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Research Paper

Impact of atrial fibrillation on the development of ischemic stroke among cancer patients classified by CHA_2DS_2-VASc score-a nationwide cohort study

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ABSTRACT

Purpose: The current study aimed to explore the impact of atrial fibrillation (AF) on risk of ischemic stroke among cancer patients classified by CHA_2DS_2-VASc score.

Methods: Study participants were identified from Registry for Catastrophic Illness Patient Database. All cancer patients whether they had comorbid AF or not were divided into 4 groups according to their CHA_2DS_2-VASc score-a score of 0–1, 2–3, 4–5 and >5. Competing risk analysis was used to evaluate the subhazard ratios (SHRs) and 95% confidence intervals (CIs) of incident ischemic stroke between cancer patients with and without AF according to their CHA_2DS_2-VASc score.

Results: A total of 781473 patients with cancer were identified. Of them, 21134 had comorbid AF whereas the remaining 760339 patients did not. After controlling for the confounding factors and the competing risk of death, among cancer patients, those with AF were associated with the highest risk of ischemic stroke than those without AF while their CHA_2DS_2-VASc score was 0~1 (adjusted SHR [aSHR] = 4.15, 95% CI = 3.29–5.23). Among those with a CHA_2DS_2-VASc score of >5, the AF group exhibited a 1.82-fold higher risk of ischemic stroke than the non-AF group (95% CI = 1.34–2.47).

Conclusions: The impact of AF on risk of ischemic stroke was attenuated with advancing CHA_2DS_2-VASc score in patients with cancer.

INTRODUCTION

Currently, cancer and ischemic stroke remain major challenges for the developed countries because of the associated high morbidity and mortality [1–6]. Although the connection between cancer and incident ischemic stroke has been explored, the underlying detailed mechanism link between cancer and ischemic stroke is still not fully understood [1–9]. Several possible factors for the development of incident ischemic stroke among patients with cancer were proposed, mainly through either cancer-related or cancer-unrelated mechanism [1–9].

Atrial fibrillation (AF), a well-recognized risk factor for ischemic stroke, is a common comorbidity in cancer patients [10–12]. In addition, the prognostic impact of AF on the clinical outcomes among patients with cancer has also been investigated [10, 13–14]. Furthermore, current guidelines suggest that CHA_2DS_2-VASc score is a useful discrimination tool for stratifying ischemic stroke risk among patients with AF [15–17]. Recently, CHA_2DS_2-VASc score has been shown to be helpful for stroke risk stratification even in individuals without AF [18–19].

To our knowledge, currently there is no study specifically addressing the issue of the link between

cancer, AF and ischemic stroke. To bridge the gaps of knowledges, the current study aimed to identify the impact of AF on risk of developing ischemic stroke among cancer patients stratified by CHA_2DS_2-VASc score. The predictive capacity of CHA_2DS_2-VASc scores for stroke risk discrimination among cancer patients whether they have comorbid AF or not was also explored.

METHODS

Data source

We undertook a retrospective nationwide cohort study using the Registry of Catastrophic Illness Patient Database (RCIPD) of the Taiwan National Health Insurance (NHI) program. A compulsory NHI program was implemented in Taiwan since 1995 and it covered nearly 99% of all residents (23.74 million beneficiaries) of Taiwan [20]. The details of the RCIPD have been described previously [21–22]. This study complied with the guidelines of the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of China Medical University and Hospital (CMUH-104-REC2-115). The diagnostic codes were based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9 codes).

Sampled participants

All cancer (ICD-9-CM 140–208) patients were identified from RCIPD and the first-time cancer diagnosis served as the index date from 2000 to 2011. The cancer patients were divided into 2 groups, based on with and without a history of atrial fibrillation (AF) (ICD-9-CM code 427.31). Patients with incomplete age or sex information were excluded. The CHA_2DS_2-VASc score was calculated for each patient to measure incident ischemic stroke risk [23–26]. Patient's baseline comorbidities included hyperlipidemia (ICD-9-CM code 272), chronic obstructive pulmonary disease (COPD) (ICD-9-CM code 491, 492, 496), chronic kidney disease (CKD) (ICD-9-CM code 585), hyperthyroidism (ICD-9-CM code 242), sleep disorder (ICD-9-CM codes 307.4 and 780.5), and gout (ICD-9-CM code 274). All subjects were followed until a diagnosis of ischemic stroke (ICD-9-CM codes 433–438) was made, until death, withdrawal from insurance, or the end of 2011, whichever came first.

Statistical analysis

Demographic characteristics and comorbidity prevalence were compared between the AF and the non-AF groups. The difference of categorical variables between the two groups was examined using the χ^2 test whereas the difference of continuous variables between the two groups was examined with the *t*-test. Cancer patients with and without AF were divided into 4 groups according to their CHA_2DS_2-VASc score-a score of 0–1, 2–3, 4–5 and >5. The incidence of ischemic stroke and death in patients with cancer whether they had comorbid AF or not were estimated according to their CHA_2DS_2-VASc score. The cumulative incidence of ischemic stroke stratified by CHA_2DS_2-VASc score among cancer patients with and without AF was assessed using the Kaplan-Meier method, and the differences between the curves were evaluated using a log-rank test. To quantify the discriminatory properties of the CHA_2DS_2-VASc score in predicting ischemic stroke among cancer patients with and without AF, we plotted the receiver operating characteristic (ROC) curves and calculated the area under the ROC curves. Considering the competing risk of death, the Fine and Gray model was used to extend the standard univariable and multivariable Cox proportional hazards models and the subhazard ratios (SHRs) and 95% confidence intervals (CIs) of incident ischemic stroke between cancer patients with and without AF according to their CHA_2DS_2-VASc score were obtained (27). All data processing and statistical analyses were performed with the SAS software version 9.4 (SAS Institute, Inc., Cary, NC, USA). A *p*-value of <0.05 was considered statistically significant.

RESULTS

A total of 781473 cancer patients were identified from RCIPD. Among them, 21134 patients had comorbid AF whereas 760339 patients did not (Table 1). Most cancer patients with AF were aged 75 years or older (57.1%) whereas most cancer patients without AF were aged 64 years or younger (56.4%). The mean (SD) ages was 75.3 (9.83) and 61.2 (14.9) years in the AF and the non-AF group, respectively. The percentage of women in AF group was significantly higher than the non-AF group (65.2% vs 55.2%, $p < 0.001$). The AF group was associated with a higher prevalence of all comorbidities than the non-AF group. The 3 major cancers in the AF group were colon cancer (18.3%), lung cancer (17.1%) and hepatoma (13.2%) whereas colon cancer (13.8 %), hepatoma (13.4%) and female breast cancer (11.4%) were three most common cancers in the non-AF groups. The mean CHA_2DS_2-VASc score of the AF and the non-AF group were 3.86 (SD = 1.72) and 1.89 (SD = 1.56). The mean follow up period for the AF and the non-AF group was 1.79 years (SD = 2.19 years) and 3.00 years (SD = 3.07 years), respectively.

The incidence of ischemic stroke was highest in cancer patients whether they had comorbid AF or not while their CHA_2DS_2-VASc score was 4~5 (6.02% vs 3.71%) (Table 2). Kaplan-Meier analyses illustrated the cumulative incidence curves of incident ischemic stroke according to CHA_2DS_2-VASc score in cancer patients without atrial fibrillation (Figure 1A) and with atrial fibrillation (Figure 1B). Among cancer patients without and with comorbid AF, the area under the ROC curves of the CHA_2DS_2-VASs score as a predictor of ischemic stroke was 0.62 (95% CI = 0.61–0.62) (Figure

Table 1: Baseline characteristics of cancer patients with and without atrial fibrillation

Characteristics	Atrial fibrillation		*p*-value
	No *N* = 760339 *n* (%)	Yes *N* = 21134 *n* (%)	
Age group (year)			<0.001
≤64	429050 (56.4)	2953 (14.0)	
65–74	174396 (22.9)	6112 (28.9)	
≥75	156893 (20.6)	12069 (57.1)	
Age, mean ± SD [a] (year)	61.2 ± 14.9	75.3 ± 9.83	<0.001
Sex			<0.001
Women	419477 (55.2)	13778 (65.2)	
Men	340862 (44.8)	7356 (34.8)	
Underlying disease (components of the CHA_2DS_2-VASc score)			
HF	34965 (4.60)	8606 (40.7)	<0.001
Diabetes Mellitus	121743 (16.0)	5274 (25.0)	<0.001
CVA or TIA	66492 (8.75)	6432 (30.4)	<0.001
Vascular disease	23472 (3.09)	2484 (11.8)	<0.001
Hypertension	336445 (44.3)	17282 (81.8)	<0.001
Other underlying disease			
Hyperlipidemia	173145 (22.8)	6603 (31.2)	<0.001
COPD	139500 (18.4)	9344 (44.2)	<0.001
Chronic kidney disease	42882 (5.64)	2837 (13.4)	<0.001
Hyperthyroidism	12812 (1.69)	775 (3.67)	<0.001
Sleep disorder	177617 (23.4)	6899 (32.6)	<0.001
Gout	94416 (12.4)	5134 (24.3)	<0.001
Type of Cancer (ICD-9-CM)			
Hematologic malignancy (200–208)	34301 (4.51)	1056 (5.00)	0.001
Head and neck (140–149, 161)	80000 (10.5)	1000 (4.73)	<0.001
Esophagus (150)	16853 (2.22)	455 (2.15)	0.54
Stomach (151)	37434 (4.92)	1446 (6.84)	<0.001
Colon (153–154)	104751 (13.8)	3858 (18.3)	<0.001
Hepatoma (155)	101416 (13.4)	2799 (13.2)	0.69
Cholangiocarcinoma (156)	8958 (1.18)	329 (1.56)	<0.001
Pancreas (157)	12803 (1.68)	436 (2.06)	<0.001
Lung (162)	84792 (11.2)	3622 (17.1)	<0.001
Skin (173)	11688 (1.54)	469 (2.22)	<0.001
Female breast (174)	86451 (11.4)	775 (3.67)	<0.001
Uterus (180–184)	49496 (6.51)	595 (2.82)	<0.001
Prostate (185)	33304 (4.38)	1762 (8.34)	<0.001

Bladder & Kidney (188, 189)	42664 (5.61)	1485 (7.03)	<0.001
Brain (191)	8429 (1.11)	170 (0.80)	<0.001
Thyroid (193)	20158 (2.65)	233 (1.10)	<0.001
Mean CHA_2DS_2-VASc score (SD)[a]	1.89 (1.56)	3.86 (1.72)	<0.001
Mean follow-up, y (SD)[a]	3.00 (3.07)	1.79 (2.19)	<0.001

Chi-square test.
[a]*t*-test.
SD denotes standard difference.
HF denotes heart failure.
CVA denotes cerebrovascular accident.
TIA denotes transient ischemic attack.
COPD denotes chronic obstructive pulmonary disease.

Table 2: The incidence of ischemic stroke according to CHA_2DS_2-VASc score among cancer patients with and without AF

	Atrial fibrillation					
	No			Yes		
CHA_2DS_2-VASc score	N	Event	Incidence (%)	N	Event	Incidence (%)
0~1	379566	4887	1.29	1712	74	4.32
2~3	260051	8809	3.39	7391	440	5.95
4~5	100790	3736	3.71	8402	506	6.02
>5	19932	184	0.92	3629	54	1.49

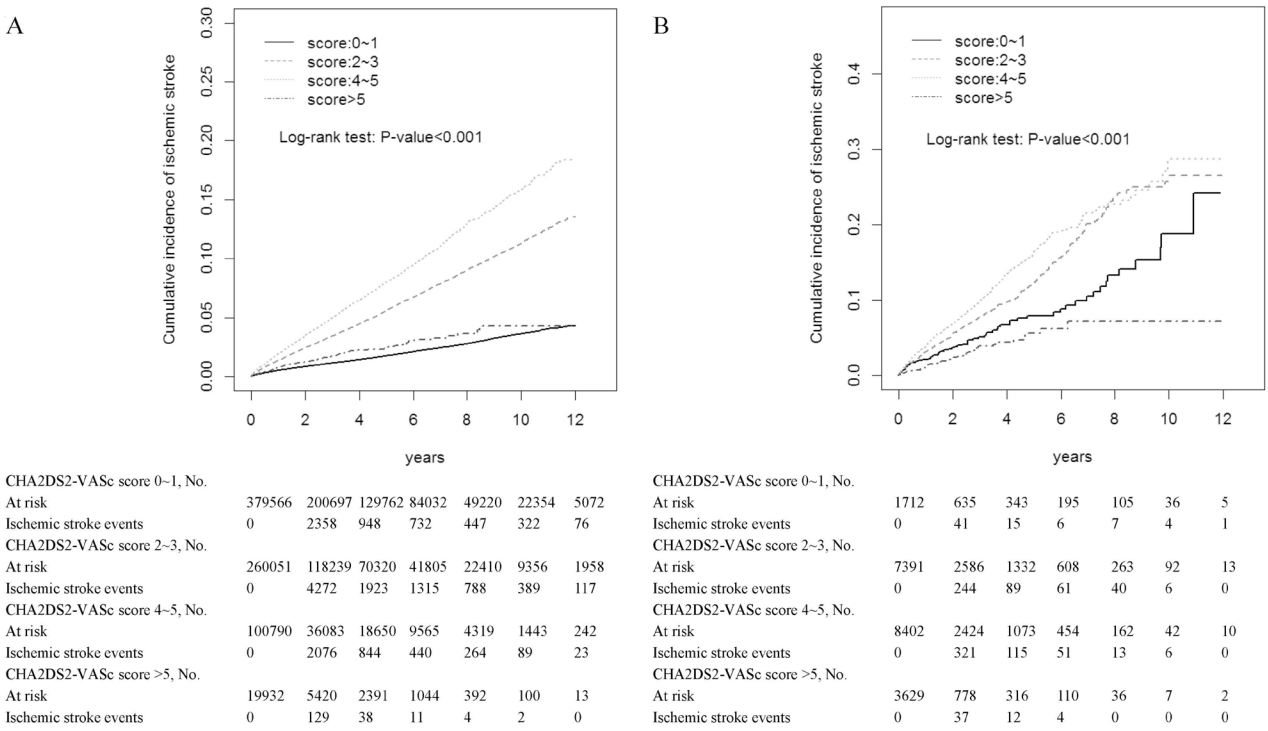

Figure 1: Cumulative incidence curves of incident ischemic stroke according to CHA_2DS_2-VASc score in cancer patients without atrial fibrillation (**A**) and with atrial fibrillation (**B**).

2A) and 0.56 (95% CI = 0.54–0.57) (Figure 2B), respectively.

The incidence of mortality was highest in cancer patients whether or not AF was present while their CHA_2DS_2-VASc score was greater than 5 (49.5% vs 47.0%) (Table 3). Estimation of incident ischemic stroke risk in the study cohorts while considering the competing risk of death was shown in Table 4. After controlling for the confounding factors and the competing risk of death, among cancer patients, those with comorbid AF were associated with the highest risk of ischemic stroke than those without AF while their CHA_2DS_2-VASc score was 0~1 (adjusted SHR [aSHR] = 4.15, 95% CI = 3.29–5.23). Additionally, among cancer patients with a CHA_2DS_2-VASc score of >5, the AF group exhibited a 1.82-fold higher risk of ischemic stroke than the non-AF group (95% CI = 1.34–2.47).

DISCUSSION

We reported for the first time regarding the impact of AF on incident ischemic stroke among cancer patients stratified by CHA_2DS_2-VASc score. Additionally, the use of CHA_2DS_2-VASc score in ischemic stroke risk discrimination among cancer patients with and without comorbid AF was also addressed.

Using CHA_2DS_2-VASc score for stratifying patients into four groups (0–1, 2–3, 4–5, and >5), the incidence of mortality increased in parallel with increasing score in cancer patients whether AF was present or not. Nevertheless, the linear shape phenomenon was not observed in the incident ischemic stroke among cancer patients with and without AF. Possible factor for the explanation is that death is a major competing risk for ischemic stroke in cancer patients, leading to the lowest incidence of ischemic stroke in those with the highest score [1–6].

The biologic mechanism link between cancer and stroke is complicated and currently not comprehensively elucidated [1–9]. Either cancer-related mechanism, such as hypercoagulable status, tumor compression, paradoxical embolism, nonbacterial thrombotic endocarditis and anti-cancer therapy associated effect or cancer-unrelated mechanism, such as overlapping atherosclerotic risk factors were proposed [1–9].

In the current study, we found that cancer patients with AF were older and had more underlying medical comorbidities. After controlling for the potential confounding factors with the competing risk regression model approach, the risk of developing ischemic stroke for cancer patients with AF relative to those without AF was in an inverse relationship with advancing CHA_2DS_2-VASc score. Possible explanation for our results is that a higher CHA_2DS_2-VASc score is associated with a significantly higher rate of ischemic stroke, which in turn might lead to the attenuated role of AF in those with a higher score.

Several advantages of the current study deserve to be highlighted. First, the study was analyzed from a large insurance administrative database which has been validated [28–30]. Second, this study is a large scale investigation with large patient population and reasonable follow up duration with the attempt to explore this clinically significant issue. Finally, statistical procedure with competing risk analysis approach was used in order to minimize the study bias [27].

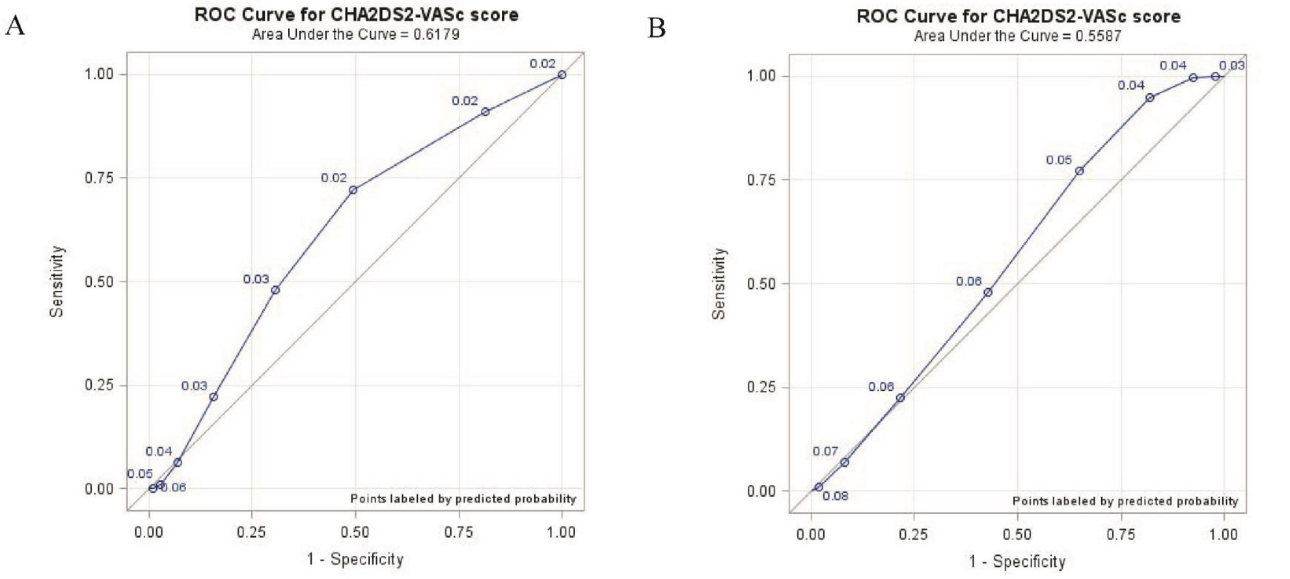

Figure 2: Receiver operating characteristic (ROC) curve for CHA_2DS_2-VASc score in predicting incident ischemic stroke in cancer patients without atrial fibrillation (**A**) and with atrial fibrillation (**B**).

Table 3: The incidence of mortality according to CHA_2DS_2-VASc score among cancer patients with and without AF

	Atrial fibrillation					
	No			Yes		
CHA_2DS_2-VASc score	*N*	Event	Incidence (%)	*N*	Event	Incidence (%)
0~1	379566	112614	29.7	1712	685	40.0
2~3	260051	96386	37.1	7391	3232	43.7
4~5	100790	43240	42.9	8402	3903	46.5
>5	19932	9372	47.0	3629	1795	49.5

Table 4: Incidence and subhazard ratios of ischemic stroke between cancer patients with and without atrial fibrillation according to CHA_2DS_2-VASc score with the use of the competing-risk regression model

	Atrial fibrillation							
	No				Yes			
CHA_2DS_2-VASc score	Event	Rate[#]	Crude SHR (95% CI)	Adjusted SHR[†] (95% CI)	Event	Rate[#]	Crude SHR (95% CI)	Adjusted SHR[†] (95% CI)
0~1	4887	37.6	1 (Reference)	1 (Reference)	74	188.8	4.67 (3.71, 5.87)***	4.15 (3.29, 5.23)***
2~3	8809	120.2	1 (Reference)	1 (Reference)	440	290.1	1.98 (1.80, 2.18)***	1.95 (1.77, 2.14)***
4~5	3736	174.7	1 (Reference)	1 (Reference)	506	362.5	1.84 (1.67, 2.01)***	1.86 (1.69, 2.04)***
>5	184	57.9	1 (Reference)	1 (Reference)	54	114.3	1.78 (1.32, 2.41)***	1.82 (1.34, 2.47)***

Rate[#], per 1,000 person-year; Crude SHR, crude subhazard ratio.
[†]Adjusted for hyperlipidemia, chronic obstructive pulmonary disease, chronic kidney disease, hyperthyroidism, sleep disorder and gout; further controlling for death to estimate adjusted subhazard ratio.
***$p < 0.001$.

Limitations

First, the absence of relevant case information from the insurance claims data is potentially a major limitation and should be outlined. However, several validation studies have been conducted and the reliability of the nationwide dataset has been confirmed [28–30]. Second, detailed personal health-associated behaviors were uncertain in this database. Finally, potential unmeasured confounding variables involved in the analyses are possible. Despite the limitations presented here, this study was extracted from a large nationwide dataset with the appropriate methodology approach to provide new insights into this context.

CONCLUSIONS

The impact of AF on risk of ischemic stroke was attenuated with the advancement of CHA_2DS_2-VASc score in cancer patients.

CONFLICTS OF INTEREST

The authors have declared no conflicts of interest.

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