (25.4)	665 (27.1)	0.06 [†]
CKD	5,411 (11.3)	413 (16.9)	<0.001 [†]
Hyperthyroidism	1,449 (3.02)	62 (2.53)	0.17 [†]
Valvular heart disease	1,171 (2.44)	131 (5.35)	<0.001 [†]
CHA₂DS₂-VASc score			<0.001 [†]
0	9,636 (20.1)	124 (5.06)	
1	1,4661 (30.6)	354 (14.5)	
2	9,731 (20.3)	583 (23.8)	
3	6,781 (14.1)	625 (25.5)	
4	3,998 (8.33)	419 (17.1)	
5	1,866 (3.89)	213 (8.69)	
6	903 (1.88)	87 (3.55)	
7	322 (0.67)	38 (1.55)	
8	74 (0.15)	5 (0.20)	
9	8 (0.02)	2 (0.08)	
CHA₂DS₂-VASc score	1.84 $\pm$ 1.56	2.85 $\pm$ 1.55	<0.001 [‡]
Follow-up (years)	6.91 $\pm$ 3.51	4.08 $\pm$ 3.00	<0.001 [‡]

Data given as n (%) or mean $\pm$ SD. [†]Chi-squared test; [‡]t-test. AF, atrial fibrillation; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; TIA, transient ischemic attack.

Figure 2. Incidence of new-onset atrial fibrillation (AF) increased with increasing CHA₂DS₂-VASc score in chronic obstructive pulmonary disease patients.

and Student's t-test, respectively. The incidence density rate (1,000 person-years) of new-onset AF was estimated according to CHA₂DS₂-VASc score. Univariable and multivariable Cox proportional hazard regression models were used to assess the risk of new-onset AF in patients with COPD according to CHA₂DS₂-VASc score. The Cox models were also used to examine the effect of factors of CHA₂DS₂-VASc score on the risk of incident AF in COPD patients. CHA₂DS₂-VASc score-specific survival probability for AF was analyzed using Kaplan-Meier survival for actual incidence and Cox modeling for estimated incidence, respectively. Area under the receiver operating characteristic (ROC) curve (AUC) was used to quantify the discriminatory performance of CHA₂DS₂-VASc score in predicting new-onset AF in COPD patients. Moreover, the c-statistic was also estimated based upon Cox regression analysis.²⁷ All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA). The significance level for all analyses was set at P<0.05.

Table 2. Incidence and HR of AF in COPD Patients vs. CHA₂DS₂-VASc Score

Variables	n	No. events	Person-years	Rate per 1,000 person-years	Age- and sex-adjusted HR	95% CI	Adjusted HR†	95% CI
CHA ₂ DS ₂ -VASc score								
0	9,760	124	73,153	1.70	1	(Ref.)	1	(Ref.)
1	15,015	354	111,981	3.16	1.45	(1.17–1.79)***	1.24	(1.01–1.52)*
2	10,314	583	71,701	8.13	1.89	(1.52–2.35)***	1.56	(1.26–1.93)***
3	7,406	625	46,050	13.6	2.26	(1.79–2.85)***	1.72	(1.38–2.15)***
4	4,417	419	23,971	17.5	2.60	(2.02–3.35)***	1.80	(1.42–2.28)***
5	2,079	213	9,406	22.7	3.14	(2.39–4.12)***	2.14	(1.73–2.90)***
≥6	1,439	132	5,103	25.9	3.28	(2.43–4.43)***	2.15	(1.62–2.86)***
P for trend					<0.001		<0.001	

*P<0.05, **P<0.01, ***P<0.001. †Adjusted for cancer, hyperlipidemia, CKD, hyperthyroidism and valvular heart disease. Abbreviations as in Table 1.

Figure 3. Actual vs. estimated survival curves for new-onset atrial fibrillation stratified by CHA₂DS₂-VASc score in patients with chronic obstructive pulmonary disease.

Results

Eligible study participants consisted of 50,430 COPD patients; among them, 2,450 patients developed new-onset AF whereas 47,980 patients did not (Table 1). Mean age was 71.6±10.7 years for the AF group and 59.1±16.3 years for the non-AF group. Hypertension was the most common comorbid illness (73.3% vs. 47.5%) in both groups. Mean CHA₂DS₂-VASc score was 2.85±1.55 for the AF group and 1.84±1.56 for the non-AF group. Mean follow-up period was 4.08±3.00 years for the AF group and 6.91±3.51 years for the non-AF group.

The incidence of new-onset AF increased from 1.27% in COPD patients with CHA₂DS₂-VASc score 0 to 9.17% in COPD patients with CHA₂DS₂-VASc score ≥6 (Figure 2). After adjusting for age and sex, as compared with COPD patients with CHA₂DS₂-VASc score 0, the corresponding adjusted hazard ratios (aHR) for new-onset AF increased with increasing CHA₂DS₂-VASc score. Furthermore, after adjusting for cancer, hyperlipidemia, chronic kidney disease, hyperthyroidism and valvular heart disease, as compared with COPD patients with CHA₂DS₂-VASc score 0, the corresponding aHR for new-onset AF for CHA₂DS₂-VASc score 1, 2, 3, 4, 5 and ≥6, were 1.24 (95% confidence interval (CI): 1.01–1.52), 1.56 (95% CI: 1.26–1.93), 1.72 (95% CI: 1.38–2.15), 1.80 (95% CI: 1.42–2.28), 2.14 (95% CI: 1.73–2.90) and 2.15 (95% CI: 1.62–2.86), respectively (trend test, $P<0.001$; Table 2).

Figure 3 shows the 12-year survival probability curves for AF stratified by CHA₂DS₂-VASc score. There was a close approximation between the estimated and actual curves, suggesting that the CHA₂DS₂-VASc score did not overfit the data in this cohort.

The AUC for CHA₂DS₂-VASc score in predicting new-onset AF in patients with COPD was 0.69 (95% CI: 0.68–0.70; Figure 4). The Harrell C-statistic for incident AF was 0.73 based on Cox-regression analysis. The results of the univariable and multivariable Cox proportional hazards regression models for analyzing the risk of new-onset AF contributed by the factors of CHA₂DS₂-VASc score are listed in Table 3. Compared with patients aged ≤64 years, the risk of AF was 3.08-fold higher in those aged 65–74

years (95% CI: 2.76–3.44), and 5.64-fold higher in those aged ≥75 years (95% CI: 5.04–6.30). The aHR of AF was 1.21-fold higher in men than in women (95% CI: 1.12–1.31). The risk of AF was greater in patients with comorbidities, namely congestive heart failure (aHR, 2.67, 95% CI: 2.39–2.98) and hypertension (aHR, 1.76, 95% CI: 1.59–1.94).

Discussion

To the best of our knowledge, the present study is the first to investigate the accuracy of CHA₂DS₂-VASc score in

Figure 4. Receiver operating characteristic (ROC) curve for CHA₂DS₂-VASc score in predicting new-onset atrial fibrillation in patients with chronic obstructive pulmonary disease (area under the curve, 0.6884).

Table 3. HR and 95% CI for AF vs. CHA₂DS₂-VASc Score Components

Variable	Crude		Adjusted†	
	HR	(95% CI)	HR	(95% CI)
Age (years)				
≤64	1.00	(Ref.)	1.00	(Ref.)
65–74	4.10	(3.69–4.55)***	3.08	(2.76–3.44)***
≥75	8.11	(7.31–8.99)***	5.64	(5.04–6.30)***
Sex				
Male	1.25	(1.15–1.35)***	1.21	(1.12–1.31)***
Female	1.00	(Ref.)	1.00	(Ref.)
Underlying disease (components of CHA₂DS₂-VASc score)				
CHF	4.89	(4.39–5.44)***	2.67	(2.39–2.98)***
Diabetes mellitus	1.34	(1.19–1.50)***	0.90	(0.80–1.01)
CVA or TIA	2.30	(2.01–2.63)***	1.13	(0.98–1.30)
Vascular disease	1.92	(1.64–2.24)***	1.09	(0.93–1.27)
Hypertension	3.27	(2.99–3.58)***	1.76	(1.59–1.94)***

*** $P<0.001$. †Adjusted for cancer, hyperlipidemia, chronic kidney disease, hyperthyroidism and valvular heart disease. Abbreviations as in Table 1.

predicting new-onset AF in COPD patients. New-onset AF risk was found to be increased in parallel with increasing CHA₂DS₂-VASc score.

Coexistence of COPD and AF is common and the interplay between them is complex. COPD patients are at an increased risk of incident AF.^{28–30} Additionally, the adverse impact of incident AF on the clinical outcomes in COPD has also been proposed.^{12–14} To our knowledge, however, there is no research specifically addressing the risk prediction model for incident AF in COPD. In order to fill the knowledge gaps, the present study investigated the role of CHA₂DS₂-VASc score in predicting incidence of AF, using a large-scale cohort of 50,430 COPD patients and a mean follow-up period of 6.77 years. CHA₂DS₂-VASc score was found to be predictive of incident AF in COPD patients. More studies are needed to clarify the present findings.

Although several risk stratification models for AF development have been proposed,^{31,32} to the best of our knowledge, research on AF prediction modeling for patients with COPD is currently unavailable. In the present study, risk of new-onset AF was increased in COPD patients with CHA₂DS₂-VASc score ≥ 1 , compared with CHA₂DS₂-VASc score 0. Unlike other complicated risk stratification models for AF prediction, the advantages of using CHA₂DS₂-VASc score in predicting incident AF are its convenience, comprehensiveness and accuracy.^{31,32} CHA₂DS₂-VASc score was also found to have moderate discriminative performance. Thus, CHA₂DS₂-VASc score is potentially useful in clinical settings.

Study Limitations

First, underestimation of AF incidence in this nationwide dataset is possible because AF cannot be identified if the patients do not seek medical advice. Second, personal health-associated behaviors were not provided by this nationwide database. Third, the severity of COPD and the types of AF were not available. Finally, we were unable to compare the predictive performance of the previously reported AF risk scores^{31,32} with the established CHA₂DS₂-VASc score due to the limitations of this nationwide database.

Conclusions

The current study is the first to evaluate the accuracy of CHA₂DS₂-VASc score in predicting incident AF in patients with COPD. The discriminatory capacity of the score was moderate. Therefore, CHA₂DS₂-VASc score might provide an easy way to stratify risk of new-onset AF in COPD patients.

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Disclosures

The authors declare no conflict of interest.

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