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Predicting outcomes in patients with cancer and atrial fibrillation

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Abstract

Background: The role of cancer-specific factors for ischemic stroke and mortality in patients with cancer and atrial fibrillation (AF) is unknown. We evaluated the utility of a previously validated risk tool for venous thromboembolism (VTE) in cancer outpatients [Khorana score (KS)] in predicting stroke and mortality in cancer patients with AF.

Methods: We conducted a retrospective cohort study of patients with cancer and AF at the Cleveland Clinic from 2008 to 2014. Outcomes, CHADS2, CHA2DS2-VASc, and KS scores were calculated from date of cancer diagnosis. Prognostic factors were identified with Fine and Gray regression (for stroke) or Cox proportional hazards analysis (for mortality).

Results: The study population comprised 1181 patients. Genitourinary (19%), lung (18%), and gastrointestinal (13%) were the most frequent cancers. Overall, 67% had CHADS2 $\geqslant 2$, 57% had an intermediate KS (1–2), and 7% high KS ($\geqslant$3). Median follow up was 26.5 months (range 0.03–76). At a median of 8.2 months (range 0–61), 45 patients (3.8%) developed a stroke and 418 (35%) died. In multivariable analysis a high KS (HR 4.5, 95% CI 3.2–6.3, $p < 0.001$) was associated with a quadruple risk of death and every point increase in CHADS2 score had a 20% increased risk of death (HR 1.19, 95% CI 1.1–1.2, $p < 0.001$). The addition of KS did not improve risk stratification for ischemic stroke to CHADS2.

Conclusion: In patients with cancer and AF, CHADS2 and CHA2DS2-VASc but not KS were predictive of ischemic stroke. A high KS represented a unique predictor of mortality beyond traditional risk scores.

Keywords: atrial fibrillation, cancer, mortality, stroke

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Background

Patients with cancer have a higher risk of developing atrial fibrillation (AF) with 2.4% of patients with cancer having pre-existing AF.[1] The relationship may be bidirectional with AF carrying a risk of developing certain cancers.[2] Cancer-specific factors including hypoxia, increased inflammation, chemotherapy, steroids, and electrolyte imbalances can all predispose to AF.[3] However, it is unclear how AF affects the outcomes of cancer patients and, owing to a lack of evidence, there are no guidelines regarding management of AF in this specific population.

Predictors of mortality in cancer patients with AF have not been established. Patients with active cancer or limited survival were excluded from trials validating stroke prediction scores such as the CHADS2 and CHA2DS2-VASc and newer studies evaluating the use of direct oral anticoagulants to prevent AF-related thromboembolic events.[4–8] Furthermore, in a subanalysis of the RELY (The Randomized Evaluation of Long-Term Anticoagulant Therapy) trial, 37.4% of all deaths were attributed to cardiac deaths including sudden cardiac death and heart failure while ischemic stroke and hemorrhage accounted for 9.8% of the deaths of AF patients treated with either warfarin or dabigatran.[9] The Khorana score (KS) was developed to predict venous thromboembolism (VTE) in cancer patients[10,11] and has been subsequently validated.[12–16] Given the theoretical

common pathophysiology between VTE and arterial events in AF, we hypothesized that a validated risk score in cancer patients that predicts the development of VTE may also predict stroke and mortality.

AF is a common comorbidity in cancer patients and factors that predict outcomes in this high-risk population are unknown. Thus, we aimed to evaluate whether the addition of a validated risk score for the development of VTE in cancer patients, the KS adds prognostic information to CHADS2 and CHA2DS2-VASc for the development of ischemic stroke and mortality in cancer patients with a pre-existing diagnosis of AF.

Methods

The Cleveland Clinic tumor registry was queried for consecutive patients with a diagnosis of AF and cancer from 2008 to 2014. The time of cancer diagnosis was used as baseline and all patients included carried a prior diagnosis of AF as indicated by the cancer registry. An electronic query system of the electronic health records (EHRs) was used to collect additional variables not available in the registry and corroborate a diagnosis of AF by ICD-10 (International Statistical Classification of Diseases) codes. The study received approval from the institutional review board (15–1411). Informed consent was waived by the IRB given this was a retrospective study and the use of anonymous clinical data for the analysis.

The CHADS2 score (defined as one point per each: congestive heart failure, hypertension, age >75 years, diabetes mellitus [DM], and two points for a history of stroke) CHA2DS2-VASc score (defined as one point for congestive heart failure, hypertension, age 65–74 years, diabetes mellitus, previous stroke, transient ischemic attack [TIA], vascular disease, and female sex, and two points for age >75 years and prior thromboembolism) and KS [calculated as one point per each: high-risk cancer site (lung, lymphoma, gynecologic, bladder or testicular cancer), hemoglobin <100 g/L or use of red cell growth factors, platelet count $\geqslant$250,000/mm^3, leukocyte count $\geqslant$11,000/mm^3 and body mass index (BMI) $\geqslant$ 35 kg/m^2; and two points for very high-risk cancer site (stomach and pancreas)]. Patients were categorized as low risk of VTE if KS is 0, intermediate risk if KS is 1–2, and high risk if KS $\geqslant$3. All three scores were calculated with baseline characteristics at the time of cancer diagnosis. Laboratory values were obtained within 90 days of cancer diagnosis. Antiplatelet and anticoagulant therapy use within 3 months of cancer diagnosis was recorded. Manual review of the EHRs was performed by two independent authors (RP, AG) for comorbidities included in CHADS2 and CHA2DS2-VASc scores, and development of stroke.

Outcomes studied were ischemic stroke and mortality. Stroke was defined as per World Health Organization criteria[17] as a new neurologic deficit due to a focal injury to the central nervous system by a vascular cause or imaging evidence confirmed by a neurologist. Strokes were classified as ischemic and hemorrhagic and patients with hemorrhagic strokes were excluded. Survival was determined by active follow up *via* chart review and appraisal of the social security death index yearly until loss to follow up or death.

Baseline characteristics are reported as mean and standard deviation or median and range for continuous variables, or as frequency counts and percentages for categorical variables. Outcomes were calculated from the date of cancer diagnosis. Ischemic stroke was estimated with the cumulative incidence method and survival was estimated by Kaplan–Meier. Univariable risk factors were identified with Fine and Gray regression for stroke and Cox proportional hazards analysis for survival. Based on Wald statistics, CHADS2, and CHA2DS2-VASc had similar association with ischemic stroke, whereas CHADS2 had a much strong association with survival than CHA2DS2-VASc. Univariable results are shown for both variables, while multivariable models included only CHADS2. Variables included in the model were: age at cancer diagnosis, gender, race, BMI, smoking status, history of hypertension, hyperlipidemia, vascular disease, diabetes, heart failure or stroke, primary cancer site, cancer stage, metastatic disease at diagnosis, baseline laboratory parameters [including hemoglobin, white blood cell count (WBC), platelet count, creatinine, blood urea nitrogen (BUN), albumin, activated partial thromboplastin time (aPTT), and prothrombin time (PT)] antiplatelet and anticoagulant therapy within 3 months of cancer diagnosis. For

each particular model variables that were part of the score being assessed (CHADS2, CHA2DS2-VASc, or KS) were excluded from the multivariable models to avoid collinearity. Multivariable analyses were performed using stepwise selection with a variable entry criterion of $p \leqslant 0.10$ and a variable retention criterion of $p \leqslant 0.05$. For overall survival two models were used. Model 1 excluded variables with >15% missing data whereas model 2 excluded variables with >10% missing data. Results are shown as hazard ratio (HR) and 95% confidence interval (CI).

Results

Baseline characteristics

The Cleveland Clinic tumor registry was queried for consecutive patients with a diagnosis of AF and cancer from 2008 to 2014 and a total of 2037 patients were identified. After excluding patients for whom the scores could not be calculated at the time of diagnosis a total of 1181 patients were included in the analysis. Baseline characteristics are shown in Table 1. More than half of patients were male (62%), mean age was 71, and the majority was White (91%). The most frequent cancer sites were genitourinary (19%), lung (18%), and gastrointestinal (13%). High-risk cancer sites stomach and pancreas comprised 1.5% and 3.5% of cases, respectively. Metastasis at the time of cancer diagnosis were present in 13% of the cohort, the most common site included bone (4.4%), liver (3.0%), lung (2.6%), and brain (1.4%). The most common comorbidities were hypertension in 72% of patients and hyperlipidemia in more than half of the cohort.

After a median follow up of 26.5 months (range 0.03–76.4) 45 patients (3.8%) had an ischemic stroke and 418 (35%) died. Ischemic strokes occurred at a median of 8.2 months after cancer diagnosis.

Overall, 67% of the sample had CHADS2 score ⩾2, and 84% had a CHA2DS2-VASc score of ⩾2. Low, intermediate, and high KS were seen in 36%, 57%, and 7% of patients, respectively. About a third of the cohort was on antiplatelet therapy and 38% were taking anticoagulants either in addition to antiplatelet therapy or in isolation.

Predictors of ischemic stroke

In univariable analysis being from a non-White race, having a history of stroke or TIA, increased serum creatinine levels, and having used antiplatelet therapy within 3 months of cancer diagnosis were significantly associated with an increased risk of ischemic stroke. In addition, a higher CHADS2 and CHA2DS2-VASc scores was associated with approximately a 40–30% increased risk of stroke per each point increase, respectively (Table 2).

KS was not associated with increased risk of ischemic stroke either analyzed as a continuous variable or as a categorical variable stratifying patients into intermediate, low, or high risk. Primary cancer site could not be analyzed given the low rate of events and the number of categories.

Three significant risk factors for ischemic stroke were identified using multivariable analysis: CHADS2 score, creatinine, and antiplatelet therapy (Table 3). When KS was added to this model to assess the effect on ischemic stroke, it was not significant analyzed either as a categorical variable (Table 3) or as a continuous variable (results not shown).

Predictors of overall survival

In univariable analysis multiple risk factors were associated with mortality risk, including age, gender, BMI, smoking status, hyperlipidemia, vascular disease, diabetes, heart failure, stroke/TIA, cancer stage, metastasis, hemoglobin, WBC, platelet count, and BUN (Table 2).

The three risk prediction scores were associated with overall survival in univariable analysis. For each point increase in the CHADS2 score the mortality risk increased by 22%, each point increase with the CHA2DS2-VASc score was associated with a 15% increase in mortality, and each point increase in the KS with a 58% increased mortality risk. Having an intermediate KS doubled the risk of death and a high risk quadrupled it. In univariable analysis, all KS components were statistically significant except for BMI >35 kg/m^2 (HR 0.80, 95% CI 0.61–1.05, $p = 0.11$). A high-risk cancer was associated with higher risk of death (HR 1.72, 95% CI 1.40–2.11, $p < 0.001$) and a very high-risk

Table 1. Baseline characteristics.

Variable	*n* (%) *n* = 1181
Age at cancer diagnosis (mean ± SD), years	71 ± 11
Gender, male	731 (61.9)
BMI (mean ± SD), kg/m^2	29.6 ± 6.8
Hypertension	855 (72.4)
Hyperlipidemia	649 (55.0)
Vascular disease	455 (38.5)
Diabetes	304 (25.7)
Heart failure	273 (23.1)
Stroke/TIA	153 (13.0)
Primary cancer site	
Stomach	18 (1.5)
Pancreas	40 (3.4)
Lung	208 (17.6)
Gynecologic	59 (5.0)
Bladder	53 (4.5)
Lymphoma	51 (4.3)
Testis	1 (0.1)
GU/other	222 (18.8)
GI/other	150 (12.7)
Breast	93 (7.9)
Hematologic/other	63 (5.3)
Intracranial	54 (4.6)
Dermatologic	48 (4.1)
Endocrine	47 (4.0)
Head and neck	29 (2.5)
All others	45 (3.8)
Metastasis (*n* = 1028)	137 (13.3)
Laboratory values (median, range)	
Hemoglobin, g/dl	12.8 (6.0–18.5)
White blood cell count, K/μl	7.6 (1.3–45.6)
Platelet, K/μl	216 (11–765)
Creatinine, mg/dl (*n* = 1176)	1.0 (0.4–18.6)
BUN, mg/dl (*n* = 1175)	18 (5–95)
Albumin, g/dl (*n* = 1062)	4.0 (1.6–5.0)
Activated partial thromboplastin time, s, (*n* = 910)	30.0 (20.9–200.0)
Prothrombin time, s (*n* = 1023)	11.9 (9.5–92.4)
Medications	
Antiplatelets	387 (32.8)
Anticoagulants	452 (38.3)

BMI, body mass index; BUN, blood urea nitrogen; GI, gastrointestinal; GU, genitourinary; SD, standard deviation; TIA, transient ischemic attack.

cancer was associated with almost three times higher risk of death (HR 3.62, 95% CI 2.56–5.13, $p < 0.001$). Hemoglobin <10 g/dl was associated higher risk of death (HR 2.84, 95% CI 2.27–3.54, $p < 0.001$), as were a platelet count ⩾350,000/mm^3 (HR 2.01, 95% CI 1.51–2.70, $p < 0.001$) and a leukocyte count ⩾11,000/mm^3 (HR 1.46, 95% CI 1.16–1.84, $p = 0.002$).

In multivariable analysis excluding variables with >15% missing data, KS and CHADS2 were both prognostic for mortality (Table 4). In this model, a high KS was associated with a twofold increased risk of death (HR 2.31, 95% CI 1.55–3.44, $p < 0.001$) while each point increase in the CHADS2 score was associated with 12% increased mortality risk (HR 1.12, 95% CI 1.02–1.22, $p = 0.018$). Other risk factors associated with higher mortality risk were metastatic disease at diagnosis, prolonged aPT, and higher BUN. Variables associated with a lower mortality risk included female gender and higher albumin. However, this model was based on data from 818 patients (69% of patients) and 302 deaths (72% of deaths). When KS was analyzed as a continuous variable in this model rather than a categorical variable, each point increase in the score was associated with 32% increased risk of death (HR 1.32, 95% CI 1.18–1.48, $p < 0.001$).

In multivariable analysis excluding variables with >10% missing data, both KS and CHADS2 remained prognostic. A high KS was associated with a fourfold increased risk of death as compared with patients with a low KS risk, and intermediate KS was associated with twofold increased risk of death. Each point increase in CHADS2 was associated with a 19% increase in risk of death. In this model having a history of vascular disease and higher BUN were associated with increased risk of death while being female and a diagnosis of hyperlipidemia were associated with a lower risk. This model was based on 99% of study patients and 99% of deaths. When KS was included in this model as a continuous variable an increase in one point in the KS was associated with 61% increased risk of death (HR 1.61, 95% CI 1.46–1.76, $p < 0.001$).

Discussion

Cancer-associated thrombosis is a leading cause of death in patients with cancer.[18] Further, cancer patients have a higher rate of thromboembolism,

Table 2. Univariable analysis identifying risk factors for stroke and survival.

	Ischemic stroke			Overall survival		
	HR	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**
Age ⩾75/<75	1.32	0.73–2.37	0.35	1.58	1.31–1.92	<0.001
Female	1.52	0.85–2.69	0.16	0.80	0.66–0.98	0.04
White	0.44	0.21–0.95	0.04	0.79	0.58–1.08	0.15
BMI						
Overweight/obese	1.22	0.62–2.37	0.57	1.23	0.98–1.55	0.07
Normal/obese	1.17	0.53–2.57	0.70	1.45	1.12–1.87	0.004
Underweight/obese	1.15	0.16–8.42	0.89	3.73	2.31–6.04	<0.001
Smoking status (*n* = 1120)						
Former/never	1.04	0.56–1.94	0.89	1.39	1.11–1.74	0.004
Current/never	0.22	0.03–1.64	0.14	1.87	1.35–2.58	<0.001
Hypertension	1.34	0.66–2.69	0.42	0.98	0.79–1.22	0.88
Hyperlipidemia	1.18	0.65–2.14	0.59	0.83	0.68–1.00	0.05
Vascular disease	1.19	0.66–2.14	0.56	1.42	1.17–1.72	<0.001
Diabetes	0.98	0.50–1.94	0.96	1.25	1.01–1.55	0.040
Heart failure	1.23	0.63–2.37	0.54	1.65	1.34–2.04	<0.001
Stroke/TIA	3.77	2.03–6.99	<0.001	1.40	1.08–1.83	0.012
Cancer stage (per 1 level increase)	0.98	0.74–1.29	0.88	2.07	1.87–2.29	<0.001
Metastasis	0.83	0.29–2.37	0.73	5.85	4.61–7.42	<0.001
Hemoglobin (per 1 g/dl increase)	0.91	0.81–1.03	0.14	0.81	0.78–0.84	<0.001
WBC (per 5 K/μl increase)	1.15	0.86–1.53	0.33	1.16	1.06–1.28	0.002
Platelets (per 25 K/μl increase)	0.96	0.89–1.02	0.21	1.03	1.00–1.06	0.022
Creatinine, per 1 mg/dl increase (*n* = 1176)	1.14	1.00–1.31	0.043	1.02	0.94–1.11	0.60
BUN, per 5 mg/dl increase (*n* = 1175)	0.99	0.85–1.15	0.89	1.08	1.04–1.12	<0.001
Antiplatelet therapy	2.34	1.30–4.21	0.004	1.17	0.96–1.43	0.13
Anticoagulants	1.16	0.64–2.09	0.62	1.04	0.86–1.27	0.66
CHADS2 (per 1 point increase)	1.40	1.13–1.74	0.002	1.22	1.13–1.31	<0.001
CHA2DS2-VASc (per 1 point increase)	1.29	1.10–1.50	0.002	1.15	1.09–1.22	<0.001
KS						
Per 1 point increase	0.91	0.66–1.24	0.55	1.58	1.44–1.72	<0.001
Intermediate/low	0.81	0.44–1.46	0.48	2.07	1.64–2.60	<0.001
High/low	0.82	0.25–2.74	0.75	4.26	3.04-5.98	<0.001

BMI, body mass index; BUN, blood urea nitrogen; KS, Khorana score; TIA, transient ischemic attack; WBC, white blood cell count.

Table 3. Multivariable analysis of risk factors for ischemic stroke.

	HR	95% CI	*p* value
Model 1: significant variables and CHADS2 score			
CHADS2, per 1 point increase	1.39	111–1.73	0.004
Creatinine, per 1 mg/dl increase	1.16	1.00–1.35	0.045
Antiplatelet therapy	2.36	1.29–4.32	0.005
Model with the addition of the KS			
CHADS2, per 1 point increase	1.41	1.13–1.76	0.002
Creatinine, per 1 mg/dl increase	1.16	0.99–1.34	0.06
Antiplatelet therapy	2.41	1.32–4.40	0.004
KS intermediate/low risk	0.70	0.38–1.27	0.23
KS high/low risk	0.74	0.23–2.44	0.63

CI, confidence interval; HR, hazard ratio; KS, Khorana score.

bleeding, and mortality compared with the general population making risk stratification difficult.[19–21] AF represents an additional challenge in the treatment of malignant conditions and mortality risk scores for cancer patients with AF have not been developed nor validated. This study attempts to fill this void of outcome prediction in cancer and AF patients. We found that CHADS2, CHA2DS2-VASc, and KS are associated with overall survival in cancer patients with pre-existing AF.

A high KS was associated with a quadruple increase in mortality risk representing a unique predictor of mortality beyond traditional risk scores in this population. In a recent study including 163 patients with active cancer and AF and a mean CHA2DS2-VASc of 3.2 anticoagulated with rivaroxaban the cumulative risk of death per year was 22.6% with a risk of stroke of 1.6%.[8] The KS has been a useful mortality risk stratification tool in some cancer cohorts. In a study including 719 patients with lung cancer, having a high KS was associated with 1.7 times higher risk of death (95% CI 1.4–2.2). This is similar to that seen in our cohort and other literature.[22,23] Other reports in different cancer types are conflicting. In a retrospective single-center study of 109 patients with more than 90% with low or intermediate KS did not predict mortality.[24] In another retrospective study specific for gastric cancer including 112 patients, high KS was not associated with worse survival.[25] However larger studies including solid tumors and lymphoma reiterate the value of KS for mortality prediction where a high score was associated with a HR of 3 and intermediate risk carried a HR of 2.3 for mortality.[26] There are no prior reports on mortality risk assessment for patients with cancer and AF. In our study all components of the KS were associated with overall survival except BMI. Further, the sensitivity analysis confirmed a relationship between KS and overall survival.

Traditional risk factors for ischemic stroke including CHADS2 and CHA2DS2-VASc were also associated with overall survival in this cohort. Prior studies in patients with and without AF support this finding. Chen *et al*. showed that in a cohort of 1311 patients with systolic heart failure with and without AF CHADS2, CHA2DS2-VASc, and R2CHADS2 which includes 2 points for renal dysfunction were all associated with overall survival.[27] In a prior study including patients with and without AF who had cardiac resynchronization therapy, CHA2DS2-VASc but not CHADS2 was associated with increased mortality at a median follow up of 30 months.[28] Further studies have shown that pre and post stroke CHADS2, CHA2DS2-VASc are associated with mortality even in patients without a

Table 4. Multivariable analysis of prognostic factors for overall survival.

	Model 1 (*n* = 818; 302 deaths)			Model 2 (*n* = 1175; 417 deaths)		
	HR	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**
Female	0.77	0.60–0.98	0.035	0.75	0.61–0.93	0.008
Metastasis	4.28	3.30–5.56	<0.001	NA	NA	NA
Vascular disease	NA	NA	NA	1.40	1.14–1.72	0.002
Hyperlipidemia	NA	NA	NA	0.70	0.57–0.86	<0.001
Laboratory parameters						
PT (per 10 s increase)	1.18	1.04–1.34	0.009	NA	NA	NA
BUN (per 5 mg/dL increase)	1.07	1.02–1.12	0.003	1.06	1.01–1.10	0.012
Albumin (per 1 g/dl increase)	0.49	0.42–0.58	<0.001	NA	NA	NA
Khorana score						
Intermediate/low	1.23	0.92–1.64	0.16	1.93	1.53–2.44	<0.001
High/low	2.31	1.55–3.44	<0.001	4.52	3.20–6.37	<0.001
CHADS2 (per 1 point increase)	1.12	1.02–1.22	0.018	1.19	1.10–1.29	<0.001

BUN, blood urea nitrogen; CI, confidence interval; HR, hazard ratio; PT, prothrombin time.

diagnosis of AF.[29–31] It is therefore of no surprise that in our cohort CHADS2 and CHA2DS2-VASc was associated with overall survival.

Prior studies have shown that the traditionally used scores such as the CHA2DS2-VASc should be used cautiously in patients with AF and cancer. In a study by D'Souza *et al.* using nationwide registries including roughly 120,000 patients those with a low CHA2DS2-VASc score of 0–1 had a higher risk of stroke than noncancer patients but in those with a score more than or equal to two the risk between cancer and noncancer patients did not differ.[20] This finding was confirmed in a larger cohort where the impact of AF on the risk of stroke decreased in high CHA2DS2-VASc scores[32] further emphasizing the need for better risk assessment tools in this cohort. In our study we tried to assess whether the addition of validated prediction scores for thromboembolism to the guideline standard prediction scores added prognostic information for stroke in patients with cancer and AF. We found that the KS was not associated with increased risk of ischemic stroke in univariable or multivariable analysis. This suggests the need of an interdisciplinary evaluation including oncologists/hematologists and cardiologists could be useful for the patient's optimal management.

Our results are consistent with the existing literature showing that both CHADS2, CHA2DS2-VASc are associated with increased risk of ischemic stroke. However, in our study the use of antiplatelet therapy within 3 months of cancer diagnosis was associated with increased risk of stroke. We speculate that this might be a marker of patients who are at increased risk of stroke or embolic events and might have contraindications to anticoagulants or other confounding factors not accounted for in our adjusted analysis that may be responsible for this seemingly paradoxical effect. Interestingly, we did not find an association of female sex with increased risk of stroke finding consistent with recently published studies.[20]

This study is limited primarily by the retrospective, single-center nature of its design. We collected information from a cancer registry and electronic medical record review but might

underestimate the number of ischemic events and deaths that could have presented elsewhere, lost to follow up, improperly coded, or deaths occurring overseas. Further, medication use was assessed within 3 months of cancer diagnosis and might not be representative of actual medications being used at the time of the index event. We were unable to purify data based on changes made during the actual study period that limit our ability for further data collection.

Conclusion

In patients with cancer and pre-existing AF, CHADS2, CHA2DS2-VASc, and KS are associated with increased mortality risk. We report here for the first time that the KS is associated with mortality with a high KS carrying a quadruple increased mortality risk representing a unique predictor of death in this cohort. Further, we demonstrate that CHADS2 and CHA2DS2-VASc predict the risk of ischemic stroke but KS is not predictive of ischemic stroke in this setting. Future research should focus on the unique factors in cancer patients with AF that impact prognostication and management.

Authors' Note

Alejandra Gutierrez and Rushad Patell contributed equally to this work.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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