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Better prediction of stroke in atrial fibrillation with incorporation of cancer in CHA_2DS_2VASC score: $CCHA_2DS_2VASC$ score

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ABSTRACT

Introduction: Atrial fibrillation (AF) is associated with an increased risk of stroke. Despite evidence linking cancer and thrombosis, cancer is not part of the CHA_2DS_2VASc score.
Hypothesis: Cancer is an independent risk factor for thromboembolic stroke in patients with AF.
Method: The SEER database was utilized to identify patients with lung, colon, breast, and prostate cancers with AF and no prior diagnosis of stroke and. compared to controls within the dataset. The primary endpoint was rates of stroke per 100 person-years. Cox regression modeling and a nested model comparing CHA_2DS_2VASc score (Model 1) with a complete model including cancer diagnosis (Model 2) were performed. Models were compared using Akaike Information Criterion (AIC) and Net Reclassification Index (NRI). A propensity-matched cohort with equivalent CHA_2DS_2VASc scores determining stroke-free survival was also performed.
Results: A total of 101,185 patients were included in the analysis, with 48,242 in the Cancer and 52,943 in the Non-cancer Group. Stroke rate per 100 person-years was significantly higher in the Cancer Group. The CHA_2DS_2VASc model (Model 1) was compared against a model including cancer (Model 2) showing improved predictability as assessed by both NRI and AIC. Cox regression analysis calculated a hazard ratio of 1.085 for Cancer, which was comparable to age >75, female sex, and diabetes. Propensity matched Kaplan-Meier curve demonstrated a decreased probability of stroke-free survival in the Cancer Group.
Conclusion: Cancers increase the risk of stroke in patients with AF. Consideration should be given to the addition of cancer to the clinical scoring system.

1. Introduction

Atrial fibrillation (AF) is a common tachyarrhythmia characterized by irregular and uncoordinated atrial depolarization leading to the disappearance of a viable atrial contraction. In combination with local changes in the endothelium [1] and activation of hemostasis pathways [2], this ineffective contraction leads to an increased risk of left atrial appendage thrombus formation with subsequent embolization and stroke. Thromboembolic strokes developing from this mechanism carry an elevated risk of mortality, disability, and poor functional outcomes [3]. Given the significant associated morbidity and mortality, efforts have been focused on identifying risk factors for the development of thromboembolism (TE) in this population, and on prevention through the use of anticoagulation [4]. Multiple models have been developed that incorporate known risk factors for AF-mediated strokes, such as hypertension, diabetes, heart failure, and increasing age [5–7]. Initial use of the $CHADS_2$ score provided clinicians a simple framework for evaluating stroke risk in this population [8]; however, 1·4% of those categorized as low risk by this scoring system developed stroke [9]. The incorporation of data from the Birmingham 2009 stratification system led to the development of the CHA_2DS_2VASc score, which was superior in identifying those who are truly low risk compared to the $CHADS_2$

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model [9–10]. While the variables in these models are used as discrete points, they exist on a continuum of increasing risk, as Abdel-Qadir et al recently demonstrated in a 66–74 years old cohort [11].

Cancers and cancer treatments place patients at a higher risk of developing AF [10,12–13]. Ongoing investigations into the exact mechanism of this risk may delineate whether this is related to the underlying disease state, or to the treatments used for malignancies [10]. Chemotherapies, particularly alkylating agents and anthracyclines, carry a known risk of cardiotoxicity that can increase the risk of developing AF and other supraventricular arrhythmias [14–15]. Furthermore, targeted therapies, such as the Bruton tyrosine kinase inhibitor class, have been well-described to confer a risk of developing AF [15–16]. Similar to the medical treatments used, surgeries for cancers have been associated with the development of AF [15]. Studies have demonstrated an elevated risk of postoperative AF in patients undergoing thoracotomy [17], esophagectomy [18], and colectomy [19]. Importantly, many of these studies were observational in nature, and questions remain as to whether this reflects an underlying pathophysiological mechanism of cancer or the invasiveness of surgery required [10]. Regardless of the mechanism, the risk of AF in patients with cancer is increased.

Another significant body of evidence supports a relationship between cancer and thrombosis, including both venous thromboembolism (VTE) and stroke [20–21]. The clinically utilized Well's scores for both DVT [22] and PE [23] include active cancer with treatment as one of the clinical criteria suggesting thrombosis. Specifically for stroke, Navi et al [24] performed an analysis of a prospective cohort that showed a significantly elevated risk of ischemic stroke within the first 30 days after a new cancer diagnosis, and this association was maintained even after other vascular risk factors were stratified. Additionally, a prior investigation performed by Hu et al [25] showed a much higher risk of stroke in a population of cancer patients than that predicted by the $CHADS_2$ score. For example, in those with a $CHADS_2$ score of 0–1, the incidence of thromboembolism was found to be nearly 30% in those with new-onset AF; this is far higher than the 1·9-2·8% predicted by the $CHADS_2$ model.

Given the significant body of evidence correlating malignancies with thrombosis, AF, and stroke, our group hypothesized that cancer is an independent risk factor for the development of stroke in patients with AF.

2. Methods

2.1. Study cohort

Our study cohort was derived from the Surveillance, Epidemiologic, and End Results (SEER) database. The SEER database is a cancer registry in the United States that covers 35% of the population. It includes cases of invasive cancer, with dates of cancer diagnosis, comorbidities, and survival. It also includes controls from Medicare beneficiaries, with data from Medicare part A (inpatient admissions) and B (Outpatient clinic visits). We identified patients with lung, colon, breast, and prostate cancers, with no diagnosis of prior AF, who developed new incident AF after the diagnosis of cancer from 2007-to 2016. We also identified non-cancer patients with a new diagnosis of AF during the same time frame. We excluded patients who had a prior diagnosis of ischemic stroke, before the diagnosis of AF. Comorbidities were ascertained from the SEER chronic conditions file, which includes important comorbidities with the date of the first diagnosis for patients in the database.

2.2. Study outcomes

The primary study outcome was an ischemic stroke. Patients were followed till death, the occurrence of first ischemic stroke, disenrollment from Medicare, or the end of the study period in December 2016. The date of stroke occurrence was ascertained from the end of year indicator and date of stroke in chronic conditions file in the SEER database. For each patient included in the study, the CHA_2DS_2VASc (congestive heart failure, hypertension, age $\geq$ 75 years, diabetes mellitus, stroke or transient ischemic attack (TIA), vascular disease, age 65 to 74 years, sex category) score was calculated. By study design, the maximum score was 7, given that patients with prior ischemic stroke were excluded. The Institutional Board Review at the Cleveland clinic approved the study with a waiver for informed consent.

2.3. Statistical analysis

Continuous baseline characteristics are reported as mean and standard deviation, and compared with student test-test, or mean and interquartile range, and compared with Mann Whitney test according to its distribution. Categorical baseline characteristics are reported as frequencies/percentages and compared using the Chi-Square test. Rates of stroke in each group were calculated as events per 100 person year and compared using incidence rate ratios. A Cox regression model was performed to demonstrate an independent parameter estimate for cancer in the prognosis of ischemic stroke after adjusting for the CHA_2DS_2VASc score. A nested model with only a CHA_2DS_2VASc score was compared to a complete model including cancer diagnosis, using a log-likelihood ratio test with a null hypothesis that the reduced nested model is sufficient in predicting the risk of stroke. Then, cancer was given one point and added to the CHA_2DS_2VASc score to create a new score, and model fit statistics of the two models were compared using Akaike information criteria (AIC). The net reclassification index (NRI) was calculated for the CHA_2DS_2VASc score compared to the new score in predicting the risk of ischemic stroke. Finally, a propensity score matching analysis was performed by matching both groups on the exact CHA_2DS_2VASc score and the Cox regression model for ischemic stroke was performed with the Breslow method to break ties, to account for the matching design. Kaplan Meier curves were constructed for the matched groups and compared using the Log-rank test. The analysis was performed using SAS version 9·4 (SAS Institute, Inc., Cary, North Carolina) and Graphpad Prism version 8.

3. Results

A total of 101,185 patients with AF were included in the analysis, including 48,242 with lung, colon, prostate, or breast cancer, and 52,943 without any diagnosis of cancer. Baseline characteristics of both groups are displayed in Table 1. Hypertension was the most prevalent comorbidity in both groups (Cancer 82·1%, Non-cancer 78·2%, $p < 0·001$), followed by hyperlipidemia (Cancer 56.5%, Non-cancer 52.8%, $p < 0·001$), coronary artery disease (CAD) (Cancer 53.9%, Non-cancer 51.6%, $p < 0·001$), and congestive heart failure (Cancer 39.3%, Non-cancer 40.1%, $p = 0·009$). The distribution of CHA_2DS_2VASc scores is displayed with a maximum score of 7, as patients with a history of stroke or TIA prior to their diagnosis of AF were excluded (Table 2). Given the size of the population studied, the differences between the majorities of these comorbidities are statistically significant; however, the magnitude of the difference is small. The largest differences in comorbidities between both groups are the notably higher prevalence of anemia (Cancer 57.8%, Non-cancer 38.0%, $p < 0·001$) and chronic obstructive pulmonary disease (COPD) (Cancer 42.3%, Non-Cancer 20.3%, $p < 0·001$) in the Cancer Group. There was also a lower number of female patients (Cancer 60.7%, Non-cancer 53.7%, $p < 0·001$) in the Non-cancer Group, possibly related to the inclusion of a large proportion of patients with breast cancer (34.0%) within the Cancer Group.

Patients with AF were censored at whichever came first of end of enrollment, the date of the first stroke, or date of death. Mean follow-up was 606 days (median 298, SD 736, IQR 69-891) in the Cancer Group versus 1,002 days (median 688, SD 946, IQR 69-891) in the Non-cancer Group. Overall mortality was higher within the Cancer Group, with 32,786 (68.0%) deaths in the Cancer Group versus 23,510 (44.4%) in

Table 1
Clinical characteristics of groups.

	Non-Cancer	Cancer	P value
Age (years, mean ± SD)	76·2 ± 10·5	76·8 ± 8·4	<0·001
Female (%)	53·7	60·7	<0·001
Race (%)			
White	85·3	87·5	<0·001
Black	6·8	7·3	
Asian	3·1	2·4	
Hispanic	2·0	0·9	
Congestive Heart Failure (%)	40·1	39·3	0·009
Hypertension (%)	78·2	82·1	<0·001
Diabetes (%)	33·1	33·5	0·1
Coronary Artery Disease (%)	51·6	53·9	<0·001
Prior Myocardial Infarction (%)	1·8	1·8	0·9
Hyperlipidemia (%)	52·8	56·5	<0·001
Asthma (%)	6·5	9·2	<0·001
COPD (%)	20·3	42·3	<0·001
Anemia (%)	38·0	57·8	<0·001
Dementia (%)	14·6	10·3	<0·001
Depression (%)	15·5	18·1	<0·001
CKD (%)	26·6	30·8	<0·001
Osteoporosis (%)	7·3	9·7	<0·001
Hypothyroidism (%)	16·0	17·6	<0·001
Lung (%)	0	42·7	NA
Prostate (%)	0	7·3	NA
Colon (%)	0	26·1	NA
Breast (%)	0	34·0	NA

Table 2
CHA_2DS_2VASc score[a] distribution in groups.

CHA_2DS_2VASc Score	No Cancer	Cancer
Median (IQR)	4 (3–5)	4 (3–5)
Mean (±SD)	4·0 ± 1·6	4·2 ± 1·4
≤1 (%)	6·1	3·1
2 (%)	11·5	9·5
3 (%)	18·6	18·0
4 (%)	23·9	26·0
5 (%)	21·8	23·9
6 (%)	13·9	15·0
7 (%)	4·3	4·7

[a] Maximum score of 7 due to patients with a history of prior stroke excluded.

the Non-Cancer Group.

Incidence of stroke was significantly higher in the Cancer Group versus the Non-cancer Group. In the Cancer Group, stroke incidence per 100 person-years was 2.962, compared to an incidence of 2.377 per 100 person-years in the Non-cancer Group (IRR 1.25, 95% CI [1.18–1.31], p < 0·01). This increased incidence was noted across all CHA_2DS_2Vasc scores (Fig. 1). The traditional CHA_2DS_2Vasc scoring system (Model 1) was compared against a new model that also incorporated breast, prostate, colon, and lung cancer (Model 2). Log-likelihood ratio test compared Model 2 versus nested Model 1 showed superiority of the full model (LLR = 6.23 [124,824.89–124,817.24], p = 0.006). The calculated Net Reclassification Index (NRI) was 12.2 (95% CI 10.7–13.7, P < 0.01) in favor of Model 2, suggesting an improvement in the predictive ability of the model with the presence of cancer as an additional risk factor. The Akaike Information Criterion (AIC) was also compared between models to assess the impact of an additional value complicating the model. Model 2 demonstrated as improvement in AIC compared with Model 1 (Model 1, 124,826.89 vs Model 2, 124,825.45). Cox regression was performed with a calculated hazard ratio (HR) for Cancer of 1.085 (95% CI [1.029–1.144], p = 0·0027). This was comparable to age greater than 75 years old, female sex, and diabetes as a contributing parameters for this model (Table 3).

Patients in the Cancer Group were matched with those in the Non-cancer Group with equivalent CHA_2DS_2VASc numerical scores; all patients were able to be matched (n = 48,242 pairs). A Kaplan-Meier curve

Table 3
Cox regression of Model 2 with incorporation of cancer as a parameter.

Parameter	X^2	p value	HR	95% CI
Age > 75	30·8111	<0·0001	1·079	1·050–1·108
Female	6·9448	0·0084	1·075	1·019–1·134
Hypertension	90·4281	<0·0001	1·592	1·446–1·752
Diabetes	15·7232	<0·0001	1·115	1·057–1·177
Vascular Disease	42·5834	<0·0001	1·215	1·146–1·289
Congestive Heart Failure	133·2964	<0·0001	1·385	1·311–1·464
Cancer[a]	9·0263	0·0027	1·085	1·029–1·144

HR = hazard ratio.
CI = confidence interval.
[a] Breast, prostate, lung, or colon cancer.

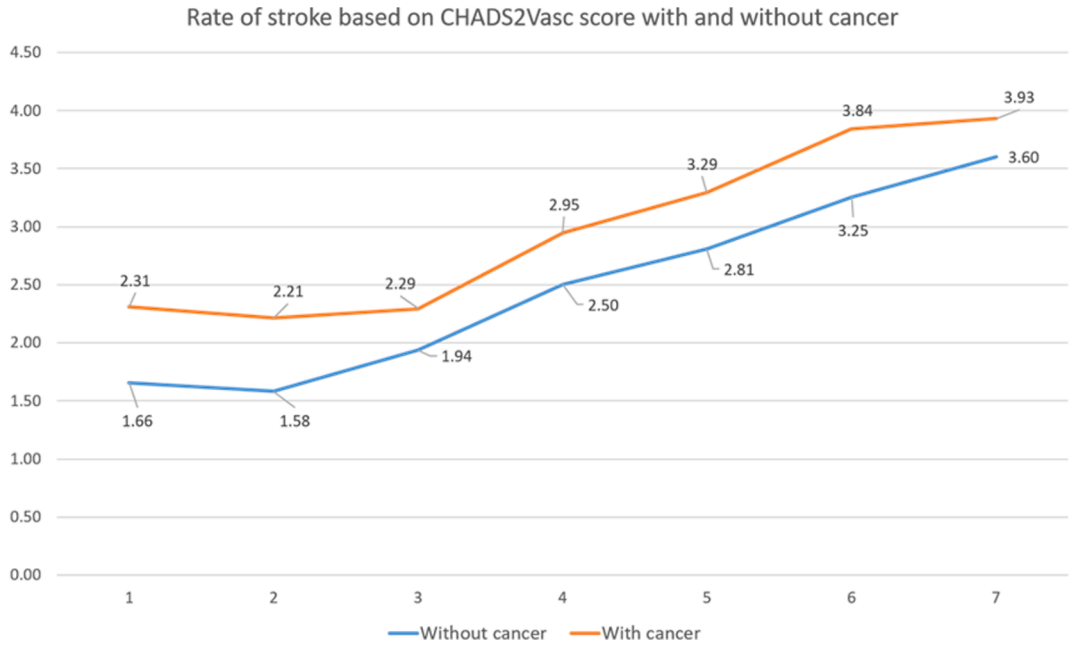

Fig. 1. Rate of stroker per 100 persons-year based on $CHADS_2$ Vasc score with and without.

was generated comparing this propensity-matched cohort with cancer against those without (Fig. 2). The probability of freedom from stroke was significantly lower in the cohort with cancer over at 9 years (p = 0·00045).

4. Discussion

Our analysis suggests that lung, breast, colon, and prostate cancer confer an increased risk of the development of TE in patients with AF, and this elevated risk was maintained across the spectrum of CHA_2DS_2VASc scores. Several analyses compared the traditional CHA_2DS_2VASc score demonstrated the superiority of the model which includes cancer as a risk factor. This included an improvement in NRI of 12.2. While measures of predictive ability typically improve with the addition of more variables [25–26], utilizing this new model also led to an improvement in AIC, which penalizes increasing complexity through the addition of less impactful variables [27]. Perhaps the biggest impact of the proposed CCHA2DS2VASc score (C: Cancer) is that it was comparable to age greater than 75 years old, female sex, and diabetes as contributing parameters for the AF risk calculating model. As previously discussed, the strength of the CHA_2DS_2VASc model over the previously used $CHADS_2$ was its ability to identify those who are and are not truly at risk [9]; the addition of cancer as a variable in this model will further improve on this. While comorbidities incorporated in the CHA_2DS_2VASc scoring system were frequent in both groups, 3.1% of the Cancer Group had a CHA_2DS_2VASc score of ≤ 1. This suggests that there is a portion of this population who may have no other risk factors for the development of TE using the prior model, and would not be offered anticoagulation. Utilizing the new model that includes cancer would remove these patients from a low-risk group and include them in the population to be offered anticoagulation for TE risk reduction.

The baseline characteristics of the groups are comparable across most medical comorbidities. While the differences between these groups are noted to be statistically significant, this is likely a function of the significant power of this analysis to detect such a difference (n = 101,185). The absolute difference between groups is small across nearly all comorbidities [28]. The most significant difference, both statistically and clinically, between these groups is the elevated prevalence of COPD and anemia within the Cancer Group. This may reflect an increased number of tobacco users within the Cancer Group given the inclusion of patients with lung cancer, which comprised the largest proportion of this group (42.7%). The increased frequency of anemia may relate to either the underlying cancer of patients in the Cancer Group or the therapies, such as cytotoxic chemotherapy, used as treatment. While both conditions have been associated with an increased incidence of AF and increased overall mortality, neither has been definitively shown to contribute to the risk of TE in patients with AF [29–30]. It is unlikely these differences between groups impacted the result.

In addition to the differences in comorbidities between groups, a large proportion of patients included in the Cancer Group were female. This likely reflects the larger contribution of patients with breast cancer (34.0%), the vast majority of which are female, relative to the contribution of patients with prostate cancer (7.3%). Female sex is included within the CHA_2DS_2VASc scoring system, but the mean scores for each group are comparable (Cancer Group 4.2 [SD 1.4] vs. Non-cancer Group 4.0 [SD 1.6], p < 0·001). Again, the large sample size of this study suggests this difference to be statistically significant, but the absolute magnitude of difference between groups is minimal.

Follow-up duration and mortality were also different between groups, with a much higher mortality rate in the Cancer Group and

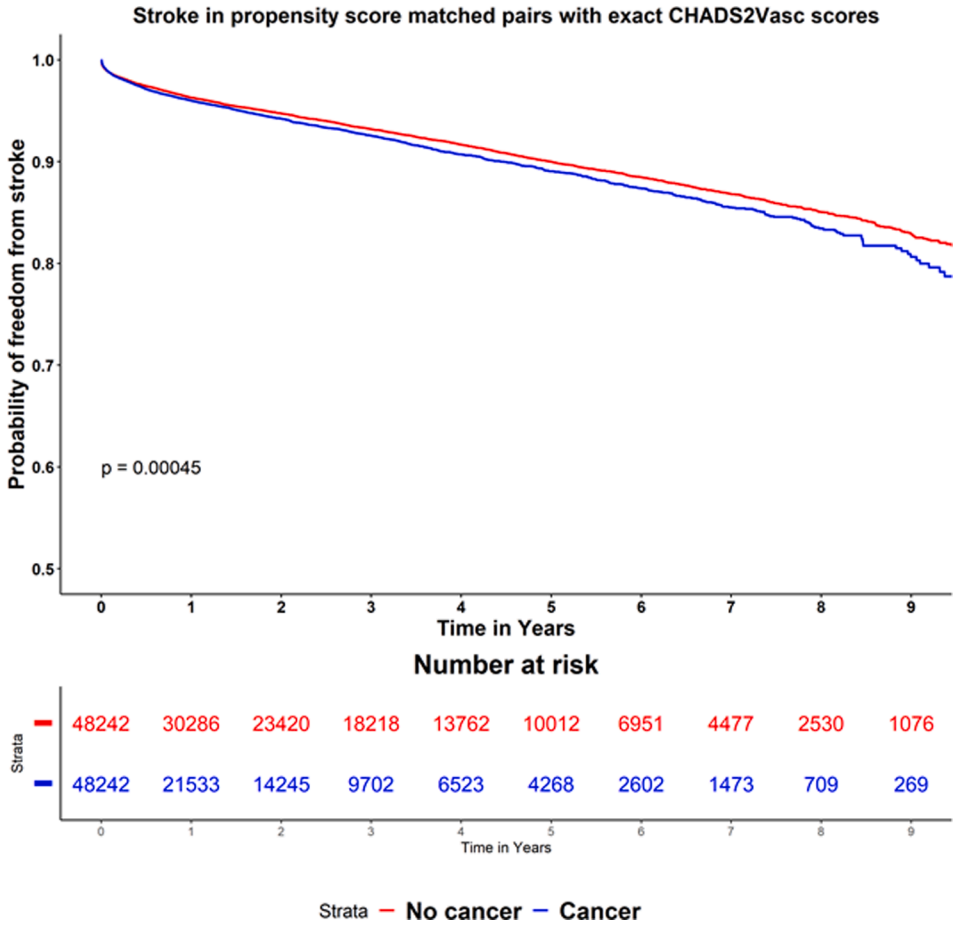

Fig. 2. Kalpana-Merier curve of propensity matched cohort based on CHA_2DS_2VASAc score.

subsequently shorted follow-up. This likely reflects the underlying disease severity within this population, especially given the inclusion of lung cancer, which carried a 20.5% 5-year relative survival rate for all SEER stages from 2010 to 2016 [31]. Despite this high mortality rate over the follow-up period, the length of follow-up is much higher than in prior studies, which had 1 to 1.25 years of follow-up [9,32].

One limitation of this analysis is the inability to identify patients who are anticoagulated. Given the potential use of cytotoxic agents leading to thrombocytopenia, the presence of GI malignancies with high bleeding risk, or the presence of intracranial metastases within the Cancer Group, there may be less patients within this population who are eligible for anticoagulation due to an unacceptable bleeding risk [33], and thus eligibility for anticoagulation may be a confounding variable. Alternatively, some of the cancer population such as breast cancer will most likely be well anticoagulated if they meet the criteria for AF, and score warranted anticoagulation. While patients prescribed anticoagulation could be identified, this introduces additional assumptions into the model, and due to the size of the population analyzed, it would not be feasible to account for anticoagulation use at an individual level. VKAs remain a commonly used anticoagulant in this population, and past studies have demonstrated that patients derive a benefit only when the time in therapeutic range (TTR) is maintained at a minimum of 58%-65% [34]. Significant variation in TTR has been reported between practice sites [35–36], with some falling below this threshold. Furthermore, in clinical practice, nearly 1/3 of patients do not undergo recommended frequency of INR monitoring to be able to identify if this goal is met [36]. Due to this variation, identifying patients prescribed VKAs would not necessarily identify those who are therapeutically anticoagulated. The prior analysis developing the $CHADS_2VASc$ scoring system noted that while only patients that were not anticoagulated were initially included, up to 18% were initiated on a VKA during the follow-up period [9]. Secondary analysis of the subset of patients of those that did not receive anticoagulation initially or during the follow-up period reportedly would not change the conclusions of the analysis [9]. Thus, while anticoagulation data is lacking, reflecting on previous studies of CHADS2-Vasc score, it may not have been a major player. Nonetheless, future studies should include stratification with anticoagulation.

The four most commonly diagnosed cancers were included in this analysis [37]. Other cancers may increase the risk of TE in patients with AF in a similar fashion, and further studies would need to be performed to demonstrate this. Our analysis did not investigate differences in stroke incidence between these different malignancies, which may be present based on the outcomes of prior studies. As an example, the Khorana score stratifies the risk of VTE by cancer type [38], as not all malignancies confer the same level of risk. Similarly, pancreatic cancer has been shown to be associated with an elevated risk of arterial thromboembolism [39], even in the absence of AF. Additionally, our analysis did not investigate the effects that the cancer stage has on the risk of TE. These questions were beyond the scope of our investigation, and are currently subjects of our future investigations.

5. Conclusion

With this data, we recommend considering the addition of breast, prostate, colon, and lung cancers as risk factors to our clinical scoring system used to estimate TE risk in patients with AF, however more thorough analysis especially stratifying patients for anticoagulation is required. The CHA_2DS_2VASc acronym that is simple and familiar to many clinicians can continue to be utilized with the addition of Cancer as another “C”. With the inclusion of this variable as **CC**HA2DS2VASc Score, we can further improve our ability to accurately stratify patients into risk categories and offer therapeutic anticoagulation to a broader population at risk of stroke, however more analysis, especially stratifying for anticoagulation status is required before it becomes a clinical tool.

6. Disclosures

None.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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