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Clinical Research

External Validation of the Model of Thromboembolic Risk in Hypertrophic Cardiomyopathy Patients

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See editorial by Veselka, pages 1629–1630 of this issue.

ABSTRACT

Background: Recently, a new risk model was developed, namely hypertrophic cardiomyopathy (HCM) risk for cerebrovascular accident, for estimating the risk of thromboembolism (TE) in patients with HCM. There is no study about the external validation of this model.

Methods: We evaluated the performance of the model for predicting TE in 417 patients with HCM recruited between 2008 and 2016, from a tertiary referral centre. The primary end point was 5-year TE, and the risk was calculated using the model formula.

Results: During a median follow-up of 3.5 years, 25 (6.0%) patients reached the TE end point, and 22 (5.3%) patients within the first 5 years. Within a 5-year time frame, the model showed a possibly helpful discrimination for TE (C-index for the whole cohort: 0.67, C-index for the subgroup without atrial fibrillation: 0.67) relative to its original C-index of 0.75. However, the calibration was not perfect, which suggested that there was an underestimation of 5-year TE risk in the whole cohort and different risk groups.

RÉSUMÉ

Contexte : Récemment, un nouveau modèle de risque a été mis au point, soit le modèle de risque d'accident vasculaire cérébral associé à la cardiomyopathie hypertrophique, afin d'évaluer le risque de thromboembolie chez les patients atteints de cardiomyopathie hypertrophique. Aucune étude de validation indépendante n'a été menée sur ce modèle.

Méthodologie : Nous avons évalué l'efficacité de ce modèle pour prédire la survenue d'une thromboembolie chez 417 patients atteints de cardiomyopathie hypertrophique, recrutés entre 2008 et 2016 dans un centre de référence tertiaire. Le critère d'évaluation principal était la survenue de la thromboembolie dans les 5 ans, le risque ayant été calculé à l'aide de la formule du modèle.

Résultats : Pendant un suivi médian de 3,5 ans, 25 patients (6,0 %) ont atteint le critère d'évaluation, soit la thromboembolie, et 22 patients (5,3 %) l'ont fait au cours des 5 premières années. En l'espace de 5 ans, le modèle a montré une discrimination qui pourrait être utile

Hypertrophic cardiomyopathy (HCM) is a myocardial disorder defined by the presence of left ventricular (LV) hypertrophy, which cannot be solely explained by abnormal loading conditions.[1] As an important complication of HCM, thromboembolism (TE) is associated with adverse clinical outcomes.[1-6] In some previous studies, TE showed an incidence of 1.0% per year and was more common in patients with atrial fibrillation (AF).[2,5,7] If we can identify individuals with HCM who are prone to TE, it may be potentially of significant benefit from preventive measures. Recently, the Hypertrophic Cardiomyopathy Outcome Investigators developed a risk model, namely HCM risk for cerebrovascular accident (HCM Risk-CVA), for estimating the risk of TE in patients with HCM, and the model showed prominent discrimination and calibration in the original study population.[4] However, before a new model can be adapted in clinical practice and acquire widespread use, it is necessary to confirm that the new model also performs well in a new set of patients.[8,9] As far as we know, there is no study about the external and independent validation of the risk model.

Therefore, the aim of this study was to assess the performance of HCM Risk-CVA by external validation in a relatively large cohort of patients with HCM derived from a tertiary referral centre.

Methods

Study population

The external validation cohort was from a retrospective, single centre, longitudinal study. From December 2008 to May 2016, 508 consecutive patients with a diagnosis of HCM

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Conclusions: HCM risk for cerebrovascular accident demonstrated a possibly helpful discrimination for TE when applied in a new set of patients with HCM. However, the accurate estimation of absolute risk should be explored in future studies.

pour prédire la survenue d'une thromboembolie (indice de concordance de 0,67 pour l'ensemble de la cohorte ainsi que pour le sous-groupe ne souffrant pas de fibrillation auriculaire, par rapport à l'indice de concordance initial de 0,75). Toutefois, la calibration était imparfaite, laissant supposer une sous-estimation du risque de thromboembolie sur 5 ans dans l'ensemble de la cohorte et les différents groupes de risque.

Conclusions : Le modèle de risque d'accident vasculaire cérébral associé à la cardiomyopathie hypertrophique a montré une discrimination qui pourrait être utile au regard de la thromboembolie lorsqu'il est appliqué à un nouveau groupe de patients atteints de cardiomyopathie hypertrophique. Toutefois, il faudrait mener d'autres études pour évaluer avec précision le risque absolu.

were enrolled in the study, and these patients were evaluated at West China Hospital of Sichuan University (Chengdu, China), which is a tertiary referral centre. The diagnosis of HCM was based on a wall thickness ≥15 mm in any LV myocardial segments, as measured by echocardiography or cardiac magnetic resonance, and that was not solely explained by abnormal loading conditions.[1] If patients were diagnosed with the inherited metabolic diseases or syndromic causes of HCM, they should be excluded from the study. According to the original study, patients with a history of AF who had experienced TE before first evaluation were also excluded from the analysis.[4] We also excluded 54 patients from the study who were lost to follow-up after first evaluation. Finally, 417 patients were included for the present analysis (Fig. 1).

The study was approved by the Ethics Committee on Medical Research of West China Hospital of Sichuan University, and performed according to the principles of the Helsinki Declaration. Individual patient consent was not required or obtained, but patients were informed of being entered into the observational study and were allowed to opt out.

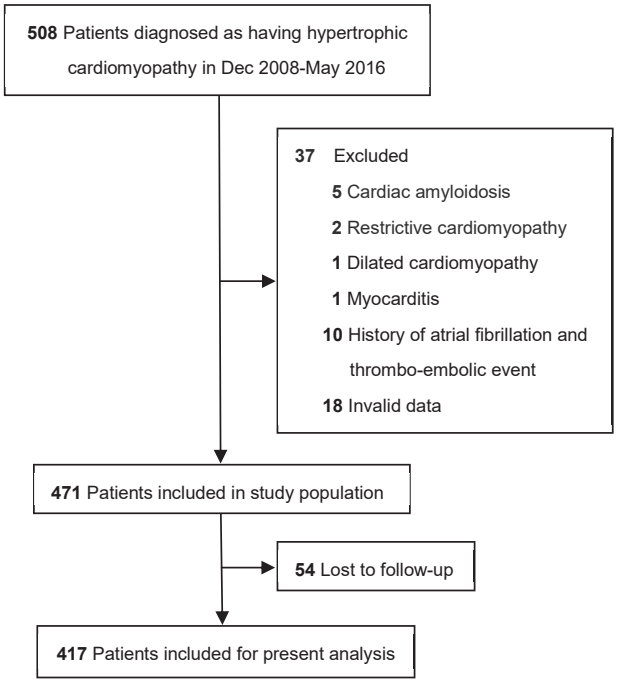

Figure 1. Study flow diagram.

Risk factors and profiles

Risk factors for TE were evaluated at baseline and based on the variables described in the original study.[4] The following risk factors were identified: (1) age at first evaluation; (2) AF determined by electrocardiogram or Holter monitoring or medical history; (3) prior TE: ischemic stroke, transient ischemic attack (TIA), and peripheral embolism; (4) New York Heart Association (NYHA) classes II to IV; (5) left atrial (LA) diameter; (6) maximal LV wall thickness (MWT); (7) vascular disease: prior myocardial infarction, peripheral arterial disease, and aortic plaque.

The risk of TE in 5 years for an individual patient with HCM could be calculated using the HCM Risk-CVA formula[4]: $P_{\text{TE at 5 years}} = 1 - 0.9999874^{\exp(\text{prognostic index})}$, where the prognostic index = 0.030417476 × age (years) + 2.129977874 × AF (yes = 1/no = 0) − 0.027069595 × age × AF + 1.288557829 × TE prior (yes = 1/no = 0) + 0.224673046 × NYHA class II (yes = 1/no = 0) + 0.728180341 × NYHA class III/IV (yes = 1/no = 0) + 0.032251831 × LA diameter (mm) + 0.3735254 × MWT (mm) − 0.008324216 × MWT^2 (mm) + 0.512492795 × vascular disease (yes = 1/no = 0).

Follow-up and clinical outcomes

Follow-up was carried out using hospital patient records or telephone interviews with the patients and/or referring relatives. The follow-up extended from first evaluation, and it continued until the date of an end point or the administrative censoring date, set at August 23, 2018. If patients were lost to follow-up, they would be censored at last known contact date.

The primary end point was a thromboembolic event defined as a composite of ischemic stroke, TIA, or peripheral embolism as defined in the original study.[4] Ischemic stroke and TIA were defined as a focal neurologic deficit of sudden onset as diagnosed by a neurologist, and they lasted >24 hours or <24 hours, respectively. Peripheral embolism was defined as TE outside the brain, heart, eyes, and lungs, which was usually confirmed by angiography, computed tomography, or abdominal ultrasonography.[10] In addition, given the difficulties in establishing the etiology of ischemic stroke

subtypes, the present study did not distinguish cardioembolic stroke from other ischemic subtypes.

Statistical analysis

For descriptive results, variables were expressed as the mean ± standard deviation, median and interquartile range, or counts and percentages as appropriate. Comparisons of baseline characteristics between patients without subsequent TE and patients with subsequent TE were performed by the independent t test and nonparametric Mann-Whitney U test where appropriate. Interactions between categorical variables were evaluated with the χ^2 test. Discrimination was assessed by Harrell's C-index. A generally accepted approach suggests that the C-index of less than 0.60 reflects poor discrimination; 0.60 to 0.75, possibly helpful discrimination; and more than 0.75, clearly useful discrimination.[11] Discrimination was also graphically presented by plotting Kaplan-Meier curves for the predefined low- and high-risk groups (group cut-offs: <3.0% and ≥3.0%). As an overall summary measure of calibration, we calculated the observed 5-year TE incidence compared with the mean 5-year predicted TE possibility ratio, and a value close to 1 suggests good overall agreement. For assessing the accuracy of calibration, the visual representation of the relationship between observed and predicted is the best way;[11] therefore, graphical comparisons of the observed and predicted TE at 5 years by risk groups were performed.

Assessing discrimination and calibration needs to involve comparing observed and predicted risk at different levels;[11,12] therefore, subgroup analyses were performed among the patients without AF. In addition, exploratory analyses were also performed to determine the relationship between anticoagulation and TE risk in the subgroup with AF.

All tests were 2 sided, and P values < 0.05 were considered statistically significant. All analyses were performed using Empower (R) (www.empowerstats.com, X&Y Solutions, Inc, Boston, MA), R (http://www.R-project.org), and SPSS (version 17.0; Chicago, IL).

Results

Baseline characteristics

The whole cohort comprised 417 consecutive patients (mean, 55.2 ± 16.1 years; 55.6% male), and Table 1 lists the baseline characteristics. At initial evaluation, 187 (44.8%) patients were in NYHA classes II to IV, and 66 (15.8%) patients had a medical history of AF. Twenty-eight (6.7%) and 11 (2.6%) patients had a history of vascular disease or prior TE, respectively. Thirty-five (8.4%) patients were taking warfarin, and 97 (23.3%) patients were receiving aspirin or clopidogrel. At study entry, the LA diameter was 40.4 ± 7.4 mm, and the MWT was 19.5 ± 4.6 mm. Other baseline characteristics are shown in Table 1.

TE during follow-up

During a follow-up period of 1601.2 person-years (median, 3.5 years; interquartile range, 2.1-5.7 years), 25 (6.0%) patients reached the primary end point from first evaluation (20 ischemic stroke and 5 peripheral embolism), and the incidence (events per 100 person-years) of TE was 1.6 (95% confidence interval [CI], 1.0-2.2). Twenty-two (5.3%) reached the primary end point within the first 5 years (17 ischemic stroke and 5 peripheral embolism).

The baseline clinical characteristics of patients with and without subsequent TE are shown in Table 1. Compared with patients who did not have an end point, patients who developed TE were older (61.4 ± 15.1 years vs 54.8 ± 16.1 years, $P = 0.045$). There was also a higher percentage of patients with AF (44.0% vs 14.0%, $P < 0.001$) and prior TE (8.0% vs 2.3%, $P = 0.084$) in patients who developed TE. Among the patients with subsequent TE, the proportion of antithrombotic therapy tended to be higher (Table 1).

Validation of HCM Risk-CVA in the whole cohort

For the whole cohort, the incidence of TE within 5 years is shown in Table 2, and the incidence (events per 100 person-years) increased as the HCM Risk-CVA score increased, corresponding to low and high risk (<3.0%, and ≥3.0%, respectively). Kaplan-Meier curves also illustrated that the model could differentiate between those with high risk and those with low risk (Fig. 2A). The C-index at 5-year follow-up was 0.67 (95% CI, 0.55-0.79), indicating a possibly helpful discrimination.

The overall 5-year TE incidence in the study population was 7.5% and the HCM Risk-CVA score predicted incidence was 2.2%, giving an observed-to-predicted ratio of 3.4 suggestive of an underestimation of overall 5-year incidence. According to the original study, the predefined low- and high-risk groups were further categorized into 4 risk groups, as follows: low risk (<1.5%), low-medium risk (1.5% to 3.0%), medium-high risk (3.0% to 5.0%), and high risk (≥5.0%). The observed vs model-predicted 5-year TE incidence in the 4 risk groups is shown in Figure 2B, and the risk was underestimated in different risk groups.

Validation of HCM Risk-CVA in the subgroup without AF

Among the 417 patients with HCM, the incidence of TE was much higher in the subgroup with AF (10/66 patients, 15.2%) than in the subgroup without AF (12/351 patients, 3.4%), and the log-rank P was less than 0.001 (Fig. 2C). In the subgroup with AF (n = 66), based on 210.2 person-years of follow-up and 10 adjudicated TE, the incidence of TE (events per 100 person-years) was 4.8 (95% CI, 1.9-7.7). For the relatively small sample size of patients with AF, we did not perform the further analysis.

At 5-year follow-up, the incidence of TE (events per 100 person-years) was 1.0 (95% CI, 0.5-1.6) in the subgroup without AF (n = 351), based on a follow-up period of 1163.2 person-years (TE = 12). The log-rank P for Kaplan-Meier analysis was 0.023 (Fig. 2D), and the C-index at 5-year follow-up was 0.67 (95% CI, 0.51-0.83), indicating a possibly helpful discriminative ability. The calibration was similar to the whole cohort (Fig. 2E).

Table 1. Baseline characteristics of patients

Variable	Whole cohort (n = 417)	Patients without subsequent TE (n = 392)	Patients with subsequent TE (n = 25)	*P* value*
Age (y)†	55.2 ± 16.1	54.8 ± 16.1	61.4 ± 15.1	0.045
Male	232 (55.6%)	222 (56.6%)	10 (40.0%)	0.105
Family history of HCM	38 (9.1%)	35 (8.9%)	3 (12.0%)	0.605
Family history of SCD	15 (3.6%)	15 (3.8%)	0 (0.0%)	0.319
NYHA II†	175 (42.0%)	161 (41.1%)	14 (56.0%)	0.143
NYHA III/IV†	12 (2.9%)	12 (3.1%)	0 (0.0%)	0.375
Symptoms				
Chest pain	216 (51.8%)	205 (52.3%)	11 (44.0%)	0.421
Palpitations	164 (39.3%)	156 (39.8%)	8 (32.0%)	0.439
Syncope/presyncope	135 (32.4%)	127 (32.4%)	8 (32.0%)	0.967
Dyspnea	224 (53.7%)	208 (53.1%)	16 (64.0%)	0.288
Comorbidities				
Atrial fibrillation†	66 (15.8%)	55 (14.0%)	11 (44.0%)	<0.001
Hypertension	132 (31.7%)	123 (31.4%)	9 (36.0%)	0.63
Diabetes	34 (8.2%)	31 (7.9%)	3 (12.0%)	0.469
Vascular disease†	28 (6.7%)	25 (6.4%)	3 (12.0%)	0.276
Prior TE†	11 (2.6%)	9 (2.3%)	2 (8.0%)	0.084
COPD	25 (6.0%)	24 (6.1%)	1 (4.0%)	0.665
Medications/devices/procedures				
Aspirin	74 (17.7%)	67 (17.1%)	7 (28.0%)	0.166
Clopidogrel	23 (5.5%)	20 (5.1%)	3 (12.0%)	0.143
Statins	112 (26.9%)	102 (26.0%)	10 (40.0%)	0.126
Warfarin	35 (8.4%)	32 (8.2%)	3 (12.0%)	0.502
Beta-blocker	301 (72.2%)	280 (71.4%)	21 (84.0%)	0.174
Diltiazem	23 (5.5%)	22 (5.6%)	1 (4.0%)	0.732
ACE inhibitor	33 (7.9%)	31 (7.9%)	2 (8.0%)	0.987
ARB	52 (12.5%)	48 (12.2%)	4 (16.0%)	0.582
ICD	33 (7.9%)	32 (8.2%)	1 (4.0%)	0.244
Pacemaker	22 (5.3%)	19 (4.8%)	3 (12.0%)	
Septal myectomy	6 (1.4%)	6 (1.5%)	0 (0.0%)	0.612
Alcohol septal ablation	33 (7.9%)	32 (8.2%)	1 (4.0%)	
Echocardiography data				
LVEDD (mm)	43.3 ± 6.2	43.3 ± 6.2	42.4 ± 6.3	0.477
LA diameter (mm)†	40.4 ± 7.4	40.3 ± 7.4	41.9 ± 6.1	0.289
MWT (mm)	19.5 ± 4.6	19.6 ± 4.7	18.3 ± 4.1	0.169
LV ejection fraction (%)	66.9 ± 8.6	67.0 ± 8.7	65.7 ± 6.9	0.472
Resting LVOTG ≥ 30 mm Hg	170 (40.8%)	163 (41.6%)	7 (28.0%)	0.180

Values are mean ± SD or n (%).

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter defibrillator; LA, left atrial; LV, left ventricular; LVEDD, left ventricular end-diastolic dimension; LVOTG, left ventricular outflow tract gradient; MWT, maximal left ventricular wall thickness; NYHA, New York Heart Association; SCD, sudden cardiac death; TE, thromboembolism.

* Between the patients with subsequent TE and the patients without subsequent TE.

† Risk model elements.

Exploratory analyses for determining the relationship between anticoagulation and TE risk in the subgroup with AF

Among the 66 patients with AF, 10 experienced TE within 5 years. Among these patients with AF, 29 (43.9%) had been given anticoagulation with warfarin. Despite that the difference was not statistically significant ($P = 0.107$, Fig. 2F), the incidence of TE was higher among patients without warfarin (8/37 patients; 21.6%) than in those treated with warfarin (2/29 patients; 6.9%). These results about antithrombotic therapies should be interpreted with caution due to the relatively small sample size.

Table 2. Crude incidence rates of thromboembolism at 5-year follow-up

	Overall	HCM Risk-CVA*	
		Low risk	High risk
Patients (n)	417	323	94
Events (n)	22	12	10
Person-years (n)	1373.4	1082.5	290.9
Incidence rate† (n, 95% CI)	1.6 (0.9-2.3)	1.1 (0.5-1.7)	3.4 (1.3-5.5)

CI, confidence interval; CVA, cerebrovascular accident; HCM, hypertrophic cardiomyopathy.

* The risk classes were defined as low (<3.0%) and high risk (≥3.0%) for 5-year risk of thromboembolism.

† Per 100 person-years.

Discussion

We evaluated the performance of HCM Risk-CVA for predicting TE by external validation in a relatively large cohort of patients with HCM. It was found that higher HCM Risk-CVA score was consistently associated with higher risk of TE, indicating a helpful risk discrimination. Although the calibration was not perfect, the model demonstrated decent risk prediction among patients by external validation.

There is a high incidence of TE in patients with HCM, especially among the patients with AF. Incidence rates of TE in patients with HCM, irrespective of AF diagnosis, have

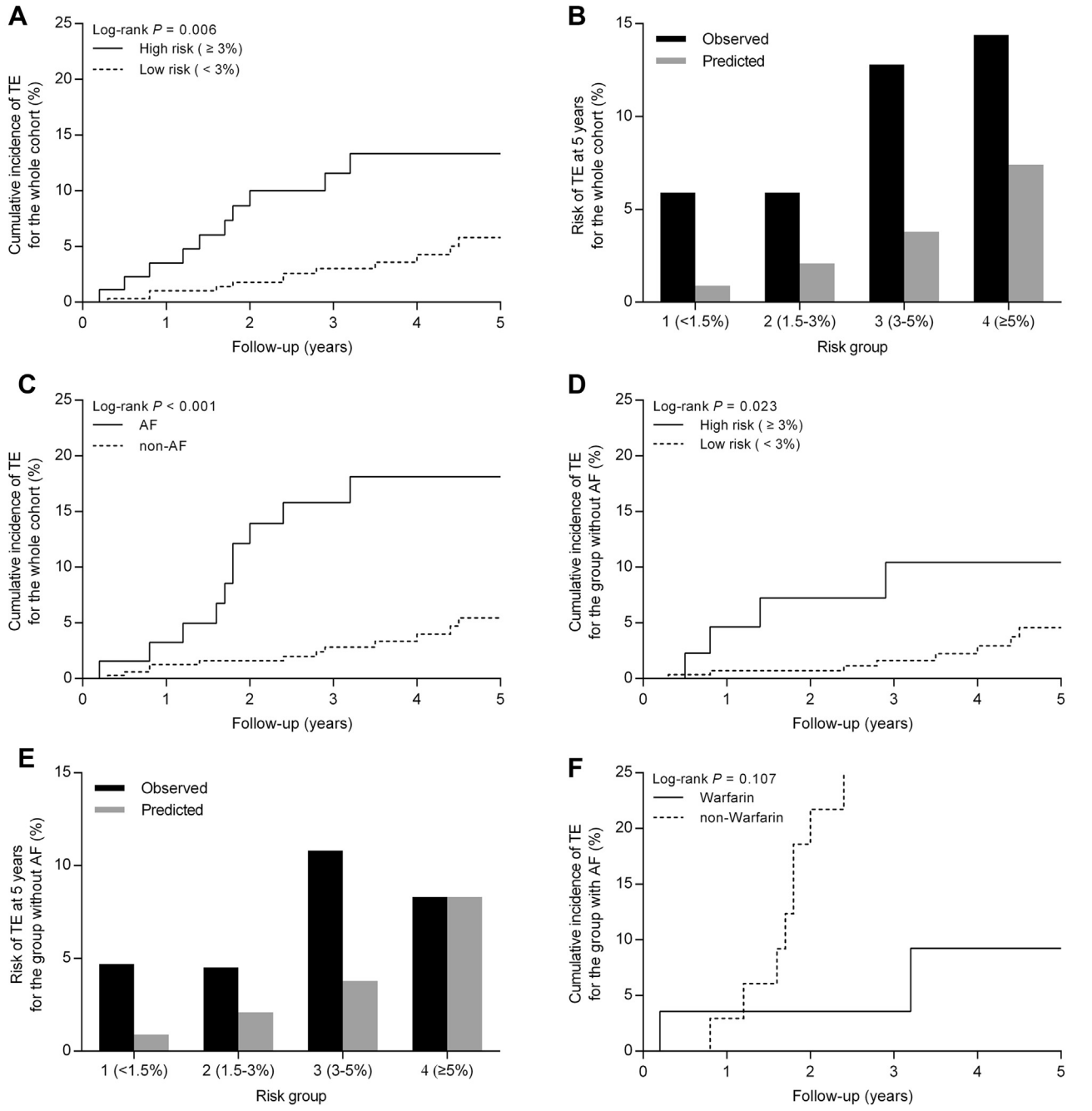

Figure 2. (**A**) Kaplan-Meier estimated cumulative 5-year incidence of thromboembolism (TE) by hypertrophic cardiomyopathy risk for cerebrovascular accident score groups. (**B**) Observed vs model-predicted 5-year TE incidence in 4 risk groups for the whole cohort. (**C**) Kaplan-Meier estimated cumulative 5-year TE incidence by the groups with or without atrial fibrillation (AF). (**D**) Kaplan-Meier estimated cumulative 5-year TE incidence by the high- and low-risk groups among the patients without AF. (**E**) Observed vs model-predicted 5-year TE incidence in 4 risk groups among the patients without AF. (**F**) Kaplan-Meier estimated cumulative 5-year TE incidence by the warfarin and nonwarfarin groups among the patients with AF. Risk groups (**B, E**) were developed using model-based predicted probabilities (<1.5%, 1.5% to 3.0%, 3.0% to 5.0%, and ≥5.0% 5-year risk of TE).

been estimated as 0.8% to 1.3% per year.[2,5,13] Compared with patients with HCM without AF, those in AF are shown to have an increase in the risk of TE, and a meta-analysis determines an overall annual incidence of stroke in patients with HCM with AF of 3.75%.[14] The prevalence of AF among patients with HCM is 20% to 25%,[2,14,15] and the prevalence gradually increases over 10 years.[6] Inevitably, the complications (eg, TE) will threaten public health resources in the future. Our results further confirm these previous studies about the high incidence of TE and the high prevalence of AF in patients with HCM. Therefore, identifying patients who are at high risk for TE and giving them preventive measures should be potentially of significant benefit.

However, prognosis is very difficult to predict; hence, risk prediction models should be necessary,[16] which could integrate several risk markers representing different pathophysiological characteristics and provide better risk estimates compared with a single marker. On the basis of these reasons, the Hypertrophic Cardiomyopathy Outcome Investigators[4] developed the HCM Risk-CVA for predicting the absolute risk of TE in individual patients with different clinical characteristics, which showed excellent discrimination and calibration in the original study population. In our study, the ability of HCM Risk-CVA to discriminate the risk of subsequent TE was reasonably good in the whole cohort and the subgroup without AF. This may suggest a fact that the relative risk of a key risk factor is frequently consistent across different populations.[17,18] However, the model calibration was not perfect. Calibration refers to the accuracy of absolute risk estimates, and poorly calibrated models will underestimate or overestimate the outcomes. An excellent model will show strong calibration for different populations; nevertheless, simulation exercises have suggested that accurate calibration for different populations might not be realistic.[11,12] The authors suggested that the patient population in their study was large and diverse, and the model might be used in patients with similar characteristics.[4] The difference in characteristics between our cohort and the original study population may be important in explaining why HCM Risk-CVA could not accurately estimate the absolute risk of TE in our cohort. For example, the present study population was older, and had a higher prevalence of comorbidities, including prior TE and vascular diseases, as well as smaller LA diameter. In addition, only 43.9% of patients had anticoagulation therapy in the subgroup with AF, which was lower than the original study, and this might also influence the accurate estimation of absolute risk. Although HCM Risk-CVA might not accurately estimate the absolute risk of TE by the external validation, the model still demonstrated decent risk prediction among patients with HCM. Therefore, it seems that the model should be particularly useful in stratifying patients into risk categories rather than estimating the absolute risk. For the small sample size of patients with AF, as well as the few number of events, we did not assess the discriminative ability of HCM Risk-CVA among the patients with AF; however, because of the high risk of TE in the subgroup with AF, we think the risk stratification might not be necessary for clinical decision making, which is in accordance with the guidelines.[1,19,20]

For preventing TE, the use of anticoagulant therapy should be helpful to patients with HCM with AF. Currently, there is no randomized controlled trial assessing the role of anticoagulant therapy,[20] and only some observational studies have reported that there is a lower rate of stroke in patients on warfarin than in those treated with antiplatelets or no therapy.[1,4,15] Although there was a small sample size and not statistically significant, our study also suggested similar results. Based on the available data, current guidelines uniformly recommend anticoagulation of all patients with HCM who develop AF, regardless of any known embolic risk factors.[1,19,20] In addition, there is no randomized controlled trial on the effectiveness of non−vitamin K antagonist oral anticoagulants in reducing thromboembolic risk in this population; nonetheless, some data show that non−vitamin K antagonist oral anticoagulants might be safe and effective for these patients.[20,21]

Limitations

There are several limitations of this study. First, this was a single-centre retrospective clinical study, and it was not prospective. Second, the study was performed at a tertiary referral centre, which might have resulted in certain inherent selection biases. In addition, the study was performed in China, and ethnicity may influence the findings potentially. Therefore, further multicentre studies are needed to confirm and extend the present findings. Third, the relatively small sample of thromboembolic events might reduce statistical power, but we still can get some useful information. It is noted that collecting large enough events can be extremely hard for rare diseases, and a multicentre large sample study with enough events should be warranted. Fourth, the antithrombotic therapy can affect the incidence of TE; however, it is not possible to withdraw patients from medications. In the original study, the model also included patients who were treated with a vitamin K antagonists. Therefore, it should be acceptable. Fifth, the prevalence of vascular disease was higher in the present study than in the original study (6.7% vs 2.48%), especially in the subsequent thromboembolic patients (12.0% vs 6.67%). Therefore, it is not inconceivable that the difference in observed vs predicted events might be due to some of these events being nonembolic. It is too difficult to establish the etiology of ischemic stroke subtypes in most clinical practice, which might be a potential reason for the imperfect calibration in our study. Further studies should be warranted.

Conclusions

In conclusion, HCM Risk-CVA reasonably predicted the risk of TE in a relatively large cohort of patients with HCM, and the model may be considered to guide risk management among patients with HCM. In addition, the accurate estimation of absolute risk should be explored in future studies.

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Disclosures

The authors have no conflicts of interest to disclose.

References

1. Authors/Task Force members, Elliott PM, Anastasakis A, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J 2014;35:2733-79.

2. Maron BJ, Olivotto I, Bellone P, et al. Clinical profile of stroke in 900 patients with hypertrophic cardiomyopathy. J Am Coll Cardiol 2002;39:301-7.

3. Camm AJ, Lip GY, De Caterina R, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation—developed with the special contribution of the European Heart Rhythm Association. Europace 2012;14:1385-413.

4. Guttmann OP, Pavlou M, O'Mahony C, et al. Prediction of thromboembolic risk in patients with hypertrophic cardiomyopathy (HCM Risk-CVA). Eur J Heart Fail 2015;17:837-45.

5. Haruki S, Minami Y, Hagiwara N. Stroke and embolic events in hypertrophic cardiomyopathy: risk stratification in patients without atrial fibrillation. Stroke 2016;47:936-42.

6. Choi YJ, Choi EK, Han KD, et al. Temporal trends of the prevalence and incidence of atrial fibrillation and stroke among Asian patients with hypertrophic cardiomyopathy: a nationwide population-based study. Int J Cardiol 2018;273:130-5.

7. Guttmann OP. Atrial fibrillation and thromboembolism in hypertrophic cardiomyopathy—an underestimated risk. Int J Cardiol 2018;273:187-8.

8. Altman DG, Vergouwe Y, Royston P, Moons KG. Prognosis and prognostic research: validating a prognostic model. BMJ 2009;338:b605.

9. Moons KG, Kengne AP, Grobbee DE, et al. Risk prediction models: II. External validation, model updating, and impact assessment. Heart 2012;98:691-8.

10. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest 2010;137:263-72.

11. Alba AC, Agoritsas T, Walsh M, et al. Discrimination and calibration of clinical prediction models: users' guides to the medical literature. JAMA 2017;318:1377-84.

12. Van Calster B, Nieboer D, Vergouwe Y, et al. A calibration hierarchy for risk models was defined: from utopia to empirical data. J Clin Epidemiol 2016;74:167-76.

13. Furlan AJ, Craciun AR, Raju NR, Hart N. Cerebrovascular complications associated with idiopathic hypertrophic subaortic stenosis. Stroke 1984;15:282-4.

14. Guttmann OP, Rahman MS, O'Mahony C, Anastasakis A, Elliott PM. Atrial fibrillation and thromboembolism in patients with hypertrophic cardiomyopathy: systematic review. Heart 2014;100:465-72.

15. Olivotto I, Cecchi F, Casey SA, et al. Impact of atrial fibrillation on the clinical course of hypertrophic cardiomyopathy. Circulation 2001;104:2517-24.

16. Aaronson KD, Cowger J. Heart failure prognostic models: why bother? Circ Heart Fail 2012;5:6-9.

17. He S, Chen X, Cui K, et al. Validity evaluation of recently published diabetes risk scoring models in a general Chinese population. Diabetes Res Clin Pract 2012;95:291-8.

18. Selvarajah S, Fong AY, Selvaraj G, et al. An Asian validation of the TIMI risk score for ST-segment elevation myocardial infarction. PLoS One 2012;7:e40249.

19. Gersh BJ, Maron BJ, Bonow RO, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2011;124:e783-831.

20. Camm CF, Camm AJ. Atrial fibrillation and anticoagulation in hypertrophic cardiomyopathy. Arrhythm Electrophysiol Rev 2017;6:63-8.

21. Noseworthy PA, Yao X, Shah ND, Gersh BJ. Stroke and bleeding risks in NOAC- and warfarin-treated patients with hypertrophic cardiomyopathy and atrial fibrillation. J Am Coll Cardiol 2016;67:3020-1.